was extracted with toluene and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was treated with sodium hydroxide (1 M) and extracted with diethyl ether and toluene. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica (gradient ethyl acetate-methanol 90:10 up to 0.06% NH_3 in ethyl acetate-methanol 90:10) Yield 1 g (18%); ^1H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

11.2 (S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

(S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (1 g, 2.34 mmol) in THF (25 mL) was added to 9-BBN (0.5 M in THF, 11.7 mL, 5.85 mmol) under nitrogen atmosphere at 0 °C. Additional 9-BBN (2.3 mL, 1.2 mmol) was added after 3 hours of stirring, the temperature was raised to room temperature and the mixture was stirred for 0.5 hour. It was then cooled to 0 °C and 1 M sodium hydroxide (10 mL) was added followed by H_2O_2 (30% in H_2O, 10 mL). After 1 hours stirring, water was added and the mixture was extracted with diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (gradient of diethyl ether to 1% NH_3 in diethyl ether). Yield 0.67 g (64%). ^1H NMR ($CDCl_3$) δ 0.90 (d, 12H), 2.10-2.18 (m, 2H), 2.30-2.37 (m, 2H), 2.80 (t, 2H), 2.90-3.0 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 5.0 (s, 2H), 6.80 (d, 1H), 7.0 (m, 1H), 7.10-7.38 (m, 11H).

EXAMPLE 12

(R)-N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

The title compound as well as the starting compounds were prepared in an analogous manner to the preparation described in Example 11, with the exception that (S)-N,N-

diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was changed to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1).

Yield 0.35 g (33%); mp 209-215 °C; $[\alpha]_D$ +9.8° (c=1.0, methanol); ^1H NMR (CD_3OD) δ 1.29 (d, 12H), 2.40-2.60 (m, 2H), 2.67 (t, 2H), 3.04 (t, 2H), 3.61-3.72 (m, 4H), 4.40 (t, 1H), 6.70 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.18-7.40 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

Preparation of starting compounds:

12.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

Yield 5.5 g (53%); ^1H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

12.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

Yield 1.2 g (75%); ^1H NMR ($CDCl_3$) δ 0.89 (d, 12H), 2.15 (m, 2H), 2.32 (m, 2H), 2.80 (t, 2H), 2.95 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 4.98 (s, 2H), 6.80 (d, 1H), 6.96 (m, 1H), 7.10-7.35 (m, 11H).

EXAMPLE 13

(R)-N,N-Diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

(R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine (1 g, 2.25 mmol) was treated as described in Example 11. Yield 0.6 g (68%); mp 105-115 °C; $[\alpha]_D$ -32.6° (c 1.02, methanol); ^1H NMR (DMSO-d_6) d 1.18-1.28 (m, 12H), 2.5 (m, 3H), 2.50-2.62 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.38 (t, 1H), 6.99 (d, 1H), 7.2 (m, 1H), 7.29-7.35 (m, 4H), 7.73 (dd, 1H), 7.85 (d, 1H), 9.90

(br, 1H), 10.70 (s, 1H). Anal. ($C_{23}H_{31}NO_2 \cdot HCl \cdot 0.4H_2O$) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

13.1 (R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine

To a stirred solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (Example 12) (10.2 g, 21.23 mmol) in DMF (100 mL) under nitrogen atmosphere at room temperature were sequentially added triethylamine (2.58 g, 25.47 mmol), TlOAc (6.15 g, 23.35 mmol), isobutylvinylether (14 mL, 106.14 mmol), DPPP (0.87 g, 2.12 mmol) and $Pd(OAc)_2$ (0.24 g, 1.06 mmol). The reaction temperature was raised to 100 °C and stirred for 3 hours, cooled to room temperature, filtered and treated with HCl (5%, 250 mL) and stirred for another 2 hours. The reaction mixture was repeatedly extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated. Triethylamine and DMF were destilled off under reduced pressure to yield 9 g (98%); ^1H NMR ($CDCl_3$) δ 1.22 (m, 12H), 2.52-2.70 (m, 7H), 3.40 (br, 2H), 4.34 (t, 1H), 5.10 (s, 1H), 6.90 (d, 1H), 7.17-7.40 (m, 10H), 7.82 (m, 1H) and 7.92 (s, 1H).

EXAMPLE 14

N,N-Diisopropyl-3(R)-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine fumarate

N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine (2.7 g, 6.05 mmol) was hydrogenated over Pd/C (0.27 g, 10%) in ethanol at atmospheric pressure for 2 hours. The catalyst was filtered off and the solvent was evaporated. The resulting oil was chromatographed on silica (toluene-triethylamine 90:10). Fumarate salt of the amine was afforded by adding fumaric acid (0.13 g, 1.13 mmol) dissolved in warm ethanol to a

solution of the free base in diethyl ether yielding white crystals (0.44 g, 83%); mp 240-244 °C; $[\alpha]_D$ +9.8° (c 1.02, methanol); ^1H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.26 (dd, 3H), 2.20-2.30 (m, 2H), 2.55-2.67 (m, 2H), 3.30 (m, 2H), 4.32 (t, 1H), 4.59 (q, 1H), 6.53 (s, 2H), 6.72 (dd, 1H), 6.93 (dd, 0.5H), 7.12-7.17 (m, 1H), 7.21-7.31 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot C_4H_4O_4 \cdot 0.3H_2O$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

14.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine

N,N-Diisopropyl-3(R)-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine, prepared as described in Example 13.1, (3.5 g, 7.90 mmol) dissolved in dry THF was added to $LiAlH_4$ (0.2 g, 5.41 mmol). After 2 hours of stirring, additional $LiAlH_4$ (50 mg, 1.32 mmol) was added and the reaction mixture was stirred for 1.5 hours. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-E_3N 90:10) to give 2.74 g (78%) of an oil that crystallised slowly upon storage at room temperature.

EXAMPLE 15

(+)-N,N-Diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine fumarate

N,N-Diisopropyl-3(R)-[2-benzyloxy 5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (0.55 g, 1.2 mmol) was treated in an analogous manner to that described in Example 14 above, which yielded white crystals, 0.32 g (55%); mp 196-200 °C; $[\alpha]_D$ +13.5° (c 1.0, methanol); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.40-2.48 (m, 1H), 2.52-2.60 (m, 1H), 3.03 (t, 2H), 3.55 (d, 2H), 3.66 (m, 2H), 4.42 (t, 1H), 4.57 (t, 1H), 6.7 (s, 2H), 6.79 (d, 1H), 7.05 (dd,

1H), 7.16-7.21 (m, 2H), 7.28 (m, 2H), 7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3 \cdot C_4H_4O_4$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

15.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine

To an ice-chilled solution of AD-mix-α (5.7 g) in H_2O (20 mL) and t-BuOH (10 mL) was added N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (Example 12.1), (1.74 g, 4.1 mmol) dissolved in t-BuOH (10 mL). After 1 hour of stirring, the ice bath was removed and the reaction mixture was stirred for additional 21 hours. Na_2SO_3 (6 g) was then added and after 1 hours of stirring the reaction mixture was partioned between H_2O and ethyl acetate. The aqueous layer was extracted 3 times with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine, 90:10) to afford 0.55 g. ^1H NMR ($CDCl_3$) δ 0.9 (s, 6H), 0.95 (s, 6H), 2.15-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.96 (m, 2H), 3.60-3.70 (m, 2H), 4.41 (t, 1H), 4.75 (m, 1H), 5.0 (s, 2H), 6.85 (d, 1H), 7.10-7.35 (m, 12H).

EXAMPLE 16

(-)-N,N-Diisopropyl-3(R)-[5-(1(S*),2-dihydroxyethyl) 2-hydroxyphenyl]-3-phenylpropanamine fumarate

N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (1.1 g, 2.4 mmol) was treated in an analogous manner to that described in Example 11 which yielded white crystals, 0.25 g (21%); mp 208-211 °C; $[\alpha]_D$ -8° (c 1.02, methanol); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.39-2.47 (m, 1H), 2.51-2.59 (m, 1H), 3.03 (t, 2H), 3.51-3.53 (m, 2H), 3.67 (m, 2H), 4.42 (t, 1H), 4.54 (dd, 1H), 6.68 (s, 2H), 6.78 (d, 1H), 7.06 (dd, 1H),

7.16-7.20 (m, 2H), 7.26 (m, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3 \cdot C_4H_4O_4$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was obtained by treating N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (obtained in Example 12.1) as described in Example 15.1 above, but with AD-mix-β replacing AD-mix-α. Yield 1.2 g (44%).

EXAMPLE 17

(R)-[N,N-Diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)-phenyl]-3-phenylpropanamine hydrochloride

N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine (0.35 g, 0.72 mmol) was treated in an analogous manner to that described in Example 14. Yield 0.10 g (31%); mp 147-156 °C; $[\alpha]_D$ +8.2° (c 1.01, methanol); ^1H NMR (CD_3OD) δ 1.25-1.32 (m, 16H), 1.45-1.54 (m, 4H), 2.40-2.48 (m, 3H), 2.51-2.59 (m, 1H), 3.0-3.10 (m, 2H), 3.51 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.72 (d, 1H), 6.86 (dd, 1H), 6.91 (d, 1H), 7.19 (m, 1H), 7.30 (t, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{27}H_{41}NO_2 \cdot HCl \cdot 2H_2O$) C, N; H: calcd, 9.6; found, 8.3.

The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine was prepared as follows:

17.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine

n-BuLi (2.5 M in hexane, 19 mL, 47.5 mmol) was added to a solution of to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3- phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8.9 g, 18.52 mmol) in dry diethyl ether (100 mL) kept at -40 °C under nitrogen atmosphere. After 1.5 hour of stirring, additional n-BuLi (10 mL, 25

mmol) was added and after 2 hours another n-BuLi (5 mL, 12.5 mmol) was added. The reaction was then stirred for 15 minutes and DMF (6 mL, 77.8 mmol) was added followed by additional DMF (5 mL, 64.8 mmol) after 20 minutes of stirring. The temperature was allowed to rise to room temperature and after 35 minutes of stirring, NH_4Cl (sat.) was added followed by water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (toluene-triethylamine 90:10) to afford 8 g (100%) of a yellowish oil; ^1H NMR ($CDCl_3$) δ 0.90 (m, 12H), 2.12-2.40 (m, 4H), 2.95 (m, 2H), 4.44 (t, 1H), 5.10 (s, 2H), 6.95 (d, 1H), 7.15-7.36 (m, 10H), 7.70 (dd, 1H), 7.91 (s, 1H), 9.88 (s, 1H).

17.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy 5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine

To a slurry of 4-carboxybutyl triphenylphosphonium bromide (4.1 g, 9.31 mmol) in THF (25 mL) at -10 °C under nitrogen atmosphere was added potassium tert-butoxide (2.1 g, 18.62 mmol). The mixture turned orange and after 10 minutes stirring, (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine (2 g, 4.65 mmol) in THF (10 mL) was added. After 4 hours of stirring, hydrochloric acid (1M) and diethyl ether were added and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine 90:10 followed by methanol) to afford 3 g containing traces of triphenylphosphine. The product was used in the next step without further purification.

17.3 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine was reduced as described in Example 10. Yield 0.35 g (15%).

EXAMPLE 18

(R)-N,N-Diisopropyl-3-[5-(2-diisopropylaminoethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine (0.6 g, 1.13 mmol) was refluxed with concentrated HCl (25 mL) overnight. The reaction mixture was then basified with 10 M sodium hydroxide and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.5 g oil that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. The resulting diethyl ether solution was treated with hydrogen chloride in diethyl ether. Yield 50 mg (9%); $[\alpha]_D$ +1.4° (c 0.94, methanol); ^1H NMR (CD_3OD) δ 1.27-1.34 (m, 12H), 1.36-1.42 (m, 12H), 2.50-2.58 (m, 1H), 2.60-2.67 (m, 1H), 2.95 (t, 2H), 3.05 (m, 2H), 3.15-3.27 (m, 2H), 3.70 (m, 2H), 3.75 (m, 2H), 4.40 (t, 1H), 6.80 (d, 1H), 7.02 (dd, 1H), 7.13 (d, 1H), 7.20 (m, 1H), 7.31 (m, 1H), 7.39-7.41 (m, 1H). Anal. ($C_{29}H_{46}N_2O \cdot 2HCl \cdot 0.4H_2O$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine was prepared as follows:

18.1 N,N-Diisopropyl-3(R)-(5-formylmethyl-2-benzyloxy-phenyl)-3-phenylpropanamine

DMSO (1.1 mL, 15.5 mmol) dissolved in dichloromethane was added dropwise to oxalyl chloride (0.64 mL, 7.74 mmol) at -78 °C under nitrogen atmosphere. After 10 minutes of

stirring, (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (Example 12.2) (2.3 g, 5.16 mmol) in dichloromethane was added and the reaction mixture was stirred for additional 1 h. Triethylamine (5.4 mL, 38.7 mmol) was then added and the temperature was allowed to rise to room temperature. The reaction mixture was taken up in water and dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated in vacuo and the product was used in the next step without further purification.

18.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine

Diisopropylamine (4.2 mL, 30 mmol) was dissolved in methanol (12 mL). 5 M HCl in methanol (2 mL) was added followed by N,N-diisopropyl-3(R)-(5-formylmethyl-2-benzyloxyphenyl)-3-phenylpropanamine (5 mmol) in methanol (10 mL) and sodium cyanoborohydride (0.22 g, 3.5 mmol). The reaction mixture was stirred at room temperature overnight. methanol was then evaporated, and diethyl ether and H_2O were added. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 3 g of a crude product that was chromatographed on silica (toluene-triethylamine 95:5). Yield 0.65 g (25%); ^1H NMR ($CDCl_3$) δ 0.88-0.91 (m, 18H), 1.20 (d, 9H), 2.10-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.87-3.10 (m, 4H), 4.34 (m, 1H), 4.98 (d, 2H), 6.75-6.97 (m, 2H), 7.10-7.30 (m, 11H).

EXAMPLE 19

(R)-N,N-Diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethyl-phenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (3.9 g, 11.5 mmol) and Al_2O_3 (115 g, 1.13 mol) refluxed in ethyl acetate (0.5 L) for 60 hours. Al_2O_3 was filtered off and ethyl acetate was evaporated. Chromatography on silica (toluene-triethylamine, 90:10) of the residue yielded 2.5 g (59%). The fumarate salt was

obtained by adding fumaric acid (0.17 g, 1.48 mmol) dissolved in warm ethanol to the free base (0.55 g, 1.48 mmol) in diethyl ether; mp 174-177 °C; $[\alpha]_D$ +5.5° (c 1.02, methanol); ^{1}H NMR (CD_3OD) δ 1.15 (t, 3H), 1.27-1.30 (m, 12H), 2.41-2.49 (m, 1H), 2.52-2.60 (m, 1H), 3.04 (dd, 2H), 3.49 (q, 2H), 3.67 (m, 2H), 4.35 (s, 2H), 4.43 (t, 1H), 6.69 (s, 2H), 6.80 (d, 1H), 7.04 (dd, 1H), 7.12 (d, 1H), 7.18-7.37 (m, 4H). Anal. ($C_{24}H_{35}NO_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 20

N-Isopropyl-3-(5-carboxy-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine (1.3 g, 2.6 mmol) was dissolved in HOAc. Palladium (10%) on charcoal (0.13 g) was added and the mixture was hydrogenated at atmospheric pressure for 48 hours. The catalyst was then filtered off and the solvent was evaporated. The resulting oil was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). This purification was done in 16 portions with about 100 mg material each time. The pure fractions were pooled and freeze-dried to give 0.57 g of trifluoroacetic acid salt. The crystals were dissolved in 1 M HCl and freeze-dried to give 0.4 g (43%) of the hydrochloride salt as white crystals; mp 155-160 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (d, 3H), 1.19 (d, 3H), 2.30-2.38 (m, 1H), 2.38-2.46 (m, 1H), 2.72 (br, 1H), 2.80 (br, 1H), 3.25 (m, 1H), 4.40 (t, 1H), 6.94 (d, 1H), 7.18-7.22 (m, 1H), 7.29-7.33 (m, 4H), 7.66 (dd, 1H), 7.76 (d, 1H); Anal. ($C_{19}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

The starting compound N-benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine was prepared as follows:

20.1 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal

3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanol (16.5 g, 41.5 mmol) (prepared as described in WO 94/11337, Example 1c) was reacted as described in Example 18.1. The combined organic layers were washed with 2 M HCl, 10% $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated to give 16 g (98%) of yellowish crystals of the product that was used in the next step without further purification; mp 99-100 °C; ^1H NMR ($CDCl_3$) δ 3.10 (dd, 2H), 5.0 (s, 2H), 4.98-5.10 (m, 1H), 6.76 (d, 1H), 7.16-7.38 (m, 12H), 9.65 (s, 1H).

20.2 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

To a solution of N-benzylisopropylamine (34 mL, 0.20 mol) in methanol (80 mL) was added 5 M HCl in methanol (16.2 mL, 80.9 mmol) followed by 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (16.0 g, 40.5 mmol) in methanol (20 mL) and sodium cyanoborohydride (1.78 g, 28.3 mmol). The resulting solution was stirred for 17 hours. The solvent was evaporated and diethyl ether was added to the resulting syrup. The solution was washed 3 times with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (hexane-ethyl acetate, 75:25) giving 15.9 g of a syrup. The hydrochloride salt of the compound was prepared by dissolving the product in diethyl ether and adding HCl dissolved in diethyl ether. The resulting oil was washed with diethyl ether, dissolved in 10 M sodium hydroxide and extracted with diethyl ether 3 times. Purification by chromatography on silica (using a gradient of dichloromethane up to 1% triethylamine in dichloromethane) yielded 7 g (33%) of the product as a colourless oil. ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H), 0.90 (d, 3H), 2.02-2.12 (m, 2H), 2.38 (t, 2H), 2.90 (m, 1H), 3.50 (d, 2H), 4.50 (t, 1H), 4.95 (s, 2H), 6.70 (s, 1H), 7.10-7.35 (m, 17H).

20.3 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine

A mixture of magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal) was warmed gently. A solution of N-benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (6.0 g, 11 mmol) and 1,2-dibromoethane (0.2 mL, 2.3 mmol) in dry THF (25 mL) was added dropwise under nitrogen atmosphere to the refluxing mixture. After 2 hours of refluxing, 1,2-dibromoethane (0.59 mL, 6.8 mmol) was added. The mixture was left overnight under nitrogen atmosphere. The mixture was then added together with 1,2-dibromoethane (0.93 mL, 10.8 mmol) to warmed magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal). After 30 minutes of refluxing, the mixture was cooled to room temperature and CO_2 (g) was bubbled through. After 3 hours, ammonium chloride (aq, 15%, 50 mL) was added followed by diethyl ether (100 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated to give 5.8 g of an oil. The crude product was chromatographed on silica (using a gradient of acetone up to 5% ethanol in acetone) to give the pure product (1.3 g, 23%) as an oil. N-benzyl-N-isopropyl-3-(2-benzyloxyphenyl)-3-phenylpropanamine (3.1 g) was obtained as a biproduct from the reaction. ^1H NMR ($CDCl_3$) δ 0.98 (d, 3H), 1.10 (d, 3H), 2.30-2.40 (m, 2H), 2.46-2.65 (m, 2H), 3.40 (br, 1H), 3.85 (br, 2H), 4.30 (br, 1H), 4.98 (br, 2H), 6.80 (d, 1H), 7.10-7.40 (m, 15H), 7.95 (d, 1H), 7.95 (d, 1H), 8.20 (s, 1H).

EXAMPLE 21

N-Benzyl-N-isopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine, prepared as described in Example 20.3, (3.1 g, 6.90 mmol) was refluxed in concentrated HCl (30 mL) for 20 h. The reaction mixture was allowed to cool to room temperature and the liquid was poured off. The remaining oil was washed with water and diethyl ether and then

dissolved in 2-propanol. The solution was evaporated and treated with 10 M sodium hydroxide to give the free base. Chromatography on silica (hexane:ethyl acetate 75:25) afforded 0.5 g of the compound that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. To the resulting diethyl ether solution was added dropwise saturated diethyl ether-HCl (g). The resulting crystals of the hydrochloric salt were collected by filtration; mp 115-122 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (m, 6H), 2.27-2.38 (m, 1H), 2.48-2.55 (m, 1H), 2.72-2.97 (m, 2H), 3.55 (m, 1H), 4.23 (m, 2H), 4.35 (m, 1H), 6.68-6.74 (m, 1H), 6.82 (dt, 1H), 6.96-7.24 (m, 7H), 7.38-7.42 (m, 3H), 7.64-7.68 (m, 2H), 9.55 (d, 1H), 10.62 (br, 1H). Anal. ($C_{25}H_{29}NO\cdot HCl$) C, H, N.

EXAMPLE 22

(R)-N,N-Diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine dihydrochloride

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine (3.20 g, 7.07 mmol) was dissolved in 100 % acetic acid and 10% Pd/C (0.52 g) was added. The mixture was hydrogenated (60 psi) overnight at room temperature. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in water, basified with sodium hydroxide (11 M), extracted with ethyl acetate, the organic phase was dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (toluene-ethyl acetate-triethylamine-methanol, 20:5:1.5:1). The amine was redissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate was filtered off wich gave 0.30 g (10 %); ^{1}H NMR (CD_3OD) δ 1.29 (m, 12H), 1.88 (m, 2H), 2.51(m, 2H), 2.59 (t, 2H), 2.88 (t, 2H), 3.04 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 4.55 (bs, 1H), 6.76 (d, 1H), 6.93 (d, 1H), 7.03 (s, 1H), 7.19 (t, 1H), 7.30 (t, 2H), 7.37 (d, 2H); mp.

226-228 °C; $[\alpha]_D$ +11.5° (c=1.0, methanol). Anal. ($C_{24}H_{36}N_2O*2HCl$) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine was prepared as follows:

22.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyano-ethenyl)phenyl]-3-phenylpropylamine

To a solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (13.87 g, 28.87 mmol) (prepared as described in WO 94/11337, Example 1) in DMF (140 mL) was added triethylamin (5.00 mL, 36.10 mmol), $Pd(OAc)_2$ (0.32 g, 1.44 mmol), tri(o-tolyl)phosphine (1.76 g, 5.77 mmol) and acrylonitrile (2.39 mL, 36.10 mmol). The reaction mixture was stirred overnight at 115 °C in a sealed flask equipped with a reflux condenser under nitrogen atmosphere. The resulting mixture was concentrated, and the residue was dissolved in diethyl ether, washed with aqueous 2 M sodium hydroxide and water. The organic phase was dried ($MgSO_4$) whereafter petroleum ether was added to the organic phase and a precipitate was formed. Recrystallisation from ethanol yielded 5.50 g (42%). ^1H NMR ($CDCl_3$) δ 0.90 (s, 6H), 0.95 (s, 6H), 2.15 (q, 2H), 2.35 (q, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.05 (s, 2H), 5.70 (d, 1H), 6.85 (d, 1H), 7.10-7.50 (m, 13H).

EXAMPLE 23

(R)-N,N-Diisopropyl-3-[5-3-(acetamidopropyl)-2-hydroxy-phenyl]-3-phenylpropanamine hydrochloride

To a solution of (R)-N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, (Example 22), (0.45 g, 1.23 mmol) in methanol (45 mL) was added acetic anhydride (0.23 mL, 2.47 mmol). The mixture was stirred for 3 h at room temperature and then evaporated to dryness. The residue was dissolved in H_2O, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried with $MgSO_4$, filtered and

evaporated. The amine was dissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate formed was filtered off to give 0.55 g (100 %). ^{1}H NMR (CD_3OD) δ 1.27 (m, 12H), 1.75 (m, 2H), 2.08 (s, 3H), 2.52 (m, 4H), 3.04 (t, 2H), 3.20 (t, 2H), 3.68 (m, 2H), 4.40 (t, 2H), 6.72 (d, 1H), 6.90 (d, 1H), 6.99 (s, 1H), 7.19 (t, 1H), 7.30 (m, 4H); mp. 171-175 °C; $[a]_D$ +3.6° (c=0.5, methanol). ($C_{26}H_{38}N_2O_2$*HCl) C, H, N.

EXAMPLE 24

(R)-N,N-Diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropylamine (Example 22.1), (4.00 g, 8.84 mmol) was treated as described in Example 22, but the hydrogenation was performed at atmospheric pressure. Yield 1.35 g (38 %); ^{1}H NMR (CD_3OD) δ 1.14 (s, 6H), 1.16 (s, 6H), 2.50 (m, 2H), 2.79 (t, 2H), 3.05 (t, 2H), 3.68 (m, 2H), 4.39 (t, 2H), 6,75 (d, 1H), 6.98 (d, 1H), 7.09 (s, 1H), 7.19 (t, 1H), 7.32 (m, 4H); mp. 156-159 °C; $[\alpha]_D$ +4.0° (c=0.5, methanol); Anal. ($C_{24}H_{32}N_2O$*1.0HCl*0.25H_2O) C, H; N: calcd, 6.9; found, 6.4.

EXAMPLE 25

(R)-N,N-Diisopropyl-3-[5-(2-carbamoylethyl)-2-hydroxy-phenyl]-3-phenylpropanamine hydrochloride.

A solution of (R)-N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine (Example 24), (2.00 g, 5.48 mmol), in conc. HCl was stirred at 50 °C for 2 h and then evaporated. The residue was dissolved in water, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried ($MgSO_4$), filtrated and evaporated. The residue was chromatographed on toluene-ethyl acetate-triethylamine-methanol, 7:2:1:1. The product was obtained from dietyl ether-hydrogen choride. Yield 0.9 g (39%); ^{1}H NMR (CD_3OD) δ 1.31 (m, 12H), 2.44 (t, 2H), 2.53 (m, 2H), 2.78 (t, 2H), 3.04 (t, 2H),

3.67 (m, 2H), 4.39 (t, 1H), 6.72 (d, 1H), 6.82 (d, 1H), 7.02 (s, 1H), 7.18 (t, 1H), 7.32 (m, 4H); mp. 200-202 °C; $[\alpha]_D$ +7.6° (c=0.5, methanol). Anal. ($C_{24}H_{34}N_2O_2$*1.0HCl *0.5H_2O) C, H, N.

EXAMPLE 26

(R)-N,N-Diisopropyl-3-[5-(2-carboxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

To a solution of (R)-N,N-diisopropyl-3-[5-(2-carbamoylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (obtained in Example 25), (0.50 g, 1.31 mmol) in ethanol (15 mL) and H_2O (10 mL) was added KOH (3.75 g, 66.8 mmol). The mixture was stirred overnight at 100 °C. The solvent was evaporated and the residue redissolved in H_2O and washed with diethyl ether. The aqueous layer was acidified with conc. HCl and the precipitate was collected by filtration and washed with 2 M HCl. The product was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using a gradient of 20-60% acetonitrile with 0.1% TFA. Fractions were pooled and hydrochloric acid (2 mL, conc.) was added and the solvent was evaporated. The residue was crystallised from methanol-diethyl ether to give 0.37 g (0.96 mmol, 74%); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 4H), 2.76 (t, 2H), 3.04 (t, 2H), 3.67 (m, 2H), 4.39 (t, 1H), 6.72 (d, 1H), 6.92 (d, 1H), 7.00 (s, 1H), 7.19 (t, 1H), 7.32 (m, 4H); mp. 205-207 °C; $[\alpha]_D$ +3.7° (c=1.0, methanol). Anal. ($C_{24}H_{33}NO_3$*1.0HCl) C, H, N.

EXAMPLE 27

(R)-(N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine dihydrochloride

(R)-N,N-Diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine (0.90 g, 2.03 mmol) was dissolved in acetic acid and 10% Pd/C (210 mg, cat.) was added. The mixture was stirred and exposed to H_2 (1 atm.) at room temperature overnight. The Pd/C catalyst was filtered off,

and the filtrate evaporated. The residue was dissolved in water and basified with aqueous 11 M sodium hydroxide, extracted with diethyl ether, dried ($MgSO_4$) filtrated and evaporated. The crude residue was chromatographed on silica (n-hexane-ethanol-triethylamine, 7:3:1). The hydrochloride was obtained from dietyl ether hydrogen chloride. The resulting oil was freeze-dried from water. Yield 0.30 g (37 %); ^1H NMR (DMSO) δ 1.13 - 1.33 (m, 12H), 2.47 (m, 2H), 2.82 (br, 1H), 2.98 (br, 1H), 3.57 (br, 2H), 4.38 (t, 1H), 6.96 (d, 1H), 7.08 (d, 1H), 7.19 (s, 1H), 7.22 (m, 1H), 7.32 (m, 4H), 10.05 (br, 2H), 10.13 (s, 1H); mp. 180-183 °C; $[\alpha]_D$ +21.0° (c=0.1, methanol). Anal. ($C_{21}H_{30}N_2O*2.0HCl*0.5H_2O$) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

27.1 (R)-N,N-Diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine

To a mixture of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (10.00 g, 20.81 mmol) (prepared as described in WO 94/11337, Example 1) and Mg (1.57 g, 64.52 mmol) in THF (50 mL) was added 1,2-dibromoethane (3.59 mL, 41.63 mmol) and the solution was self-refluxing for a while. The mixture was refluxed for 1 h whereafter the solution was cooled and tosyl azide (4.10 g, 20.81 mmol) in diethyl ether (100 mL) was added with constant stirring while keeping the temperature at 0 °C wherafter the temperature was allowed to rise to room temperature for 4 h. A solution of tetra-sodium pyrophosphate decahydrate (4.46 g, 10.00 mmol) in 50 mL water was added. A precipitate was filtered off and the filtrate was evaporated. The residue was extracted with diethyl ether, the organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (n-hexane-ethanol, 8:2). The product was crystallised from ethanol to give 1.15 g (13 %); IR (KBr) 2116 (N_3) cm^{-1}; ^1H

NMR ($CDCl_3$) δ 0.92 (d, 12H), 2.10 (m, 2H), 2.33 (m, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.00 (s, 2H), 6.81 (d, 2H), 6.97 (s, 1H), 7.10 - 7.40 (m, 10H).

EXAMPLE 28

(R)-N,N-Diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

To a solution of (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine (0.25 g, 0.76 mmol) in 0.78 M HCl (5.35 mL, 4.20 mmol) was added $NaNO_2$ (0.05 g, 0.76 mmol) dissolved in H_2O (0.4 mL) at -10 °C and the mixture was stirred for 20 minutes. To the mixture was added NaN_3, (57 mg, 0.88 mmol) dissolved in H_2O (0.4 mL), and the mixture was stirred at -10 °C for 30 minutes. The mixture was basified (pH 7-8) with aqueous 11 M sodium hydroxide and extracted with diethyl ether. The diethyl ether phase was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:2:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The precipitate was filtered to give (0.07 g, 0.18 mmol, 24%) of light-brown crystals. IR (KBr) 2111 (N_3) cm^{-1}; ^1H NMR (CD_3OD) δ 1.29 (m, 12H), 2.50 (m, 2H), 3.04 (m, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.68 (s, 1H), 6.81 (m, 2H), 7.23 (m, 1H), 7.35 (m, 4H); mp. 131-134 °C; $[\alpha]_D$ -5.0° (c=0.1, methanol).

The starting compound (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine was prepared as follows:

28.1 (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine

A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1)(7.30 g, 15.2 mmol) treated as described in Example 1.3 above. Yield 4.47 g (94 %).

28.2 (R)-N,N-Diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine

$NaNO_2$ (0.27 g, 4.30 mmol) was added to a mixture of hydrochloric acid (0.64 mL, 7.70 mmol, conc.) and p-methylaniline (0.41 g, 3.80 mmol) in ice-water (20 mL). The mixture was stirred at 0 °C for 10 min. and then added to an ice-cold solution of (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine (1.00 g, 3.21 mmol) in THF (3mL), H_2O (12 mL) and sodium hydroxide (0.69 g, 17.32 mmol). After stirring the mixture for 20 minutes, it was extracted with toluene, dried ($MgSO_4$), and evaporated to give an oil, which was chromatographed on (toluene-ethyl acetate-triethylamine 8:1:1) to give 0.83 g, 1.93 mmol, (60%) of the title compound. ^1H NMR ($CDCl_3$) δ 1.12 (d, 6H), 1.19 (d, 6H), 2.22 (m, 1H), 2.43 (m, 5H), 2.79 (m, 1H), 3.32 (m, 2H), 4.57 (d, 1H), 6.98 (d, 1H), 7.24 (m, 3H), 7.36 (m, 4H), 7.66 (m, 4H).

28.3 (R)-N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine

A solution of $Na_2S_2O_4$ (1.23 g, 12.8 mmol) in water (10 mL) was added to a solution of (R)-N,N-diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine (0.55 g, 1.28 mmol) in ethanol (50 mL) at 75 °C during 15 min. More dry $Na_2S_2O_4$ (1.23 g, 12.8 mmol) was added in 10 portions. Water was added to the solution which was then extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (n-hexane-ethanol-triethylamine 7:3:1) to give an oil. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. The solvent was evaporated, redissolved in water and vacuum-dried wich yielded 0.25 g (60%).

EXAMPLE 29

(R)-N,N-Diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phenyl]-3-phenylpropanamine hydrochloride

A solution of (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (2.0 g, 4.86 mmol) in THF (50 mL) was added dropwise to LAH (0.28 g, 7.29 mmol). After stirring for 2 h, the reaction was quenched and the solvent evaporated. The residue was recrystallized from ethanol-water. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. White crystals were filtered off to give 0.82 g (46%); mp. 204-207 °C; $[\alpha]_D$ +12.8° (c=1.0, methanol); ^{1}H NMR (DMSO) δ 1.18 (t, 6H), 1.24 (t, 6H), 1.63 (m, 2H), 2.47 (m, 4H), 2.87 (br, 2H), 3.38 (q, 2H), 3.57 (br, 2H), 4.32 (t, 1H), 4.42 (t, 1H), 6.74 (d, 1H), 6.83 (d, 1H), 7.03 (s, 1H), 7.17 (t, 1H), 7.30 (m, 4H) Anal. ($C_{24}H_{35}NO_2$*1.0HCl) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine was prepared as follows:

29.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine

A solution of triethyl phosphonoacetate (6.93 mL, 34.92 mmol) in THF (50 mL) was added dropwise to NaH (0.84 g, 29.10 mmol, 80%). The mixture was cooled to 0 °C and (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine, prepared as described in Example 17.1, (5.00 g, 11.64 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 3 h at 0 °C. The solvent was evaporated and the residue was redissolved in toluene and washed twice with water. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give 5.0 g (86%).

29.2 (R)-N,N-Diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine (3.0 g, 5.98 mmol) was treated as described in Example 1.3. Yield 2.0 g (81%); ^{1}H NMR ($CDCl_3$) δ 1.08 (d, 6H), 1.12 (d, 6H), 1.18 (t, 3H), 2.05 (m, 2H), 2.37 (m, 4H), 2.72 (t, 2H), 3.22 (m, 2H), 4.03 (q, 2H), 4.48 (m, 1H), 6.55 (s, 1H), 6.86 (m, 2H), 7.28 (m, 5H).

EXAMPLE 30

N,N-Diisopropyl-3-(5-ethylaminomethyl-2-hydroxyphenyl)-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (prepared in Example 7.1) (1.23 g, 3.62 mmol) was dissolved in methanol (20 mL). Ethylamine [3.62 mL, 21.7 mmol (6M hydrochloric acid in methanol)] and sodium cyanoborohydride (0.14 g, 2.17 mmol) were added. The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:3:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The resulting oil was stirred in diethyl ether over night to give crystals. Yield 0.70 g (44%); mp. 140-142 °C; $[\alpha]_D$ -5.0° (c=0.5, methanol); ^{1}H NMR (CD_3OD) δ 1.30 (m, 15H), 2.59 (m, 2H), 3.05 (m, 4H), 3.70 (m, 2H), 4.07 (s, 2H), 4.42 (t, 1H), 6.85 (d, 1H), 7.20 (m, 2H), 7.30 (t, 2H), 7.41 (d, 2H), 7.50 (s, 1H) Anal. ($C_{24}H_{36}N_2O*2.0HCl*0.5H_2O$) C,H,N.

EXAMPLE 31

N-Cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

A solution of N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (1.60 g, 3.44 mmol) was hydrogenated over Pd/C (160 mg, 10%) in acetic acid at room temperature overnight. The solution was basified with

sodium hydroxide (11 M) and the mixture was filtered. The filtrate was extracted with ethyl acetate, dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluen-triethylamine 9:1). The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to give an oil. The oil was crystallised in 2-propanol to give 0.90 g (79%); mp. 153-155 °C; ^1H NMR (CD_3OD) δ 1.78 (m, 2H), 2.22 (m, 4H), 2.48 (m, 2H), 2.72 (s, 3H), 2.95 (br, 2H), 3.68 (m, 1H), 4.44 (t, 1H), 6.78 (t, 1H), 6.79 (d, 1H), 7.03 (t, 1H), 7.12 (d, 1H), 7.18 (t, 1H), 7.28 (t, 2H), 7.34 (d, 2H); Anal. ($C_{20}H_{25}NO*1.0$ HCl*0.3 2-propanol) C, H, N.

The starting compound N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

31.1 N-Cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

5 M HCl-methanol (3.50 mL, 17.71 mmol) was added to a solution of cyclobutylamine (4.50 mL, 53.15 mmol) in methanol (14 mL). The mixture was added to 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (Example 20.1), (3.50 g, 8.86 mmol), followed by sodium cyanoborohydride (0.389 g, 6.20 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 92:4:4).Yield 2.61 g (65%); ^1H NMR ($CDCl_3$) δ 1.57 (m, 5H), 2.14 (m, 4H), 2.47 (t, 2H), 3.16 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.47 (m, 12H).

31.2 N-Cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

5 M HCl-methanol (0.46 mL, 2.32 mmol), formaldehyde (0.870 g, 28.97 mmol) and sodium cyanoborohydride (0.255 g, 4.056 mmol) were added to a solution of N-cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.61 g, 5.79

mmol) in methanol (8 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (hexane-triethylamine, 9:1). Yield 1.59 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2H), 1.73 (m, 2H), 1.91 (m, 2H), 2.06 (s, 3H), 2.16 (m, 4H), 2.68 (m, 1H), 4.38 (t, 1H), 5.00 (s, 2H), 6.72 (d, 1H), 7.12-7.58 (m, 12H).

EXAMPLE 32

N-Cyclopentyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

N-Cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.46 g, 5.14 mmol) was treated as described in Example 31. The crude was not chromatographed but crystallised from aqueous ethanol. Yield 1.24 g (70%) ^{1}H NMR (DMSO) δ 1.48 (br, 1H), 1.66 (br, 2H), 1.85 (br, 1H), 2.46 (br, 2H), 2.68 (s, 3H), 2.87 (br, 2H), 3.53 (m, 1H), 4.35 (t, 1H), 6.77 (t, 1H), 6.83 (d, 1H), 7.01 (t, 1H), 7.16 (t, 1H), 7.27 (t, 3H), 7.33 (d, 2H), 9.57 (br, 1H), 10.85 (br, 1H); mp 169-172 °C; Anal. ($C_{21}H_{27}NO*HCl$) C, H, N.

The starting compound N-cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

32.1 N-Cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal, prepared as described in Example 20.1, (7.00 g, 17.71 mmol) was treated with cyclopentylamine as described in Example 31.1. Yield 4.9 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 2H), 1.40-1.80 (m, 6H), 2.18 (m, 2H), 2.55 (t, 2H), 2.98 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.45 (m, 12H).

32.2 N-Cyclopenthyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

A solution of N-cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (3.50 g, 7.53 mmol) was treated as described in Example 31.2. Yield 2.46 g (68%); ^{1}H NMR ($CDCl_3$) δ 1.10-1.80 (m, 8H), 2.19 (m, 5H), 2.36 (m, 2H), 2.58 (m, 1H), 4.37 (t, 1H), 4.98 (s, 2H), 6.72 (d, 1H), 7.10-7.50 (m, 12H).

EXAMPLE 33

N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropanamine hydrochloride

LAH (0.94 g, 24.8 mmol) was added to a solution of N,N-diisopropyl-3-(2-aminophenyl)-3-phenylpropenylamide (1.6 g, 4.98 mmol) in THF (90 mL). The mixture was stirred for 72 h at room temperature. The reaction was quenched and the solvent evaporated. The crude residue was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using 20 % acetonitrile with 0.1% TFA. Hydrochloric acid was added to the pure fractions and the solvent was evaporated. The residue was redissolved in water and freeze-dried giving 88 mg (5%); mp 138 - 142 °C; ^{1}H NMR (DMSO) δ 1.25 (m, 12H), 2.47 (m, 1H), 2.65 (m, 1H), 2.87 (m, 1H), 3.13, (m, 1H), 3.59 (br, 2H), 4.58 (t, 1H), 7.20 - 7.37 (m, 5H), 7.42 (m, 2H), 7.54 (d, 2H), 9.94 (br, 2H). Anal. ($C_{21}H_{30}N_2$*HCl*H_2O) C, N, H: calcd.8.5; found 7.9.

The starting compound N,N-diisopropyl-3-(2-aminophenyl)-3-phenylpropenylamide was prepared as follows:

33.1 2-(3,5-Dimethyl-4-hydroxyphenylazo)benzophenone

A slurry of ice (500 mL), hydrochloric acid (16.8 mL, 202 mmol, conc.), 2-aminobenzophenone (20.00 g, 101 mmol) and $NaNO_2$ (9.0 g, 131 mmol) were added to a stirred solution of 2,6-dimethylphenol (18.40 g, 151 mmol) and sodium hydroxide (16.20 g, 404 mmol) in ice-cold water (100 mL). After 20 minutes the mixture was extracted with

diethyl ether. The organic phase was washed with hydrochloric acid (6 M), $NaHCO_{3(aq)}$, dried ($MgSO_4$) and the solvent evaporated. The crude residue was chromatographed on silica (toluene) and pure fractions were pooled and evaporated to give a red oil. The oil was crystallised in hexane/toluene to give 7.73 g (23%).

33.2 2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone

A mixture of 2-(3,5-dimethyl-4-hydroxyphenylazo)-benzophenone (7.73 g, 23.41 mmol) and tosyl chloride (9.4 g, 49 mmol) in pyridine (20 mL) was stirred at 90 °C for 9 h. Water was added and the mixture was extracted with diethyl ether. The organic phase was washed with sodium hydroxide (2 M) and hydrochloric acid (2 M), dried ($MgSO_4$) and the solvent evaporated. The product was crystallised in ethanol to give 7.62 g (67%); ^1H NMR ($CDCl_3$) δ 2.08 (s, 6H), 2.49 (s, 3H), 7.05 (s, 2H), 7.37 (m, 4H), 7.48 (m, 1H), 7.62 (m, 3H), 7.82 (m, 5H).

33.3 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenyl-azo)phenyl]-3-phenylpropenamide

2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone (7.22 g, 14.9 mmol) was treated as described in Example 4.2 but with 3 eq of N,N-diisopropylacetamide diethylphosphonate and sodium hydride. Yield 4.5 g (50%). ^1H NMR ($CDCl_3$) δ 0.72 (d, 3H), 0.82 (br, 3H), 1.28 (d, 3H), 1.42 (d, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 2.45 (s, 3H), 3.25 (m, 1H), 4.28 (m, 1H), 6.05 and 6.63 (s, 1H), 7.00 - 7.90 (m, 15H).

33.4 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenyl-azo)phenyl]-3-phenylpropenamide

A solution of potassium hydroxide (10.3 mL, 6 M) and N,N-diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenyl-azo)phenyl]-3-phenylpropenamide (3.5 g, 5.74 mmol) in ethanol (110 mL) was refluxed for 1 h. The mixture was acidified with hydrochloric acid (conc.) and the solvent evaporated. The residue was partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent

evaporated. The crude residue was chromatographed on silica (toluene-ethyl acetate 9:2). Yield 1.3 g (50%). ^{1}H NMR ($CDCl_3$) δ 0.71 (d, 3H), 0.80 (br, 3H), 1.27 (d, 3H), 1.40 (d, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 3.25 (m, 1H), 4.35 (m, 1H), 5.52 (brd, 1H), 6.05 and 6.60 (s, 1H), 7.00 - 7.80 (m, 11H).

33.5 N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropenamide

N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenyl-azo)phenyl]-3-phenylpropenamide (2.58 g, 5.68 mmol) was treated as described in Example 28.3. The crude residue gave crystals from aqueous ethanol. Yield 1.23g (67%).

EXAMPLE 34

N,N-Diisopropyl-3-(benzoxazol-2-yl)-3-phenylpropanamine, hydrochloride

A mixture of N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (2.51 g, 8.6 mmol), 75% aqueous ethanol (15 mL) and 2 M NaOH (8.5 mL, 17 mmol) was refluxed over night. After evaporation of the solvent, the residue was made acidic with 2 M HCl and the solvent was evaporated. A mixture of the residual semicrystalline oil was heated with o-aminophenol (1.8 g, 16.5 mmol) and polyphosphoric acid (12 g) at 200°C for 2 hours under N_2. The somewhat cooled hard solid was dissolved in water and washed once with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether/triethylamine 97:3). The pure amine was precipitated as hydrochloride from diethyl ether affording white crystals, 1.27 g (39%): mp 197-198°C; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 12H), 2.80-3.20 (m, 4H), 3.48 (br, 2H), 4.45 (t, 1H), 7.25-7.48 (m, 8H), 7.70 (m, 1H), 11.48 (br, 1H).

The starting compound N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine was prepared as follows:

34.1 N,N-Diisopropyl-3-cyano-3-phenylpropanamine

Sodium hydride, 80% in mineral oil (2.82 g, 94 mmol), was washed with petroleum ether and dried under a N_2-stream. Dry DMF (100 mL) was added. Benzyl cyanide (12.1 g, 103 mmol) was added to the stirred suspension over a period of 20 min. The temperature rose to approx. 45°C. The mixture was stirred for another 15 min. 2-Chloroethyl-diisopropylamine (15.4 g, 94 mmol) was added. All the amine was consumed within 30 min. Most of the DMF was evaporated under reduced pressure and the residue was dissolved in water/diethyl ether. The aqueous phase was extracted once with diethyl ether and the combined organic phases were extracted twice with 2 M HCl. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent was evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 40:1), affording the title compound, 16.8 g (67%), as a colourless liquid. ^{1}H NMR ($CDCl_3$) δ 1.01 (m, 12H), 1.97 (m, 2H), 2.62 (m, 2H), 3.00 (m, 2H), 4.02 (dd, 1H), 7.17-7.40 (m, 5H).

34.2 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamine

N,N-Diisopropyl-3-cyano-3-phenylpropanamine (11.6 g, 47.5 mmol) was mixed with H_2SO_4 (90%, 100 mL) and the mixture was stirred at 100°C for 30 min. The reaction mixture was poured on ice, made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated, affording the title compound as a colourless oil, 12.4 g (100%); ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 12H), 2.14 (m, 1H), 2.60 (m, 1H), 2.73 (t, 2H), 3.31 (m, 2H), 3.86 (t, 1H), 6.06 (br, 2H), 7.51- 7.61 (m, 5H).

34.3 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine

N,N-Diisopropyl-3-carbamyl-3-phenylpropanamine (26.5 g 0.100 mol) was added into aqueous ethanol (90%, 300 mL)

containing conc. HNO_3 (13.3 g, 0.21 mol) and refluxed for five days. Most of the solvent was evaporated under reduced pressure and the residue was mixed with water/diethyl ether. The organic phase was washed once with water. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 97/3), to afford the title compound as a colourless liquid, 20.1 g (68.7%): ^1H NMR ($CDCl_3$) δ 0.96 (m, 12H), 1.21 (t, 3H), 1.81 (m, 1H), 2.22 (m, 1H), 2.40 (t, 2H), 3.66 (dd, 1H), 4.12 (m, 2H), 7.20-7.32 (m, 5H).

EXAMPLE 35

N,N-Diisopropyl-3-(oxazol-5-yl)-3-phenylpropanamine hydrochloride

Freshly distilled methylisonitrile (1.66 g, 40.4 mmol) was dissolved in dry THF (75 mL) under N_2-atmosphere and the mixture was cooled to -78°C. 1.4 M n-BuLi (29 mL, 40.5 mmol) was slowly added to the solution, followed by N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (4.71 g, 16.2 mmol) in THF (10 mL). The reaction temperature was allowed to rise to -20°C, at which the reaction was quenched with HOAc (10 mL). The solvent was evaporated and the residue was mixed with diethyl ether/water. The organic phase was washed once with water and the combined aqueous phases were made alkaline with 11 M NaOH and extracted twice with diethyl ether. The organic phases were put together, dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 490:10:1). The pure amine was precipitated with HCl-saturated diethyl ether, affording the title compound as a glassy oil, 1.4 g (48%). ^1H NMR (CD_3OD) δ 1.21-1.40 (m, 12H), 2.57 (m, 1H), 2.68 (m, 1H), 2.91 (m, 1H), 3.23 (m, 1H), 3.72 (m, 2H), 4.41 (dd, 1H), 7.39 (m, 5H), 7.52 (s, 1H), 9.13 (s, 1H).

EXAMPLE 36

N,N-Diisopropyl-3-(imidazol-4(5)-yl)-3-phenylpropanamine dihydrochloride

N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was mixed with formamide (5 mL). The mixture was heated at 175°C for 6 hours. The solvent was evaporated under vacuum (1 mm Hg) and the residue was partitioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The light brown oil was dissolved in diethyl ether and added to a suspension of lithium aluminium hydride (LAH) (0.70 g, 5.4 mmol) in diethyl ether. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched, and the solvent was evaporated. The crude amine was dissolved in EtOAc and precipitated as a hydrochloride salt with HCl-saturated diethyl ether to afford the title compound as hygroscopic crystals, 0.32 g (35%): ^1H NMR ($CDCl_3$) δ 1.38 (m, 12H), 2.80 (m, 2H), 3.00 (m, 1H), 3.16 (m, 1H), 3.64 (br, 2H), 4.41 (m, 1H), 6.89 (s, 1H), 7.27-7.41 (m, 5H), 8.78 (s, 1H), 10.32 (br, 2H).

The starting compound N,N-diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was prepared as follows:

36.1 3-Cyano-3-phenylpropanoic acid

Ethyl cinnamate (85.3 g, 0.484 mol), potassium cyanide (64.2 g, 0.986 mol) and ammonium chloride (38.9 g, 0.726 mol) were mixed with aqueous DMF (90%, 360 mL). The mixture was stirred at 105°C for 7 hours. The somewhat cooled mixture was filtered and most of the DMF was evaporated. The residue was taken up in diethyl ether and 1 M HCl. The aqueous phase was extracted twice with diethyl ether. The combined diethyl ether phases were evaporated and the black oil was suspended in EtOH (200 mL) and 2 M NaOH (250 mL) and stirred at ambient temperature for 2 hours. The mixture

was diluted with brine (200 mL) and water (400 mL) and washed twice with diethyl ether. After acidification (12 M HCl) the aqueous phase was extracted three times with diethyl ether. The pooled organic phases were dried (Na_2SO_4) and the solvent evaporated affording the title compound as a black oil, 74 g (87%): ^1H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.17 (d, 3H), 1.22 (d, 6H), 2.68 (dd, 1H), 3.16 (dd, 1H), 3.4 (br, 1H), 3.76 (m, 1H) 4.19 (dd, 1H), 7.31 (m, 5H), 8.9 (br, 1H).

36.2 N,N-Diisopropyl-3-cyano-3-phenylpropanamide

3-Cyano-3-phenylpropanoic acid (67.7 g, 0.389 mol) was dissolved in 2-PrOH. To the filtered acid solution was carefully added KOH (18.4 g, 0.33 mol) dissolved in 2-PrOH (200 mL), diethyl ether (100 mL) was added and the precipitate was filtered off. The dried acid salt (51.9 g, 0.24 mol) was suspended in benzene (400 mL) and oxalyl chloride was carefully added. The reaction mixture was stirred at 80°C for 2 hours. The solvent was evaporated and the residue was co-evaporated twice with benzene. The brown oil was dissolved in benzene (200 mL) and cooled in an ice-bath. A solution of diisopropylamine (82 g, 0.81 mol) in benzene (200 mL) was added to the stirred reaction mixture during 45 min. The mixture was left to slowly warm up to room temperature overnight. The solvent was evaporated and the residue was taken up in diethyl ether and 1 M HCl. The organic phase was washed once with water, once with 1 M NaOH, again with water, dried (Na_2SO_4) and the solvent evaporated to afford the title compound as a dark brown oil, 41.7 g (41%): ^1H NMR ($CDCl_3$) δ 1.07 (d, 3H), 1.17 (d, 3H), 1.36 (m, 6H), 2.77 (m, 1H), 2.97 (m, 1H), 3,51 (br, 1H), 3.81 (m, 1H), 4.50 (dd, 1H), 7.39 (m, 5H).

36.3 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide

N,N-Diisopropyl-3-cyano-3-phenylpropanamide (21.1 g, 82 mmol) was dissolved in EtOH (130 mL) and 2 M NaOH (100 mL). Hydrogen peroxide (30%, 20.2 mL, 200 mmol) was added and the mixture was stirred at ambient temperature for two

hours. The resulting precipitate was filtered, washed with water and dried, yielding the title compound as white crystals, 15.6 g (69%): ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3H), 1.19 (d, 3H), 1.31 (m, 6H), 2.51 (dd, 1H), 3.30 (dd, 1H), 3.41 (m, 1H), 4.02 (m, 1H), 4.18 (dd, 1H), 5.7 (br, 1H), 6.4 (br, 1H), 7.21-7.42 (m, 5H).

36.4 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide

N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide was treated as described in Example 34:3 (two days of reflux and no chromatography) which gave the title compound as a colourless semicrystalline oil, 15.9 g (93%): ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 9H), 1.36 (m, 6H), 2.53 (dd, 1H), 3.18 (dd, 1H), 3.4 (br, 1H), 3.98 (m, 1H), 4.15 (m, 3H), 7.31 (m, 5H).

36.5 N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide

The method described for Example 35 above was used, starting from N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide. The crude was chromatographed on silica (petroleum ether-EtOAc, 3:2), affording the title compound as a light yellow oil, 0.77 g (46%): ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3H), 1.14 (d, 3H), 1.29 (m, 6H), 2.98 (m, 2H), 3.4 (br, 1H), 3,93 (m, 1H), 4.79 (t, 1H), 6.82 (s, 1H), 7.28 (m, 5H), 7.76 (s, 1H).

EXAMPLE 37

N,N-Diisopropyl-3-(oxazol-2-yl)-3-phenylpropanamine hydrochloride

A mixture of N,N-diisopropyl-3-carbamoyl-3-phenylpropanamine, prepared in Example 34.2 (4.05 g, 15.4 mmol), 1,2-dichloroethyl ethyl ether (2,32 g, 16.2 mmol), water (0.300 g, 16.6 mmol) and formic acid (50 mL) was stirred at 75°C for 3 hours. The formic acid was evaporated and the residue was dissolved in water/diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were

dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine 97:3). The pure amine was precipitated as hydrochloride salt with HCl-saturated diethyl ether, affording the title compound as white crystals, 0.61 g (12%): mp 157-158°C; ^1H NMR (DMSO(d_6)) δ 1.11 (m, 12H), 2.35 (m, 1H), 2.63 (m, 1H), 3.03 (m, 2H), 3.56 (m, 2H), 4.45 (m, 1H), 7.21-7.40 (m, 6H) 8.06 (d, 1H), 10.20 (br, 1H).

EXAMPLE 38

N,N-Diisopropyl-3-phenyl-3-(thiazol-2-yl)propanamine hydrochloride

The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine (1.11 g, 4.0 mmol) yielded white crystals of the title compound, 1.12 g (82%): mp 155-156°C; ^1H NMR ($CDCl_3$) δ 1.37 (m, 12H), 2.75-3.15 (m, 4H), 3.60 (m, 2H), 4.45 (t, 1H), 7.25-7.36 (m, 6H), 7.71 (d, 1H), 11.30 (br, 1H).

The starting compound N,N-diisopropyl-3-phenyl-3-thiocarbamoylpropanamine was prepared as follows:

38.1 N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine

H_2S was bubbled into a solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine, prepared in Example 34.1, (3.45 g, 14.3 mmol) and triethylamine (2.0 g, 20 mmol) in dry pyridine (10 mL) until saturation was achieved. The stirred reaction was held under H_2S-atmosphere at 65°C for 5 days. The pyridine was evaporated and the crude product was chromatographed on silica (chloroform-methanol-conc. ammonia 380:20:1), yielding the title compound as a colourless glassy oil, 3.1 g (78%): ^1H NMR ($CDCl_3$) δ 0.99 (m, 12H), 2.07 (m, 1H), 2.40 (m, 3H), 3.05 (m, 2H), 4.10 (t, 1H), 7.20-7.45 (m 5H), 7.7-8.1 (b, 1H), 8.0-8.5 (br, 1H).

EXAMPLE 39

N,N-Diisopropyl-3-(4-methylthiazol-2-yl)-3-phenyl-propanamine hydrochloride

The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine, prepared in Example 38.1, (1.5 g, 5,4 mmol), and 2-chloroacetone (0.75 g, 8.1 mmol) yielded the title compound as a white amorphous substance, 1.1 g (56%): mp 178-181°C; ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 12H), 2.50 (s, 3H), 2.98 (m, 3H), 3.18 (m, 1H), 3.60 (m, 2H), 6.94 (d, 1H), 7.30-7.47 (m, 5H), 11.15 (br, 1H).

EXAMPLE 40

N,N-Diisopropyl-3-(thiazol-5-yl)-3-phenylpropanamine hydrochloride

The title compound was prepared in an analogous manner to that described in Example 35. Reaction with N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine (1.14 g, 3.7 mmol) gave a crude that was chromatographed on silica (petroleum ether-triethylamine 97:3), affording white crystals of the title compound, 0.19 g (30%): mp 193-194°C; ^{1}H NMR ($CDCl_3$) δ 1.1.34 (m, 12H), 2.85 (m, 4H), 5.56 (m, 2H), 4.29 (t, 1H), 7.26-7.39 (m, 5H), 7.73 (s, 1H), 8.71 (s, 1H) 11.61 (br, 1H).

The starting compound N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine was prepared as follows:

40.1 N,N-Diisopropyl-3-ethoxythiocarbonyl-3-phenyl-propanamine

HCl-gas was bubbled through an ice-cold solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine (2.9 g, 12 mmol), prepared in Example 34.1, in dried ethanol (50 mL, molecular sieve 3 Å) until saturation. The stirred reaction was held under HCl-atmosphere at room temperature overnight. The solvent was carefully evaporated and the

remaining oil was dissolved in dry pyridine (100 mL). To this solution was added triethylamine (5.7 g, 56 mmol) and to the now thick suspension was bubbled H_2S until saturation was achieved. The dark olive-green reaction mixture was held under a H_2S-atmosphere at 65°C overnight. The solvent was evaporated and the residue was partioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 198:1:1), affording the title compound as a straw-coloured liquid, 1.24 g (33%): ^1H NMR ($CDCl_3$) δ 0.95 (m, 12H), 1.34 (t, 2H), 1.97 (m, 1H), 2.37 (m, 3H), 2.98 (m, 2H), 4.10 (t, 1H) 4.46 (m, 2H), 7.13-7.39 (m, 5H).

EXAMPLE 41

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)-propanamine fumarate

To a suspension of lithium aluminium hydride (LAH) (0.51 g 13.3 mmol) in THF (30 mL), N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide (2.0 g, 5.33 mmol) was added and warmed to 50°C overnight. The reaction mixture was quenched and the solvent was evaporated. The residue was dissolved in diethyl ether and extracted twice with 2 M HCl, and the combined aqueous phases were washed twice with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted three times with diethyl ether, the combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent evaporated. The pure amine was crystallised from methanol as its fumarate, yielding the title compound as white crystals, 1.52 g (58%): mp 203-205°C; ^1H NMR (DMSO) δ 1.00 (d, 12H), 2.02 (q, 2H), 2.33 (m, 2H), 3.18 (m 2H), 4,62 (t, 1H), 6.50 (s, 1H), 6.68-7.18 (m, 6H), 7.28 (t, 1H).

The starting compound N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide was prepared as follows:

41.1 N,N-Diisopropyl-3-(2-thienyl)propenamide

2-Bromothiophene (2.28 g, 14.0 mmol), N,N-diisopropylacrylamide (1.55 g, 10.0 mmol), palladium(II)acetate (34 mg, 0.15 mmol), tri-o-tolylphosphine (183 mg, 0.6 mmol), tri-n-butyl amine (2.04 g, 11.0 mmol) and dry DMF (5 mL) were mixed under a N_2-atmosphere. The mixture was heated to 130°C for 9 hours. Diethyl ether and H_2O was added to the somewhat cooled mixture. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed twice with 2 M HCl, once with water, once with brine, and dried ($MgSO_4$), and the solvent was then evaporated. The crude product was chromatographed on silica (petroleum ether-ethyl acetate 4:1), affording a yellow oil, 1.58 g (66%): ^1H NMR ($CDCl_3$) δ 1.35 (br, 12H), 3.9 (br, 1H), 4.1 (br 1H), 6.65 (d, 1H), 7.00-7.30 (m, 3H), 7.72 (d, 1H).

41.2 2-Methoxyphenyllithium

2-Methoxybromobenzene (8.44 g 45.1 mmol) was dissolved in dry diethyl ether (15 mL). The mixture was cooled to -78°C. n-BuLi (17.8 mL, 45.0 mmol) was added and the mixture was stirred for one hour at -78°C and then for 20 min. at -10°C. The aryl lithium solution was used immediately.

41.3 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide

Copper(I)bromide dimethyl sulfide complex (4.63 g 22.5 mmol) was dissolved in dimethyl sulfide (18 mL), and diethyl ether (15 mL). The solution was cooled to 0°C, whereafter 2-methoxyphenyllithium (41.2) (45 mmol) was added. After 10 min., the temperature was lowered to -78°C. Trimethylsilylchloride (4.89 g, 45.0 mmol) was added, followed by N,N-diisopropyl-3-(2-thienyl)propenamide (41.1)

(3.56 g, 15 mmol) in diethyl ether (20 mL). The temperature was allowed to slowly rise to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and conc. ammonia (10 mL). Diethyl ether (80 mL) was added and the mixture was filtered through Celite. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed once with brine and dried ($MgSO_4$). The solvent was evaporated and the crude product was chromatographed on silica (petroleum ether-ethyl acetate 3:1), affording a yellow oil, 3.75 g (73%): ^1H NMR ($CDCl_3$) d 1.12 (t, 6H), 1.29 (t, 6H), 3.02 (m, 2H), 3.4 (br, 1H), 3.80 (s, 3H), 4.03 (m, 1H), 5.26 (t, 1H), 6.8-7.3 (m, 7H).

41.4 N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide

A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide (2.37 g, 6.9 mmol) in dichloromethane(35 mL) was cooled down to -78°C and boron tribromide (5.9 g 23.57 mmol) was added. The reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched by slow addition of water (20 mL). The pH was adjusted to around 6 with $NaHCO_3$(s) and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent was evaporated. This crude product (2.46 g, 107%) was used without further purification. ^1H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.20 (m, 6H), 1.35 (d, 3H), 3.16 (m, 2H), 3.4 (br, 1H), 4.0 (m, 1H), 5.24 (dd. 1H), 6.7-7.2 (m, 7H).

Examples 42-54 and 57 and 58 were prepared with the methodology described for Example 41, starting with the appropriate acrylamides and aryl bromides.

EXAMPLE 42

N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-(2-thienyl)propanamine

The crude product was crystallised from petroleum ether/ethyl acetate affording the title compound, 0.41 g as slightly pink crystals: mp 102-109°C; ^{1}H NMR ($CDCl_3$) δ 1.11 (m, 12H), 2.01 (m, 1H), 2.41 (m, 2H), 2.72 (m, 1H), 3.26 (m, 2H), 4.66 (dd, 1H), 6.30 (dd, 1H), 6.45 (d, 1H), 6.73 (d, 1H), 6.91-7.00 (m, 2H), 7.17 (dd, 1H).

EXAMPLE 43

N,N-Diisopropylamine-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine, fumarate

White crystals, 0.95 g: mp 153-155°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 2H), 3.05 (m, 2H), 3.68 (m, 2H), 3.85 (s, 3H), 4.71 (t, 1H), 6.68 (s, 2H), 6.89-7.03 (m, 4H), 7.20-7.30 (m, 3H).

EXAMPLE 44

N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-(2-thienyl)propanamine fumarate

White crystals, 1.52 g: mp 103-109°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.46 (m, 2H), 3.04 (m, 2H), 3.66 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.60 (t, 1H), 6.46-6.58 (m, 2H), 6.68 (s, 2H), 6.91-6.97 (m, 2H), 7.09- 7.26 (m, 2H).

EXAMPLE 45

N,N-Diisopropyl-3-(3-methoxyphenyl)-3-(2-thienyl)propanamine hydrochloride

White crystals, 1.16 g: mp 95-97°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.49 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.68 (m, 2H), 3.77 (s, 3H), 4.31 (t, 1H), 6.83 (m, 1H), 6.68-7.02 (m, 4H), 7.27 (m, 2H).

EXAMPLE 46

N,N-Diisopropyl-3-(4-methoxyphenyl)-3-(2-thienyl)-propanamine hydrochloride

White amorphous substance, 0.50 g: mp 157-160°C; ^{1}H NMR (CD_3OD) δ 1.31 (m, 12H), 2.47 (m, 2H), 2.94 (m, 1H), 3.12 (m, 1H); 3.68 (br, 2H), 3.77 (s, 3H), 4.28 (t, 1H), 6.87-7.00 (m, 4H), 7.23-7.32 (m, 3H).

EXAMPLE 47

N-Isopropyl-N-methyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine fumarate

White crystals, 1.32 g: mp 141-143°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.50 (m, 2H), 2.73 (s, 3H), 3.04 (m, 2H), 3.58 (m, 1H), 3.84 (s, 3H), 4.73 (t, 1H), 6.68 (s, 2H), 6.96 (m, 4H), 7.24 (m, 3H).

EXAMPLE 48

N,N-Diisopropyl-3-phenyl-3-(2-thienyl)propanamine, hydrochloride

White crystals, 0.74 g: mp 165-166°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.52 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.70 (br, 2H), 4.34 (t, 2H), 6.92-7.04 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 49

N-Cyclohexyl-N-methyl-3-phenyl-3-(2-thienyl)propanamine hydrochloride

White crystals, 1.1 g: mp 197-199°C; ^{1}H NMR (CD_3OD) δ 1.15-1.52 (br, 5H), 1.68 (br, 1H), 1.90 (br, 4H), 2.51 (br, 2H), 2.78 (s, 3H), 2.91-3.40 (m, 3H), 4.31 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 50

N,N-Diethyl-3-phenyl-3-(2-thienyl)propanamine fumarate

White crystals, 1.7 g (tot. 49 %): mp 135-137°C; ^{1}H NMR (CD_3OD) δ 1.22 (t, 3H), 2.50 (m, 2H), 2.90-3.26 (m, 6H),

4.30 (t, 1H), 6.68 (s, 2H), 6.92-7.03 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 51

N-Isopropyl-N-methyl-3-phenyl-3-(2-thienyl)propanamine hydrochloride

White crystals, 1.6 g: mp 139-144°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.52 (m, 2H), 2.75 (s, 3H), 3.03 (m, 2H), 3.59 (m, 1H), 4.32 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 52

N-[3-Phenyl-3-(2-thienyl)propyl]pyrrolidine fumarate

Crystallisation from 2-propanol, 1.1 g: mp 144-145°C; ^{1}H NMR (CD_3OD) δ 2.02 (m, 4H) 2.31 (m, 2H), 2.97-3.42 (m, 6H), 4.29 (t, 1H), 6.69 (s, 2H), 6.91-7.01 (m, 2H), 7.18-7.38 (m, 6H).

EXAMPLE 53

N-[3-Phenyl-3-(2-thienyl)propyl]piperidine hydrochloride

The hydrochloride was crystallised from ethylmethylketone, 0.84 g: mp 193-194°C; ^{1}H NMR (CD_3OD) δ 1.40-2.00 (b, 6H), 2.54 (m, 2H), 2.82-3.80 (m, 6H), 4.29 (t, 1H), 6.91-7.03 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 54

N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine hydrochloride

White crystals, 2.1 g: mp 205-210°C; ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 12H), 2.18 (s, 3H), 2.63 (m, 2H), 2.95 (m, 2H), 3.54 (m, 4H), 4.61 (t, 1H), 6.76-7.01 (m, 5H), 7.16 (d, 1H).

EXAMPLE 55

(R*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

To the racemic free base of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-2-thienylpropanamine (20 g, 0.06 mol), prepared in Example 54, in abs. ethanol (50 g) was added L-(+)-tartaric acid (9.5 g 0.063 mol) in ethanol (60 g). The salt formed was filtered off and crystallised twice from ethanol/methanol 10/1, 10 mL per gram of crystals, affording the title compound as white crystals, (6.8 g, 14.1 mmol): mp 214-215°C; $[\alpha]_{Hg}$=+17.3° (c=3.82 in methanol).

EXAMPLE 56

(S*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

From the mother liquid from the first crystallisation to obtain (R*) N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine in Example 55, the free base was recovered. The amine was treated with a 5% excess of D-(-)-tartaric acid in ethanol as above, yielding the title compound as white crystals, 6.1 g (12.7 mmol): mp 214°C; $[\alpha]_{Hg}$=-17.5° (c=3.85 in methanol).

EXAMPLE 57

N,N-Diisopropyl-3-phenyl-3-(3-thienyl)propanamine hydrochloride

White crystals, 0.94 g: mp 141-142 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 12H), 2.87 (m, 4H), 3.56 (br, 2H), 3.98 (t, 1H), 6.94 (dd, 1H), 7.27 (m, 7H), 11.4 (br, 1H).

The starting compound was prepared as follows:

57.1 N,N-Diisopropyl-3-(3-thienyl)propenamide

Sodium hydride, 60% in mineral oil (3.9 g, 98 mmol), was washed several times with petroleum ether and dried under a stream of nitrogen. Sodium-dried THF was added

followed by diethyl N,N-diisopropyl acetamidephosphonate (27.4 g, 98 mmol). When the evolution of gas had ceased, thiophene-3-aldehyde (10.0 g, 89.2 mmol) in THF(50 mL) was added at such a rate that the temperature never exceeded 45°C. After one hour of stirring at ambient temperature, the reaction was quenched with 4 mL of water and stirred for another hour. The solvent was evaporated and the residue was taken up in diethyl ether/2M NaOH. The organic phase was washed once with water and once with brine, dried (Na_2SO_4) and evaporated. The crude was chromatographed on silica (petroleum ether-ethyl acetate 4:1) affording the title compound as a light-brown oil, 14.8 g (70%): ^{1}H NMR ($CDCl_3$) δ 1.37 (b, 12H), 3.86 (br, 1H), 4.10 (br, 1H), 6.68 (d, 1H), 7.27-7.41 (m, 3H), 7.59 (d, 1H).

EXAMPLE 58

N,N-Diisopropyl-3-(2-furanyl)-3-phenylpropanamine hydrochloride

White crystals, 60 mg: mp 139-141 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (br, 12H), 2.64 (m, 1H), 2.85 (m, 3H), 3.55 (m, 2H), 3.98 (t, 1H), 6.16 (d, 1H), 6.31 (dd, 1H), 7.30 (m, 6H), 11.4 (br, 1H).

The starting compound was prepared as follows:

58.1 N,N-Diisopropyl-3-(2-furanyl)propenamide

The title compound was obtained from furfural with the procedure described in Example 57.1, as a colourless oil, 11.2 g (75%): ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 12H), 4.0 (br, 2H), 6.41 (m, 2H), 6.76 (d, 1H), 7.38 (m, 2H).

EXAMPLE 59

N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl-propanamine fumarate

A solution of N,N-diisopropyl-3-(N-methyl-pyrr-2-yl)-3-phenyl-propanamide (4.92 g, 15.7 mmol) in THF (75 mL), was dropped into a stirred mixture of LAH (2.38 g, 62.8

mmol). Stirring was continued at 50 °C overnight. Standard work-up gave the amine as a yellow oil, which was isolated as the fumarate salt, 2.74 g (42 %): m.p. 134-6°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 6H), 1.29 (d, 6H), 2.24 (m, 1H), 2.48 (m, 1H), 2.97 (dt, 1H), 3.26 (dt, 1H), 3,32 (s, 3H), 3.69 (septet, 2H), 4.08 (t, 1H), 6.05 (t, 1H), 6.16 (m, 1H), 6.57 (dd, 1H), 6.71 (s, 2H) and 7.19-7.34 (m, 5H).

The starting compound was prepared as follows:

59.1 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide

The title compound was prepared from N-methyl-2-pyrrolaldehyde and N,N-diisopropyl-dimethylphosphon acetamide analogously to Example 4.2, giving 7.61 g (92%): ^{1}H NMR($CDCl_3$) δ 1.32 (d, 6H), 1.35 (d, 6H), 3.68 (s, 3H), 4.00 (m, 2H), 6.13 (t, 1H), 6.55-6.66 (3H) and 7,57 (d, 1H).

59.2 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl-propanamide

The title compound was prepared from N,N-diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide by a method analogous to that described in Example 41.3, giving 4.92 g (78 %): ^{1}H NMR ($CDCl_3$) δ 0.85-1.32 (4d from rotamers, 12H), 2.91 (d, 2H), 3.31 (s, 3H) 3.45 (m, 1H), 3.88 (m, 1H), 4.65 (t, 1H), 6.07 (2H), 6.50 (dd, 1H) and 7.15-7.22 (5H).

EXAMPLE 60

3-(N-Methylpyrrol-2-yl)-3-phenyl-1-pyrrolidinopropane fumarate

The title compound was prepared analogously to Example 59, using N,N-tetramethylene-dimethylphosphon acetamide, yield 950 mg (36 % tot.): m.p. 194-5°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 12H), 2.2-2.6 (m, 2H) 3.05 (m, 2H), 3.66 (sept., 2H), 4.03 (t, 1H), 6.02 (two d, 2H), 6.64 (t, 1H), 6.69 (s, 2H) and 7.28 (m, 5H).

BIOLOGICAL EVALUATION

The pharmacological activity of compounds prepared in the Examples was tested using in vitro methods.

Functional in vitro studies

Male guinea pigs, weighing about 300 g, were killed by a blow on the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were vertically mounted between two hooks in thermostatically controlled (37°C) organ baths (5 ml). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip and the preparations were allowed to stabilise for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilisation period.

Carbachol (carbamylcholine chloride) was used as the standard muscarinic receptor agonist. In each experiment, the viability of the preparations and the reproducibility of their contractile responses were initially tested by two consecutive additions of a submaximal concentration (3 x 10^{-6} M) of carbachol. A concentration-response curve to carbachol was then generated by cumulative addition of carbachol to the organ-bath (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min. before a fix concentration of the test compound (antagonist) was added to the organ-bath. After 60 min. of incubation with the antagonist, a second cumulative concentration-response curve to carbachol was generated. Responses were expressed as per cent of the maximal response to carbachol. EC_{50}-values for carbachol in the absence (control) and presence of antagonist were graphically derived and dose ratios (r)

were calculated. Dissociation constants, K_B, for the antagonists were calculated using equation (1) (Schild, H.I., Br. J. Pharmacol. Chemother. 1949, 4, 277-280), where [A] is the concentration of test compound:

$$K_B = [A]/r-1 \quad (1)$$

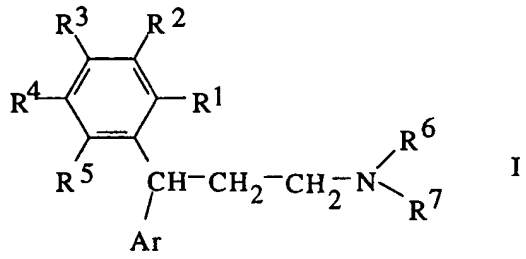
The KB values obtained are presented in Table 1 below.

Table 1

Example No.	K_B-value nM	Example No.	K_B-value nM	Example No.	K_B-value nM
1	499	23	1.05	45	51
3	236	24	1.91	46	286
4	132	27	7.1	47	91
5	336	28	8.55	48	31
6	10	29	1.5	49	590
7	13	30	139	50	154
8	26	31	14	51	118
9	3.8	32	36	52	350
10	171	33	56	53	154
11	431	34	803	55	2
12	1.18	35	1773	56	360
13	15	36	2640	59	690
14	4.5	37	520	60	707
15	15	38	207		
16	32	39	235		
17	3.5	40	814		
18	172	41	7.6		
19	2.9	42	286		
20	3315	43	29		
22	2.8	44	2285		

CLAIMS

1. A compound of Formula (I):



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,

R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,

R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, alkoxycarbonylalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl having at least two carbon atoms, alkoxy having at least two carbon atoms, hydroxyalkyl having at least two carbon atoms,

R^5 is hydrogen, halogen, alkyl,

Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and

R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen;

with the provisos that (a) when:
(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or
(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or
(iii) Ar is heteroaryl, or
(iv) at least one of R^6 and R^7 is aromatic hydrocarbyl or cycloalkyl, then
R^4 may also be hydrogen, methyl, methoxy, hydroxymethyl, hydroxy, halogen, carbamoyl, sulphamoyl;
and (b), when Ar is unsubstituted phenyl, then R^1, R^2, R^3, R^4 and R^5 can not all be hydrogen;
their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. The compound according to claim 1, wherein R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, or azido.

3. The compound according to claim 2, wherein R^1 is hydrogen or methyl, R^2, R^3 and R^5 are either all hydrogen or one of R^2, R^3 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

4. The compound according to claim 1, wherein Ar is heteroaryl.

5. The compound according to claim 4, wherein R^1 is hydrogen or methyl, and R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen.

6. The compound according to claim 1, wherein R^1 is hydrogen, alkyl, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, or halogen, and Ar is other than phenyl that is ortho-substituted by hydroxy or alkoxy.

7. The compound according to claim 6, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

8. The compound according to claim 1, wherein at least one of R^6 and R^7 is aromatic hydrocarbyl, cycloalkyl or a hydrocarbyl chain wherein carbon atoms are interconnected by an oxygen atom in at least one position.

9. The compound according to claim 8, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

10. The compound according to any one of claims 1 to 9, wherein R^1 is hydroxy, halogen, trifluoromethyl, amino, methoxy or hydroxymethyl.

11. The compound according to any one of claims 1 to 10, wherein R^2 and R^3 independently are hydrogen, hydroxy or hydroxymethyl.

12. The compound according to any one of claims 1 to 10, wherein R^4 is hydrogen, formyl, alkoxycarbonyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxamidoalkyl, carbamoylalkyl, aminoalkyl, amino, azido, cyanoalkyl, carboxy or carboxyalkyl.

13. The compound according to claim 12, wherein R^4 is hydrogen, formyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethoxymethyl, methoxycarbonyl, amino, aminopropyl, acetyl, 1,2-hydroxyethyl, ethylaminomethyl, or hydroxyethoxyethyl-aminoethyl.

14. The compound according to any one of claims 1 to 13, wherein R^5 is hydrogen.

15. The compound according to any one of claims 1 to 14, wherein each of R^6 and R^7 independently signify a saturated hydrocarbyl group, especially a saturated aliphatic hydrocarbyl group such as C_{1-8}alkyl, especially C_{1-6}alkyl, or adamantyl, R^6 and R^7 together containing at least three, preferably at least four carbon atoms.

16. The compound according to any one of claims 1 to 14, wherein R^6 and R^7 taken together form a ring with the amine nitrogen.

17. The compound according to any one of claims 1 to 16, wherein at least one of R^6 and R^7 comprises a branched carbon chain.

18. The compound according to any one of claims 1 to 17, wherein Ar is thienyl, pyrryl, thiazolyl, oxazolyl, methylthiazolyl or methylpyrryl.

19. The compound according to claim 1, which is:
N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride,
N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(2-hydroxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine, or its 3(R)-isomer,
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its 1(S*)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)-phenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phenyl]-3-phenylpropanamine, or its (R)-isomer,
N-cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine,
N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamine, or
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine, or its (R)-isomer.

20. The compound according to any one of claims 1 to 19 for use as a pharmaceutically active substance, especially as an anticholinergic agent.

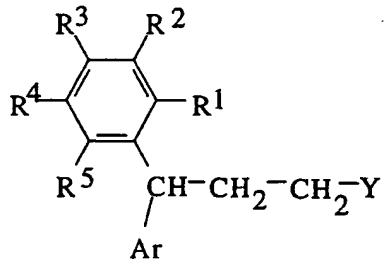
21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 19, and preferably a compatible pharmaceutical carrier.

22. Use of a compound according to any one of claims 1 to 19 for preparing an anticholinergic drug.

23. A method of treating a living body suffering from a disorder related to urinary incontinence, which method comprises the step of administering to said living body an effective amount of a compound according to any one of claims 1 to 19.

24. A method of preparing a compound according to any one of claims 1 to 19, which comprises:

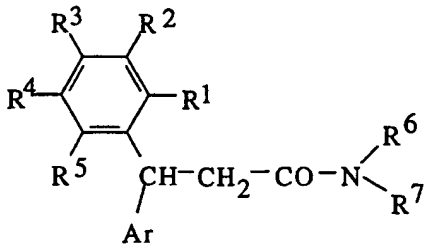
a) reacting a compound of Formula II



II

wherein R^1 to R^5 and Ar are as defined in claim 1, and Y is a leaving group, with an amine HNR^6,R^7, wherein R^6 and R^7 are as defined above, or

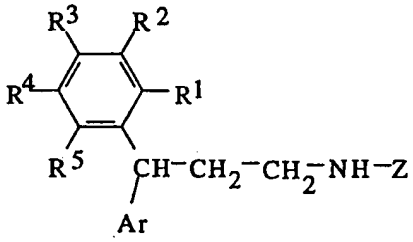
b) reducing a compound of Formula III



III

wherein R^1 to R^7 and Ar are as defined in claim 1 and any hydroxy groups may be protected, or

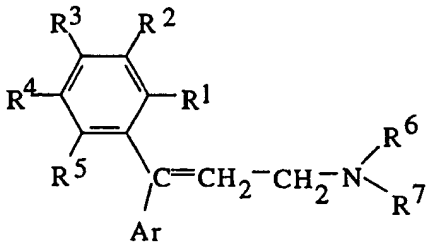
c) N-alkylating a secondary amine of Formula IV



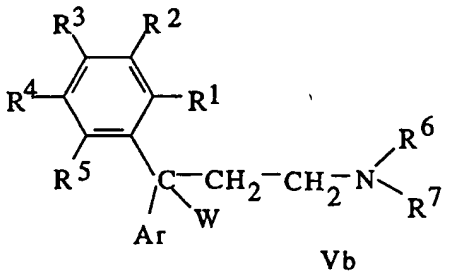
IV

wherein R^1 to R^5 and Ar are as defined in claim 1 and any hydroxy groups may be protected, and wherein Z has the same meaning as R^6 and R^7, or

d) reducing a compound of Formula Va or Vb



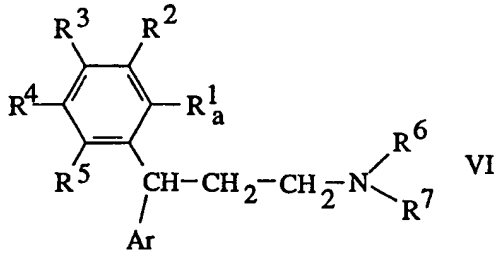
Va



Vb

wherein R^1 to R^7 and Ar are as defined in claim 1 and any hydroxy groups may be protected, and W signifies a hydroxy group or halogen, or

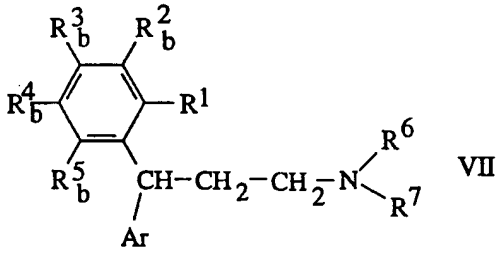
e) in a compound of Formula VI



VI

wherein R^2 to R^7 and Ar are as defined in claim 1, and R^1a is carboxyl or alkoxy, converting R^1a to hydroxy, or

f) in a compound of Formula VII

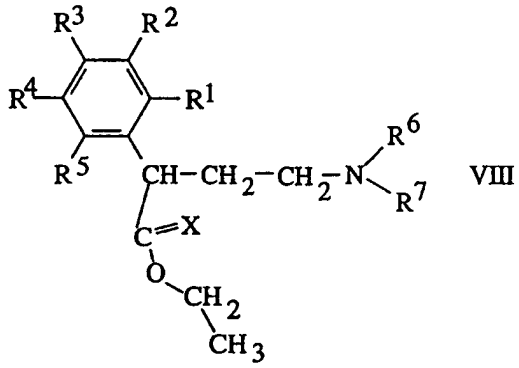


VII

wherein R^1, R^6, R^7 and Ar are as defined in claim 1, and one of R^2b to R^5b is alkylene and the others are as defined in claim 1 for R^2 to R^5, reducing alkylene to alkyl, hydroxyalkyl or dihydroxyalkyl, or

g) in a compound of Formula I as defined in claim 1, converting one or more of groups R^1 to R^5 to another or other groups R^1 to R^5, or

h) reacting a compound of Formula VIII

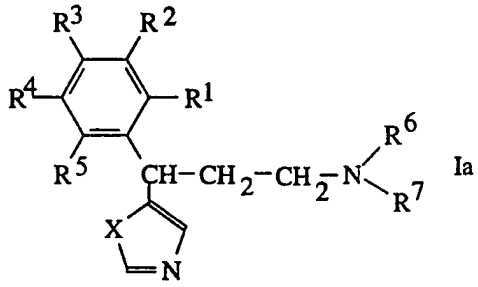


VIII

wherein R^1 to R^7 are as defined in claim 1, and X is oxygen or sulphur, with a compound of Formula IX

$CH_3N{=}C:$ IX

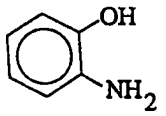
to form a compound of Formula Ia



Ia

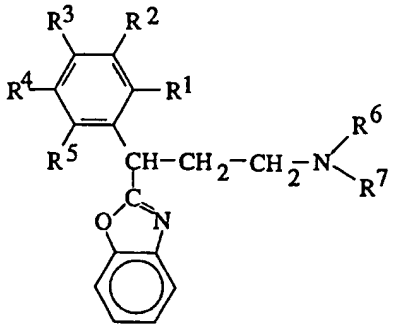
wherein R^1 to R^7 and X are as defined above, or

i) reacting a compound of Formula VIII above, wherein X is oxygen, with a compound of Formula X



X

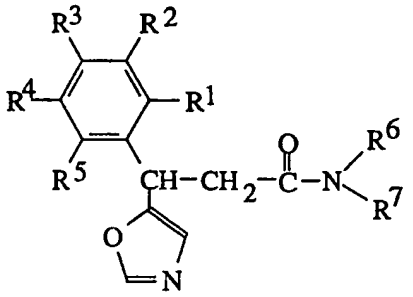
to form a compound of Formula Ib



Ib

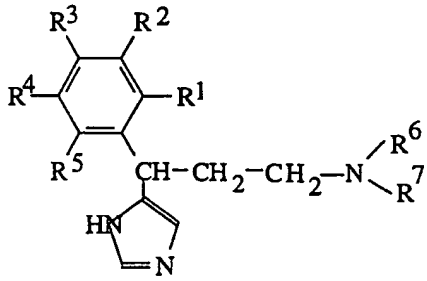
wherein R^1 to R^7 are as defined in claim 1, or

j) converting a compound of Formula XI



XI

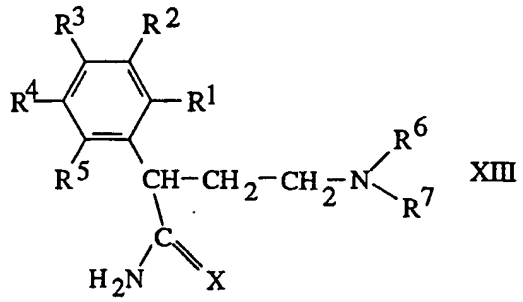
wherein R^1 to R^7 are as defined in claim 1, to a compound of Formula XII



XII

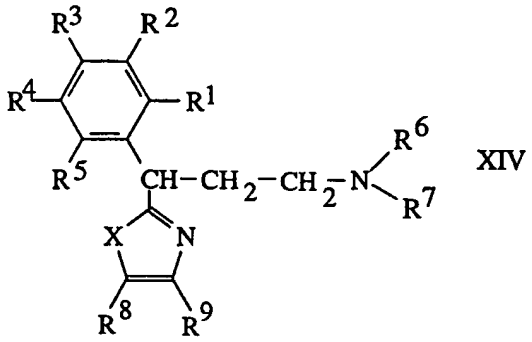
wherein R^1 to R^7 are as defined in claim 1, or

k) converting a compound of Formula XIII



XIII

wherein R^1 to R^7 are as defined in claim 1, and X is oxygen or sulphur, to a compound of Formula XIV



XIV

wherein R^1 to R^7 and X are as defined above, and R^8 and R^9 independently are hydrogen or alkyl, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained,

ii) if desired converting the obtained bases of Formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 211/06, C07C 215/54, C07C 217/62, C07C 237/30, C07C 255/33, C07D 333/20, A61K 31/135, A61K 31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9411337 A1 (KABI PHARMACIA AB), 26 May 1994 (26.05.94)	1-22,24
	--	
X	WO 8906644 A1 (KABIVITRUM AB), 27 July 1989 (27.07.89)	1-22,24
	--	
X	DE 1216318 B1 (FARBWERKE HOECHST AKTIENGESELLSCHAFT VORMALS MEISTER LUCIUS & BRüNING), 12 May 1966 (12.05.66), column 4, line 1 - line 4, the claims	1-21,24
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 1998	29 -06- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1169944 A (ED. GEISTLICH SÖHNE AG FüR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 12, the claims --	1-21,24
X	GB 1169945 A (ED GEISTLICH SÖHNE AG FüR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 11, the claims -- --------	1-21,24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

09/06/98

International application No.
PCT/SE 98/00556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411337 A1	26/05/94	AT 164828 T	15/04/98
		AU 672458 B	03/10/96
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		DE 69317898 D	00/00/00
		EP 0667852 A,B	23/08/95
		FI 952179 A	05/05/95
		HU 72742 A	28/05/96
		HU 9501329 D	00/00/00
		JP 8503208 T	09/04/96
		NO 951775 A	05/05/95
		SE 9203318 D	00/00/00
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		US 5686464 A	11/11/97
WO 8906644 A1	27/07/89	AU 635493 B	25/03/93
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		DK 172590 A	19/07/90
		DK 538289 A	27/10/89
		EP 0325571 A,B	26/07/89
		SE 0325571 T3	
		EP 0354234 A	14/02/90
		FI 894902 D	00/00/00
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		HU 9400053 A	30/01/95
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		NO 173496 C	22/12/93
		SE 8800207 D	00/00/00
		US 5382600 A	17/01/95
DE 1216318 B1	12/05/66	DK 111894 A	00/00/00
GB 1169944 A	05/11/69	NONE	
GB 1169945 A	05/11/69	US 3446901 A	27/05/69

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Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 :		(11) Internationale Veröffentlichungsnummer: **WO 98/56359**
A61K 9/22	**A2**	(43) Internationales Veröffentlichungsdatum: 17. Dezember 1998 (17.12.98)

(21) Internationales Aktenzeichen: PCT/DE98/01659

(22) Internationales Anmeldedatum: 12. Juni 1998 (12.06.98)

(30) Prioritätsdaten:

197 25 911.1	13. Juni 1997 (13.06.97)	DE
60/068,977	30. Dezember 1997 (30.12.97)	US

(71)(72) Anmelder und Erfinder: BODMEIER, Roland [DE/DE]; Ravenweg 18, D–14163 Berlin (DE). McGINITY, James, W. [US/US]; 4209 Dunning Lane, Austin, TX 78746 (US).

(74) Anwalt: SCHUBERT, Klemens; Im Schönower Park 1E, D–14167 Berlin (DE).

(81) Bestimmungsstaaten: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Veröffentlicht
Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.

(54) Title: COMPOUNDS WHICH DELAY THE RELEASE OF ACTIVE SUBSTANCES

(54) Bezeichnung: ZUSAMMENSETZUNGEN, DIE DIE WIRKSTOFFFREISETZUNG VERZÖGERN

(57) Abstract

The invention relates to compounds which delay the release of active substances. The invention also relates to a method for the production thereof. The compounds are produced, for instance, by wet or spray granulation, spray drying or extrusion of a conventional filling material (e.g. microcrystalline cellulose or lactose) and a carrier material (hydroxypropylmethyl cellulose or polyethylene oxide). The inventive composition can be processed together with the active substance and other auxiliary agents into a solid medicament form, e.g. a tablet, which releases the active substance in a delayed manner.

(57) Zusammenfassung

Es werden Zusammensetzungen, welche die Wirkstofffreisetzung verzögern, sowie Verfahren zu ihrer Herstellung beschrieben. Die Zusammensetzungen werden z.B. durch Feucht– oder Sprühgranulierung, Sprühtrocknung oder Extrusion aus einem üblichen Füllstoff (z.B. mikrokristalline Cellulose oder Lactose) und einem Trägermaterial (z.B. Hydroxypropylmethylcellulose oder Polyethylenoxid) hergestellt. Diese erfindungsgemäße Zusammensetzung kann zusammen mit dem Wirkstoff und anderen Hilfsstoffen in eine feste Arzneiform, z.B. eine Tablette, verarbeitet werden, die den Wirkstoff verzögert freigibt.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AL	Albanien	**ES**	Spanien	**LS**	Lesotho	**SI**	Slowenien
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CU	Kuba	**KZ**	Kasachstan	**RO**	Rumänien		
CZ	Tschechische Republik	**LC**	St. Lucia	**RU**	Russische Föderation		
DE	Deutschland	**LI**	Liechtenstein	**SD**	Sudan		
DK	Dänemark	**LK**	Sri Lanka	**SE**	Schweden		
EE	Estland	**LR**	Liberia	**SG**	Singapur		

Zusammensetzungen, die die Wirkstofffreisetzung verzögern

Die Erfindung betrifft Zusammensetzungen, die die Wirkstofffreisetzung verzögern.

Zur Tablettenherstellung werden verschiedene Hilfsstoffe wie Füllstoffe, Zerfallsmittel, Bindemittel, Schmiermittel usw. eingesetzt. Aufgrund der wenigeren Herstellungsschritte und geringeren Wirkstoffbelastung ist die Direkttablettierung der Naß- oder Trockengranulierung vorzuziehen. Für die Direkttablettierung sind jedoch Hilfsstoffe mit besonderen Eigenschaften notwendig. Die verwendeten Hilfsstoffe sollen zahlreiche, z. T. gegenläufige Anforderungen, wie gute Fließfähigkeit, gute Komprimierbarkeit bei geringem Druck, hohe Härte und Abriebsfestigkeit und gute Zerfallsneigung nach der Einnahme erfüllen. Die Verwendung von Füllstoffen wie mikrokristalliner Cellulose (MCC), Cellulose, Dicalciumphosphat, Lactose u.a. ist für die Tablettenherstellung weithin üblich. Die gewünschten Anforderungen werden von den handelsüblichen Füllstoffen nur mehr oder weniger gut erfüllt. Weitere Hilfsstoffe wie Gleitmittel, Bindemittel, Sprengmittel u.a. werden deshalb bei der Tablettenherstellung hinzugefügt.

Es ist daher wünschenswert, "bessere" Hilfsstoffe, die möglichst viele wünschenswerte Tablettiereigenschaften in sich vereinigen, zu entwickeln. In der Patentliteratur und der wissenschaftlichen Literatur sind einige Direkttablettiermittel, bestehend aus Mischungen verschiedener Hilfsstoffe, beschrieben. Dabei wird meist ein Füllstoff mit einem weiteren Hilfsstoff kombiniert und durch entsprechende Verfahren, z.B. Sprühtrocknung oder Sprühgranulierung, in einem bestimmten Verhältnis in Gra-

nulat- oder Pulverkörnchen fixiert. Dazu zählen z.B. bereits vermarktete Gemische aus MCC mit Lactose oder MCC mit Siliciumdioxid oder MCC mit Natriumcarboxymethylcellulose, die den oben genannten idealen Eigenschaften nahekommen und Vorteile gegenüber den Einzelkomponenten oder Gemischen der Einzelkomponenten besitzen.

Diese Zusammensetzungen werden meist in rasch zerfallenden festen Arzneiformen eingesetzt und haben selbst keinen retardierenden Effekt auf die Wirkstofffreisetzung.

Die Herstellung fester Arzneiformen mit verzögerter Wirkstofffreigabe kann durch verschiedene Maßnahmen erreicht werden. Dazu zählen vor allem das Überziehen der Arzneiform mit einer Diffusionsbarriere, meist einem Polymer und die Herstellung von Matrix-Systemen (z.B. Tabletten) auf der Basis wasserunlöslicher oder wasserlöslicher Trägermaterialien (Hilfsstoffe, welche die Wirkstofffreisetzung retardieren). Bei den letztgenannten Systemen werden der Wirkstoff und die Hilfsstoffe mit dem Trägermaterial gemischt und in eine feste Arzneiform, meist Tabletten, verarbeitet. Das Trägermaterial ist für die Verzögerung der Wirkstofffreisetzung verantwortlich. Als wasserlösliche Trägermaterialen werden unter anderem Cellulosederivate wie Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC) oder Polyethylenoxide eingesetzt. Diese Polymere quellen in Kontakt mit wäßrigen Medien. Der Arzneistoff wird z.B. aus Tabletten entweder durch Erosion der Gelschicht und/oder durch Diffusion durch die Gelschicht verzögert freigesetzt.

Den Trägermaterialien fehlen meist die oben beschriebenen idealen Tablettiereigenschaften, wie z.B. gute Fließeigenschaften oder Komprimierbarkeit. Die Tabletten werden daher meist über Granulierverfahren und unter Zusatz von Hilfsstoffen hergestellt.

Aufgabe der Erfindung ist es daher, Kombinationen des Trägermaterials mit geeigneten Hilfsstoffen zu entwikkeln, welche die genannten Anforderungen weitgehend erfüllen und eine Direkttablettierung mit dem Wirkstoff erlauben.

Die Aufgabe wird dadurch gelöst, daß eine Zusammensetzung zur Verfügung gestellt wird, welche aus einer innigen Mischung eines Hilfsstoffes und einem Trägermaterial besteht und die Wirkstofffreisetzung aus Zubereitungen retardiert.

Während die bekannten Hilfsstoff-Kombinationen die Wirkstofffreisetzung nicht oder nur unerheblich retardieren, sind die erfindungsgemäßen neuen Hilfsstoff-Trägermaterial-Kombinationen Zusammensetzungen, welche die Wirkstofffreisetzung verzögern.

Erfindungsgemäß ist vorgesehen, daß das Trägermaterial retardierende Eigenschaften aufweist.

Erfindungsgemäß bevorzugt ist es, daß das Trägermaterial ein hydrophiles Polymer, ein Cellulosederivat, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Polyethylenoxid und/oder ein Vinylderivat (z.B. Polyvinylpyrrolidon, Polyvinylalkohol, Polyvinylacetate oder Copolymere) ist.

Erfindungsgemäß bevorzugt ist es, daß der Hilfsstoff ein Füllstoff ist. Besonders bevorzugt ist es dabei, daß der Hilfsstoff Cellulose oder mikrokristalline Cellulose, ein Zucker oder Zuckeralkohol, wie Sorbit oder Mannit, Lactose und/oder ein Calciumsalz ist.

Bevorzugt ist es ferner, daß weitere Hilfsstoffe vor der Herstellung der Zusammensetzung zugegeben werden.

Erfindungsgemäß ist es ferner, daß die Zusammensetzung in wesentlich frei von Wirkstoffen ist und ein retardierendes hydrophiles oder hydrophobes Trägermaterial und einen Hilfsstoff ausgewählt aus der Gruppe bestehend aus Cellulosen, Kohlenhydraten, Calciumsalzen oder Polyolen enthält, wobei das Trägermaterial und der Hilfsstoff in einem derartigen Verhältnis vorliegen, daß eine verzögerte Freisetzung eines Wirkstoffes erzielt wird, wenn man den Wirkstoff mit der Zusammensetzung formuliert.

Insbesondere bevorzugt ist es dabei, daß das retardierende Material aus der Gruppe bestehend aus Polyethylenoxid, Hydroxypropylmethylcellulose, Hydroxymethylcellulose, Acrylatpolymeren, Fetten, Wachsen, hydrierten Pflanzenölen, Lipiden, Fettsäuren, Fettalkoholen oder aus Kombinationen von zwei oder mehreren dieser Materialien ausgewählt ist.

Weiterhin bevorzugt ist es, daß das retardierende Material Polyethylenoxid umfaßt.

Bevorzugt sind ferner erfindungsgemäße Ausführungsformen, wobei das retardierende Material etwa 10 bis 90 Gew.-% der retardierenden Zusammensetzung umfaßt, besonders bevorzugt etwa 15 bis 35 Gew.-% der retardierenden Zusammensetzung umfaßt, insbesondere bevorzugt etwa 15 bis 85 Gew.-% der Zusammensetzung umfaßt. Ganz besonders bevorzugt ist es, daß das Polyethylenoxid etwa 20 Gew.-% der Zusammensetzung umfaßt.

Weiterhin bevorzugt ist es, daß der Hilfsstoff mikrokristalline Cellulose ist. Besonders bevorzugt ist hierbei, daß die mikrokristalline Cellulose etwa 15 bis 95 Gew.-%

der Zusammensetzung umfaßt, insbesondere etwa 65 bis 95 Gew.-% der Zusammensetzung umfaßt und ganz besonders bevorzugt etwa 70 Gew.-% der Zusammensetzung umfaßt.

Bevorzugterweise sind erfindungsgemäße Ausführungsformen, wobei das Wachs hydriertes Pflanzenöl, Glycerin, Carnaubawachs, Bienenwachs, ein Acrylatpolymer oder eine Mischung von zwei oder mehreren der genannten Stoffe ist. Hierbei ist es ferner bevorzugt, daß das Fett ein Monoglycerid, ein Diglycerid, ein Triglycerid oder eine Mischung von zwei oder mehreren der genannten Stoffe ist. Bevorzugt ist außerdem, daß das Polyol Xylit, Mannit, Sorbit oder eine Mischung aus zwei oder mehreren der genannten Stoffe ist. Ganz besonders bevorzugt ist es, daß das Wachs hydriertes Pflanzenöl ist.

Bevorzugt sind erfindungsgemäße Zusammensetzungen, die als Pulver oder Granulat vorliegen. Auch ist bevorzugt, daß das Wachs Glycerin ist.

Erfindungsgemäß bevorzugt ist es ferner, daß der Hilfsstoff mikrokristalline Cellulose ist und in einer Menge von etwa 50 Gew.-% in der Zusammensetzung vorliegt.

Bevorzugt ist auch, daß das retardierende Material eine wäßrige Polymerdispersion ist, insbesondere eine Cellulosepolymer oder eine Acrylatpolymerdispersion ist.

Ein weitere Gegenstand der vorliegenden Erfindung ist eine Zubereitung, enthaltend eine erfindungsgemäße Zusammensetzung. Dabei ist bevorzugt, daß die Zubereitung weiterhin mindestens einen Wirkstoff enthält.

Gegenstand der vorliegenden Erfindung ist auch eine Zubereitung, erhältlich durch Verpressen einer erfindungsge-

mäßen Zusammensetzung mit mindestens einem Wirkstoff und gegebenenfalls weiteren Hilfsstoffen.

Erfindungsgemäß ist die Freisetzung eines Wirkstoffes durch das Verhältnis von Wirkstoff zur erfindungsgemäßen Zusammensetzung kontrolliert und einstellbar.

Erfindungsgemäß ist es auch, daß man die Freisetzung eines Wirkstoffes durch das Verhältnis von Hilfsstoff zu Trägermaterial einer erfindungsgemäßen Zusammensetzung kontrolliert und einstellt. Erfindungsgemäß ist es ferner, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier Zusammensetzungen gemäß Anspruch 1 mit voneinander unterschiedlichem Hilfsstoff-Trägermaterial-Verhältnis kontrolliert und einstellt.

Erfindungsgemäß ist es außerdem, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier oder mehrerer Zusammensetzungen gemäß Anspruch 1 mit jeweils unterschiedlichen Trägermaterialien und/oder Hilfsstoffen kontrolliert und einstellt.

Ein weiterer Gegenstand der vorliegenden Erfindung ist auch ein Verfahren zur Herstellung einer erfindungsgemäßen Zubereitung, wobei man das retardierende Trägermaterial mit dem Hilfsstoff bei einer Temperatur trocken vermischt, bei welcher das retardierende Trägermaterial schmilzt oder erweicht, wobei man eine erfindungsgemäße Zusammensetzung erhält, und daß man der Zusammensetzung einen pharmakologisch wirksamen Stoff hinzufügt und vermischt und man die so erhaltene Mischung einer Schmelzextrusion unterwirft, wobei der Hilfsstoff der Zusammensetzung bei der Temperatur der Schmelzextrusion nicht schmilzt.

Bevorzugt ist es dabei, daß der Hilfsstoff ein Calciumsalz, ein Polyol oder ein Kohlenhydrat ist. Besonders bevorzugt ist es hierbei, daß man die Extrusion wasserfrei ausführt.

Die Herstellung der erfindungsgemäßen Zusammensetzungen erfolgt nach bekannten Methoden, z. B. durch Sprühgranulierung, Feuchtgranulierung, Extrusion oder Sprühtrocknung. Bei den erfindungsgemäßen Zusammensetzungen handelt es sich um eine innige Mischung der Hilfsstoffe und Trägermaterialien. Die Komponenten sind also in dieser Mischung in einem bestimmten Verhältnis fixiert und unterscheiden sich dadurch auch von einfachen physikalischen Mischungen der Einzelkomponenten. Es kann also nicht zur Entmischung während der weiteren Verarbeitung kommen, während physikalische Mischungen entmischbar sind.

Zu den Trägermaterialien zählen hydrophile Hilfsstoffe die in Kontakt mit wäßrigen Medien, z.B. Körperflüssigkeiten, die Wirkstofffreisetzung verzögern. Dazu gehören vor allem Polymere wie Cellulosederivate (z. B. Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose) Polysaccharide, Acrylatderivate, Polyethylenoxide, Vinylderivate (z.B. Polyvinylpyrrolidon, Polyvinylalkohol, Polyvinylacetate) und Derivate (z.B. vernetzte Polymere) oder Copolymere.

Die geeigneten Hilfsstoffe kommen in erster Linie aus der Gruppe der Füllstoffe. Füllstoffe wie mikrokristalline Cellulose, Cellulose, Dicalciumphosphat oder Lactose sind für die Tablettenherstellung weithin üblich. Als Füllstoffe können auch Zucker/Zuckeralkohole wie Saccharose, Mannit oder Sorbit verwendet werden. Es können auch Mischungen von Füllstoffen wie z. B. Lactose/mikrokristalline Cellulose verwendet werden.

Selbstverständlich können den Füllstoff-Trägermaterial-Mischungen auch noch andere Bestandteile zugesetzt werden, die während der Herstellung entsprechend mit eingearbeitet werden. Diese Bestandteile gehören zu den üblicherweise bei pharmazeutischen Zusammensetzungen verwendeten Hilfsstoffen, z. B. Schmiermittel, Gleitmittel, Geschmacksstoffe, Farbstoffe u.a.

Die Herstellung der Mischungen aus den verschiedenen Komponenten erfolgt nach bekannten Methoden, z. B. durch Sprühgranulierung, Feuchtgranulierung, Sprühtrocknung oder Extrusion.

Im Falle der Sprühgranulierung wird die Pulvermischung im Wirbelbett bei leicht erhöhter Temperatur vorgelegt und mit einer Flüssigkeit, meist Wasser oder Alkohol oder einer wäßrigen (organischen) Lösung eines entsprechenden Hilfsmittels besprüht, agglomeriert und dann getrocknet.

Zur Feuchtgranulierung mischt man beispielsweise den Hilfsstoff mit dem Trägermaterial in einem geeigneten Mischer, granuliert mit Wasser oder einer geeigneten Flüssigkeit und trocknet das Feuchtgut, nachdem es durch ein Sieb passiert wurde.

Bei den Granulierverfahren können die Hilfsstoffe und/oder Trägermaterialien oder Teilmengen auch in die Granulierflüssigkeit gegeben werden.

Bei der Sprühtrocknung wird eine flüssige Mischung der Komponenten in einer geeigneten Sprühvorrichtung bei erhöhten Temperaturen versprüht. Der Füllstoff kann dabei dispergiert (z. B. Cellulose, MCC oder Calciumsalze) oder gelöst (z. B. Lactose, Sorbit, Mannit) vorliegen.

Zur Retardierung der Freisetzung werden häufig HPMC-Typen mit hoher Molmasse eingesetzt. Diese HPMC-Typen bilden im Kontakt mit Wasser schon bei niedrigen Konzentrationen eine hochviskose Masse, die sich nur schwer verarbeiten läßt. Bei der Feuchtgranulierung wird daher meist nicht mit einer wäßrigen sondern mit einer alkoholischen Granulierflüssigkeit gearbeitet. Bei der Herstellung einer erfindungsgemäßen Zusammensetzung aus Füllstoff und HPMC, z.B. durch Sprühtrocknung, können daher nur sehr niedrig konzentrierte wäßrige HPMC-Lösungen versprüht werden. Alternativ kann mit organischen Lösungsmitteln und damit mit Dispersionen gearbeitet werden.

Ein besonderer Aspekt der Erfindung ist daher die Herstellung einer erfindungsgemäßen Zusammensetzung aus höherkonzentrierten wäßrigen Systemen von Celluloseethern wie HPMC. Die Löslichkeit von HPMC in Wasser nimmt mit steigender Temperatur ab. Bei erhöhten Temperaturen können höherkonzentrierte HPMC-Dispersionen hergestellt werden. HPMC ist also bei erhöhten Temperaturen überwiegend dispergiert und nicht mehr gelöst. Zusammen mit dem Füllstoff können nun höherkonzertrierte wäßrige Mischungen versprüht werden. Der Vorteil liegt in der Verarbeitung konzentrierterer flüssiger Systeme und damit kürzeren Prozeßzeiten und Kosteneinsparungen.

Bestimmte MCC- und Lactose-Typen werden industriell bereits durch Sprühtrocknung gewonnen. Das Trägermaterial könnte also den Hilfsstoffdispersionen oder -lösungen vor der Trocknung beigegeben werden.

Die Teilchengröße der Zusammensetzungen läßt sich durch entsprechende Auswahl der Prozeß- und Formulierungsparameter kontrollieren.

Die erfindungsgemäßen Mischungen haben bessere Tablettiereigenschaften als der reine Träger und zeichnen sich durch folgende Vorteile aus: gute Fließfähigkeit, gute Komprimierbarkeit, hohe Härte, geringer Abrieb. Durch die Vorabherstellung der innigen Mischung wird die nachfolgende Tablettierung durch Einsparung von Herstellungsschritten erleichtert.

Die erfindungsgemäßen Zusammensetzungen können dann mit dem Wirkstoff und anderen Hilfsstoffen vermischt werden und z.B. in eine Tablette verpreßt werden. Zu den Wirkstoffen zählen nieder- und höhermolekulare Arzneistoffe (z.B. auch Peptide, Proteine) zur human- und veterinärmedizinischen Anwendung und Substanzen, die in der Landwirtschaft, im Haushalt, in der Nahrungsmittel-, kosmetischen und chemischen Industrie und anderen Industriezweigen genutzt werden. Selbstverständlich können auch Kombinationen von Wirkstoffen verwendet werden.

Die Arzneistofffreisetzung aus Matrixsystemen basierend auf hydrophilen Trägermaterialien wird neben den Eigenschaften des Trägermaterials auch von den Eigenschaften des Wirkstoffes beeinflußt. Dazu zählen in erster Linie die notwendige Dosis und die Löslichkeit des Wirkstoffes. Um die gewünschten Freisetzungsprofile zu erhalten, kann der Wirkstoff mit erfindungsgemäßen Zusammensetzungen mit unterschiedlichem Hilfsstoff-Trägermaterial-Verhältnis verarbeitet werden. Die Freisetzung kann dabei durch das Hilfsstoff-Trägermaterial-Verhältnis variiert werden. Das für den jeweiligen Wirkstoff ideale Hilfsstoff-Trägermaterial Verhältnis kann auch durch Zusammenmischen zweier Hilfsstoff-Gemische unterschiedlicher Zusammensetzung erreicht werden, z.B. durch Mischen zweier mit Trägermaterial hoch und niedrig konzentrierten Zusammensetzungen.

Die neuen Tablettierhilfsstoffe können selbstverständlich auch in anderen Herstellungsverfahren von Retardsystemen eingesetzt werden, z.B. zur Pelletherstellung oder zur Befüllung von Kapseln.

Durch die nachfolgenden Beispiele wird die Erfindung erläutert, soll dadurch jedoch nicht eingeschränkt werden.

Beispiel 1

Der Hilfsstoff (z.B. Lactose, $Ca_3(PO)_4$ oder mikrokristalline Cellulose) und das Trägermaterial (Hydroxypropylmethylcellulose - HPMC K4M oder Polyethylenoxid - Polyox) werden mit einem wäßrigen oder alkoholisch-wäßrigen Medium in unterschiedlichen Verhältnissen feucht granuliert, durch ein Sieb gedrückt und anschließend zu Granulaten getrocknet.

Beispiel 2

Der Hilfsstoff (Lactose, $Ca_3(PO)_4$ oder mikrokristalline Cellulose) und das Trägermaterial (Hydroxypropylmethylcellulose - HPMC K4M) werden in heißem Wasser in einer Konzentration von 30% in unterschiedlichen Verhältnissen gelöst oder dispergiert und in einem Sprühtrockner bei einer Einlaßtemperatur von ca. 130 °C versprüht. Das getrocknete Agglomerat kann direkt verwendet werden.

Beispiel 3

Wie Beispiel 1, nur wurden die Granulate durch Sprühgranulierung in einem Sprühgranulator (Aeromatic) durch ein Top-Spray Verfahren hergestellt. Der Hilfsstoff (z.B. Lactose, $Ca_3(PO)_4$ oder mikrokristalline Cellulose) und das Trägermaterial (Hydroxypropylmethylcellulose - HPMC K4M oder Polyethylenoxid - Polyox) wurden vorgelegt und

durch Einsprühen der Lösungsmittel bei leicht erhöhten Temperaturen granuliert. Alternativ kann auch etwas Trägermaterial in die Granulierflüssigkeit eingearbeitet werden.

Beispiel 4

Das Beispiel beschreibt ein Verfahren zur Herstellung einer Zusammensetzung zur raschen Wirkstofffreisetzung unter Verwendung eines Schmelzextrusionsverfahrens.

Materialien:

	Gew.-%
MCC (mikrokristalline Cellulose)	82
Xylit	10
kreuzvernetztes PVP, Sprengmittel	5
Natriumstearylfumarat, Schmiermittel	3

Die Extrusion bei ca. 90 °C liefert rasch freisetzende Granulate enthaltend Füllstoffe, Bindemittel, Sprengmittel und Schmiermittel. Diese rasch freisetzenden Granulate werden dann mit trockenen Inhaltsstoffen nach Wahl, einschließlich Wirkstoffen, einem Gleitmittel und bei bestimmten Ausführungsformen der Erfindung gegebenenfalls mit erfindungsgemäßen Zusammensetzungen gemischt und zu Tabletten verpreßt.

Beispiel 5

Im folgenden wird eine exemplarische Liste von Füllstoffen wiedergegeben, welche in der Praxis erfindungsgemäß allein oder in Kombination mit den Zusammensetzungen der vorliegenden Erfindung verwendet werden können.

MCC (mikrokristalline Cellulose)
Calciumsulfat

Polyole (z.B. Mannit, Sorbit, Malit, Xylit)
Calciumphosphat
Calciumcarbonat
Dextrose, Lactose
Saccharose, Maltose
Fructose
Polysaccharide

Beispiel 6

Im folgenden wird eine exemplarische Liste von retardierenden Materialien wiedergegeben, welche in der Praxis der vorliegenden Erfindung verwendet werden können. Diese retardierenden Materialien, welche auch als Trägermaterial bezeichnet werden können, können erfindungsgemäß allein oder in Kombination mit anderen Trägermaterialien und/oder den Zusammensetzungen der vorliegenden Erfindung verwendet werden.

HPC
Polysaccharide
HPMC, Polyethylenoxid
Lipide und Triglyceride, Monoglyceride, Diglyceride
Wachse, Fettsäuren und hydrierte Pflanzenöle
Acrylatpolymere
Ethylcellulose
Carbomere (Carbopol® 97IP) Polycarbophil
HPMCAS und HPMCP

Andere Inhaltsstoffe:
Die Zusammensetzungen können ferner enthalten:0,1 bis 20% Zerfallsmittel oder Bindemittel (z. B. Natruimstärkeglycolut (Expoltab®, Prinojel®)
Natriumcroscarmellose (Ac-Di-Sol®)(Zerfallsmittel)
kreuzvernetztes PVP (Polyplasdone® XL10)

Veegum® und andere Tone, Stärken, Alginate, PVP und andere dem Fachmann bekannte Zerfallsmittel und Bindemittel.

Die erfindungsgemäße Zusammensetzung kann ferner Xylit, AHA's und andere wasserlösliche Materialien, Elektrolyten und Nichtelektrolyten enthalten, welche unterhalb 150 °C Schmelzen. Die Mittel wirken als porenbildende Stoffe in der erfindungsgemäßen Zusammensetzung.

Die erfindungsgemäße Zusammensetzung kann ferner Schmiermittel und Gleitmittel enthalten, welche den Fließvorgang in Tablettier- und Kapselfüllmaschinen unterstützen und auch ein gutes Fließen in Kapselzubereitungen fördern. Schmiermittel umfassen Magnesium- und Calciumstearat und Stearinsäure, Natriumstearlyfumarat und hydrierte Pflanzenöle.

Wichtige Inhaltsstoffe der Zusammensetzung:

1. HPC oder HPMC
2. MCC in einem Verhältnis 80:20 oder 50:50 (MCC:HPC oder MPMC:PE)in Kombination mit MCC im beschriebenen Verhältnis stellen eine beispielhafte Ausführungsform der erfindungsgemäßen Zusammensetzung dar.

Optionale Inhaltsstoffe:
Siliciumdioxid, Talkum, Stärke und Polyethylenglycol

Beispiel 7

Das Beispiel beschreibt ein Verfahren zur Anwendung bei der Schmelzextrusion der langsam freisetzenden Zusammensetzung.

Die Verfahrenstemperatur der Schmelzextrusion liegt typischerweise bei 60 bis 150 °C während 1 ½ bis 3 Minuten, abhängig von der Größe der Vorrichtung und der Chargen-

größe und den Eigenschaften der Stoffe der Pulvermischung.

Das Maß der Erosion und der verzögerten Freisetzung der Wirkstoffe aus einer Matrixtablette hängt vom Verhältnis der retardierenden Stoffe zu den Hilfsstoffen in der Zusammensetzung ab. Das Material wird ferner keinen hohen Temperaturen über längere Zeiträume ausgesetzt. Restfeuchte und Lösemittel sind daher nicht von Bedeutung.

Die Anwendung der Schmelzextrusion sichert eine hohe Gleichförmigkeit der Inhaltsstoffe in der Zusammensetzung, da eine zusätzlich Mischung in inneren des Extruders erfolgt. Entmischung, welche bei der direkten Verpressung auftritt, wird gleichfalls vermieden.

Die Vorteile der erfindungsgemäßen Zusammensetzung, welche mittel der Schmelzextrusion hergestellt werden, sind u. a.:

- kontinuierliches und rasches Verfahren
- keine Lösemittel oder Wasser
- durchführbar mit hohen Gehalten an Bindemitteln/retardierenden Stoffen
- Recycling und erneute Verarbeitung der Stoffe ist möglich
- anwendbar bei retardierenden Stoffen und Füllstoffen, wenn ein Inhaltsstoff bei der Verarbeitungstemperatur schmilzt oder erweicht
- gute Fließ- und physikalische Eigenschaften
- gleichförmige Verteilung der Komponenten in der fertigen Zusammensetzung
- Zusammensetzung ist trocken mischbar mit Wirkstoffpulver und -granulat
- weitere in der Tablettenformulierung enthaltene inaktive Stoffe können sein:
  Füllstoffe

Bindemittel
Zerfallsmittel
Farbstoffe
Puffer
Gleitmittel
Schmiermittel

Zusätzliche Schmiermittel oder Zerfallsstoffe können der Zusammensetzung gleichzeitig zusammen mit dem Wirkstoff oder der erfindungsgemäßen Zusammensetzung zugesetzt werden.

Beispiel 8

Sprühgranulations-, Sprühtrocknungs- und Feuchtgarnulationsverfahren

Die Verbindungen können mit Hilfe der dem Fachmann bekannten klassischen Verfahren zur Herstellung pharmazeutischen Formulierungen im Lichte der vorliegenden Offenbarung hergestellt werden. Derartige Verfahren umfassen beispielsweise Feucht- oder Sprühgranulation, Sprühtrocknung, Sprüherstarrung, Schmelzgranulation oder Kaltextrusion.

Bei der Sprühgranulation wird die Pulvermischung, bestehend aus dem retardierenden Trägermaterial und der Hilfsstoff in einem fluidisierten Bett mit einem Lösemittel/Lösemittelgemisch (z. B. Wasser oder Alkohol) granuliert. Ein Bindemittel oder das retardierende Trägermaterial oder Teile davon können dem Lösemittel/Lösemittelgemisch zugegeben werden.

Bei der Sprühtrocknung wird eine flüssige Lösung oder Dispersion der Komponenten durch Einsprühen in eine beheizte Luftkammer und Entfernung des Lösemittels in die

trocknen Komponenten überführt. Verschiedene direkt verpreßbare Zusammensetzungen (z. B. MCC, Lactose) wurden durch eine Sprühtrocknung hergestellt. Die Zusammensetzungen können durch Zugabe der Komponenten zur Flüssigkeit vor dem Versprühen hergestellt werden.

Bei der Schmelzgranulation wird das geschmolzene Trägermaterial mit anderen Hilfsstoffen gemischt und in einer beheizten Kammer zusammengegeben und dann gekühlt und gemahlen. Bei der Sprüherstarrung wird das geschmolzene Trägermaterial mit den anderen Hilfsstoffen dispergiert und dann in Partikel versprüht und gekühlt.

Bei der Sprüherstarrung wird der Hilfsstoff zum geschmolzenen retardierenden Trägermaterial hinzugefügt, gefolgt von der Sprüherstarrung der Masse in Partikel.

Lipide (Wachse, Triglyceride und dergleichen) könnten in die langsam freisetzende Zusammensetzung in Form eines Pulvers oder einer heißen Schmelze eingefügt werden, wobei die Zusammensetzung mit der heißen Schmelze granuliert wird.

Bei den wäßrigen Polymerdispersionen werden die Hilfsstoffe in der Dispersionsmischung gelöst oder dispergiert, gefolgt von einer Sprühtrocknung, oder der Hilfsstoff wird mit der Polymerdispersion granuliert. Plastifizierungsmittel können zur Spaltung der Polymerpartikel zugesetzt werden. Geeignete Polymerdispersionen enthalten entweder Celluluse- (Ethylcelluluose in Aquacoat oder Surelease) oder Acryl- (Eudragit) Polymere.

Die erfindungsgemäße Zusammensetzung besteht aus einer innigen Mischung des retardierenden Materials und des Hilfsstoffs in einem festgelegten Verhältnis. Diese Zu-

sammensetzungen entmischen sich nicht im Vergleich mit physikalischen Mischungen.

Die erfindungsgemäßen Zusammensetzungen weisen bessere Tablettierungseigenschaften auf, als die reinen retardierenden Materialien, einschließlich Fließverhalten, Kompressibilität, Härte und Abrieb.

Sprühtrocknung und Feuchtgranulation sind gebräuchliche Verfahren in der pharmazeutischen Industrie, um Granulate zum Verpressen zu Tabletten herzustellen. Da Tablettenformulierungen viele Komponenten enthalten, ermöglicht die erfindungsgemäße Zusammensetzung die Herstellung eines Granulats durch physikalisches Mischen des Wirkstoffs mit einer erfindungsgemäßen Zusammensetzung unter anschließendem Verpressen der Mischung zu einer langsam freisetzenden Matrixtablette.

Die hier beschriebenen Zusammensetzungen und Verfahren können vom Fachmann in einfacher Weise ohne großen experimentellen Aufwand nachvollzogen werden. Neben den ausführlich beschriebenen bevorzugten Ausführungsformen kann der Fachmann diese verändern und anpassen, ohne damit die erfinderische Idee zu verlassen. Es ist klar, daß neben den beschriebenen und verwendeten Materialien auch solche, dem Fachmann geläufige, verwendet werden können, die zu den gleichen oder vergleichbaren Ergebnissen führen und unter den Umfang der vorliegenden Erfindung fallen.

Patentansprüche

1. Zusammensetzung, dadurch gekennzeichnet, daß sie
a) aus einer innigen Mischung eines Hilfsstoffes und einem Trägermaterial besteht und
b) die Wirkstofffreisetzung aus Zubereitungen retardiert.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial retardierende Eigenschaften aufweist.

3. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial ein hydrophiles Polymer ist.

4. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial ein Cellulosederivat ist.

5. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial Hydroxypropylmethylcellulose ist.

6. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial Hydroxypropylcellulose ist.

7. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial Polyethylenoxid ist.

8. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial ein Vinylderivat (z.B. Polyvinylpyrro-

lidon, Polyvinylalkohol, Polyvinylacetate oder Copolymere) ist.

9. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff ein Füllstoff ist.

10. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff Cellulose oder mikrokristalline Cellulose ist.

11. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff ein Zucker oder Zuckeralkohol, wie Sorbit oder Mannit ist.

12. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff Lactose ist.

13. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff ein Calciumsalz ist.

14. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß weitere Hilfsstoffe vor der Herstellung der Zusammensetzung zugegeben werden.

15. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Zusammensetzung in wesentlich frei von Wirkstoffen ist und ein retardierendes hydrophiles oder hydrophobes Trägermaterial und einen Hilfsstoff ausgewählt aus der Gruppe bestehend aus Cellulosen, Kohlenhydraten, Calciumsalzen oder Polyolen enthält,

wobei das Trägermaterial und der Hilfsstoff in einem derartigen Verhältnis vorliegen, daß eine verzögerte Freisetzung eines Wirkstoffes erzielt wird, wenn man den Wirkstoff mit der Zusammensetzung formuliert.

16. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material aus der Gruppe bestehend aus Polyethylenoxid, Hydroxypropylmethylcellulose, Hydroxymethylcellulose, Acrylatpolymeren, Fetten, Wachsen, hydrierten Pflanzenölen, Lipiden, Fettsäuren, Fettalkoholen oder aus Kombinationen von zwei oder mehreren dieser Materialien ausgewählt ist.

17. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material Polyethylenoxid umfaßt.

18. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material etwa 10 bis 90 Gew.-% der retardierenden Zusammensetzung umfaßt.

19. Zusammensetzung nach Anspruch 18, dadurch gekennzeichnet, daß das retardierende Material etwa 15 bis 35 Gew.-% der retardierenden Zusammensetzung umfaßt.

20. Zusammensetzung nach Anspruch 19, dadurch gekennzeichnet, daß das retardierende Material etwa 15 bis 85 Gew.-% der Zusammensetzung umfaßt.

21. Zusammensetzung nach Anspruch 17, dadurch gekennzeichnet, daß das Polyethylenoxid etwa 20 Gew.-% der Zusammensetzung umfaßt.

22. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß der Hilfsstoff mikrokristalline Cellulose ist.

23. Zusammensetzung nach Anspruch 22, dadurch gekennzeichnet, daß die mikrokristalline Cellulose etwa 15 bis 95 Gew.-% der Zusammensetzung umfaßt.

24. Zusammensetzung nach Anspruch 23, dadurch gekennzeichnet, daß die mikrokristalline Cellulose etwa 65 bis 95 Gew.-% der Zusammensetzung umfaßt.

25. Zusammensetzung nach Anspruch 24, dadurch gekennzeichnet, daß die mikrokristalline Cellulose etwa 70 Gew.-% der Zusammensetzung umfaßt.

26. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß das Wachs hydriertes Pflanzenöl, Glycerin, Carnaubawachs, Bienenwachs, ein Acrylpolymer oder eine Mischung von zwei oder mehreren der genannten Stoffe ist.

27. Zusammensetzung nach Anspruch 15 oder 17, dadurch gekennzeichnet, daß das Fett ein Monoglycerid, ein Diglycerid, ein Triglycerid oder eine Mischung von zwei oder mehreren der genannten Stoffe ist.

28. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das Polyol Xylit, Mannit, Sorbit oder eine Mischung aus zwei oder mehreren der genannten Stoffe ist.

29. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß das Wachs hydriertes Pflanzenöl ist.

30. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß diese als Pulver oder Granulat vorliegt.

31. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß das Wachs Glycerin ist.

32. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß der Hilfsstoff mikrokristalline Cellulose ist und in einer Menge von etwa 50 Gew.-% in der Zusammensetzung vorliegt.

33. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material eine wäßrige Polymerdispersion ist.

34. Zusammensetzung nach Anspruch 33, dadurch gekennzeichnet, daß die wäßrige Polymerdispersion eine Cellulosepolymer oder eine Acrylatpolymerdispersion ist.

35. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 1, in dem man das Trägermaterial und den Hilfsstoff in inniger Weise mischt.

36. Verfahren nach Anspruch 35, dadurch gekennzeichnet, daß man eine Sprüh- oder Feuchtgranulierung durchführt.

37. Verfahren nach Anspruch 35, dadurch gekennzeichnet, daß man eine Extrusion durchführt.

38. Verfahren nach Anspruch 35, dadurch gekennzeichnet, daß man eine Sprühtrocknung durchführt.

39. Verfahren nach Anspruch 38, dadurch gekennzeichnet, daß man eine Lösung oder Dispersion des Hilfsstoffes

mit einem überwiegend dispergiertem Trägermaterial sprühtrocknet.

40. Verfahren nach einem oder mehreren der Ansprüche 35 bis 39, wobei als Flüssigkeit Wasser eingesetzt wird.

41. Verfahren nach einem oder mehreren der Ansprüche 35 bis 40, wobei eine Flüssigkeit eingesetzt wird, in der das Trägermaterial während der Herstellung der Zusammensetzung überwiegend nicht löslich ist.

42. Zubereitung, enthaltend eine Zusammensetzung nach Anspruch 1.

43. Zubereitung nach Anspruch 42, enthaltend weiterhin mindestens einen Wirkstoff.

44. Zubereitung nach einem der Ansprüche 42 oder 43, erhältlich durch Verpressen einer Zusammensetzung gemäß Anspruch 1 mit mindestens einem Wirkstoff und gegebenenfalls weiteren Hilfsstoffen.

45. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 44, wobei die Freisetzung eines Wirkstoffes durch das Verhältnis von Wirkstoff zur Zusammensetzung gemäß Anspruch 1 kontrolliert und einstellbar ist.

46. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 45, dadurch gekennzeichnet, daß man die Freisetzung eines Wirkstoffes durch das Verhältnis von Hilfsstoff zu Trägermaterial einer erfindungsgemäßen Zusammensetzung kontrolliert und einstellt.

47. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 46, dadurch gekennzeichnet, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier Zusam-

mensetzungen gemäß Anspruch 1 mit voneinander unterschiedlichem Hilfsstoff-Trägermaterial-Verhältnis kontrolliert und einstellt.

48. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 47, dadurch gekennzeichnet, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier oder mehrerer Zusammensetzungen gemäß Anspruch 1 mit jeweils unterschiedlichen Trägermaterialien und/oder Hilfsstoffen kontrolliert und einstellt.

49. Verfahren zur Herstellung einer Zubereitung nach Anspruch 42, dadurch gekennzeichnet, daß man das retardierende Trägermaterial mit dem Hilfsstoff bei einer Temperatur trocken vermischt, bei welcher das retardierende Trägermaterial schmilzt oder erweicht, wobei man eine Zusammensetzung gemäß Anspruch 1 erhält, und daß man der Zusammensetzung einen pharmakologisch wirksamen Stoff hinzufügt und vermischt und man die so erhaltene Mischung einer Schmelzextrusion unterwirft, wobei der Hilfsstoff der Zusammensetzung bei der Temperatur der Schmelzextrusion nicht schmilzt.

50. Verfahren gemäß Anspruch 49, dadurch gekennzeichnet, daß der Hilfsstoff ein Calciumsalz, ein Polyol oder ein Kohlenhydrat ist.

51. Verfahren nach einem der Ansprüche 49 oder 50, dadurch gekennzeichnet, daß man die Extrusion wasserfrei ausführt.

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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60/068,977	30. Dezember 1997 (30.12.97)	US

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(81) Bestimmungsstaaten: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Veröffentlicht

Mit internationalem Recherchenbericht.

Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 18. März 1999 (18.03.99)

(54) Title: COMPOUNDS WHICH DELAY THE RELEASE OF ACTIVE SUBSTANCES

(54) Bezeichnung: ZUSAMMENSETZUNGEN, DIE DIE WIRKSTOFFFREISETZUNG VERZÖGERN

(57) Abstract

The invention relates to compounds which delay the release of active substances. The invention also relates to a method for the production thereof. The compounds are produced, for instance, by wet or spray granulation, spray drying or extrusion of a conventional filling material (e.g. microcrystalline cellulose or lactose) and a carrier material (hydroxypropylmethyl cellulose or polyethylene oxide). The inventive composition can be processed together with the active substance and other auxiliary agents into a solid medicament form, e.g. a tablet, which releases the active substance in a delayed manner.

(57) Zusammenfassung

Es werden Zusammensetzungen, welche die Wirkstofffreisetzung verzögern, sowie Verfahren zu ihrer Herstellung beschrieben. Die Zusammensetzungen werden z.B. durch Feucht– oder Sprühgranulierung, Sprühtrocknung oder Extrusion aus einem üblichen Füllstoff (z.B. mikrokristalline Cellulose oder Lactose) und einem Trägermaterial (z.B. Hydroxypropylmethylcellulose oder Polyethylenoxid) hergestellt. Diese erfindungsgemäße Zusammensetzung kann zusammen mit dem Wirkstoff und anderen Hilfsstoffen in eine feste Arzneiform, z.B. eine Tablette, verarbeitet werden, die den Wirkstoff verzögert freigibt.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DE 98/01659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Y. KAWASHIMA ET AL.: "preparation of a directly tabletable controlled-release matrix filler with microcrystalline cellulose modified with hydroxypropylmethylcellulose" CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 41, no. 12, December 1993, pages 2156-2160, XP000422466 Tokyo (JP) see the whole document --- -/--	1-6,9, 10,15, 16, 18-20, 22-25, 30, 32-35, 38-46

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 January 1999	25/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DE 98/01659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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International Application No
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INTERNATIONALER RECHERCHENBERICHT

Ir ationales Aktenzeichen
PCT/DE 98/01659

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K9/22

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	Y. KAWASHIMA ET AL.: "preparation of a directly tabletable controlled-release matrix filler with microcrystalline cellulose modified with hydroxypropylmethylcellulose" CHEMICAL & PHARMACEUTICAL BULLETIN, Bd. 41, Nr. 12, Dezember 1993, Seiten 2156-2160, XP000422466 Tokyo (JP) siehe das ganze Dokument	1-6,9, 10,15, 16, 18-20, 22-25, 30, 32-35, 38-46

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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

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INTERNATIONALER RECHERCHENBERICHT

Ir ationales Aktenzeichen
PCT/DE 98/01659

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

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X	DATABASE WPI Week 9439 Derwent Publications Ltd., London, GB; AN 94-313633 XP002090093 & JP 06 239764 A (SHINETSU CHEM IND CO LTD), 30. August 1994 siehe Zusammenfassung ---	1-6,9, 10,15, 16, 18-20, 22-25, 30, 32-35, 38-46
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E	DE 196 51 734 A (MÜLLER) 2. Juli 1998 siehe das ganze Dokument siehe Spalte 6, Zeile 31 - Zeile 58 ---	1-6, 8-16, 18-20, 26,28, 30, 33-35, 38-46
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(57) Abstract

The invention concerns novel derivatives of 3,3–diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

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Description

Novel derivatives of 3,3-diphenylpropylamines

The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to

result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine - a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage com-

pared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

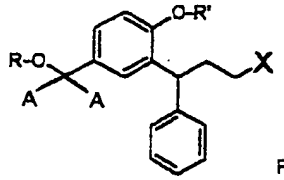
However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

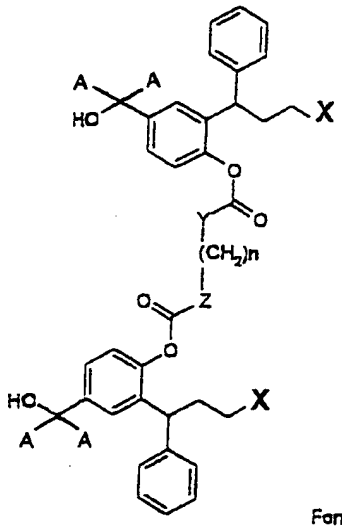
A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds

and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

According to the present invention, novel 3,3-diphenylpropyl-amines are provided, which are represented by the general formulae I and VII'



Formula I



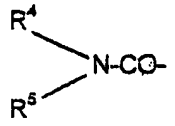
Formula VII'

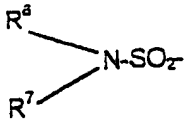
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

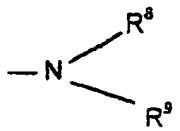
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

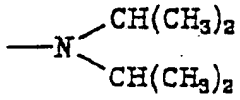
The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide and the like.

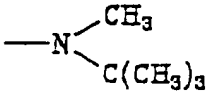
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

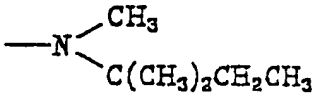
Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

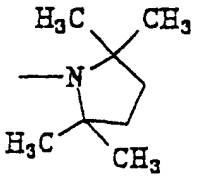
According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

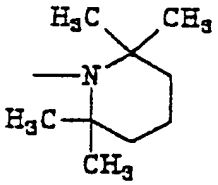
Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

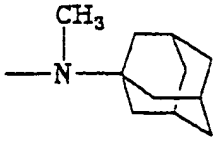
a) 

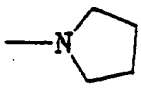
b) 

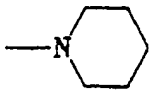
c) 

d) 

e) 

f) 

g) 

h) 

Group a) is particularly preferred.

The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

The term "substituted or unsubstituted benzyl" denotes a benyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen, nitro and the like. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-), anthryl- ($C_{14}H_9$-), etc. Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

The term "benzoyl" denotes an acyl group of the formula -CO-C_6H_5 wherein the phenyl ring may have one or more substituents.

Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro*. *As* substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and correponding carbohydrate groups are, for example, described in Aspinal, The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

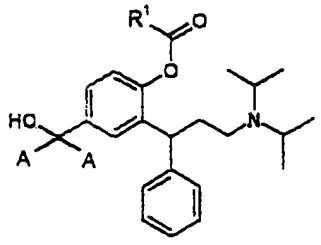
The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

The term "Bn" as used herein denotes a benzyl group.

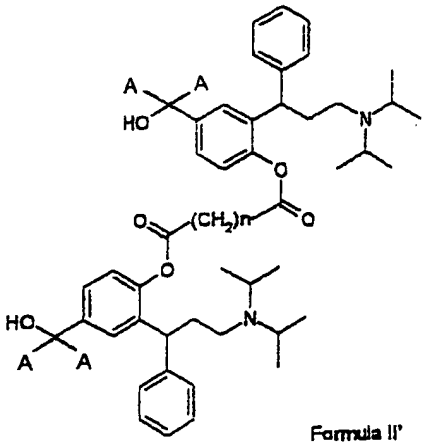
Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

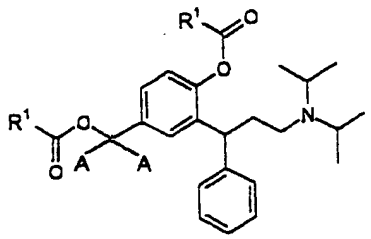
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



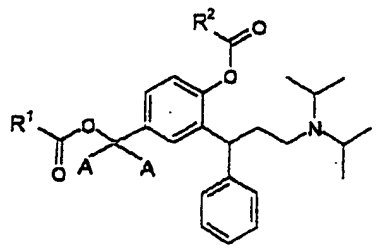
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is as defined above

and

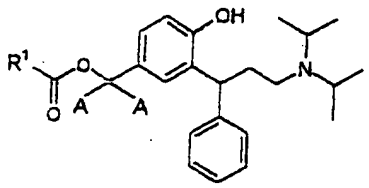
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



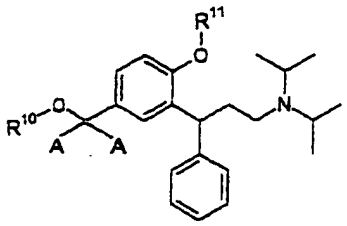
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

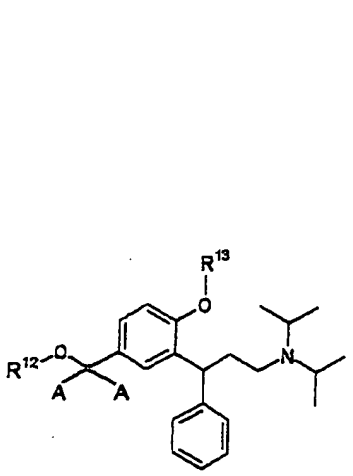
Particularly preferred ethers and silyl ethers are listed below:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

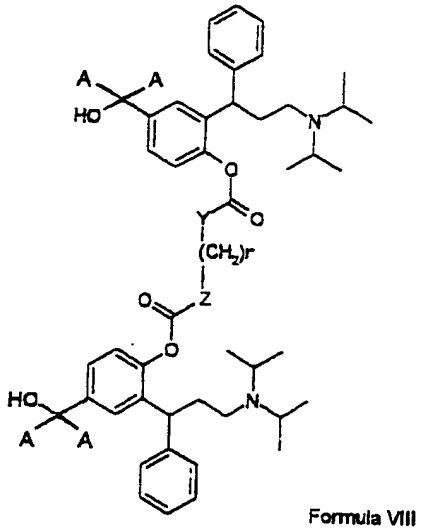
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

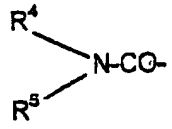


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

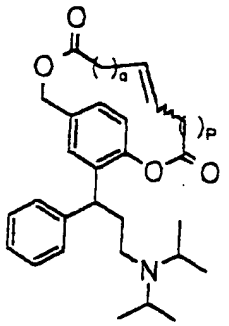
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

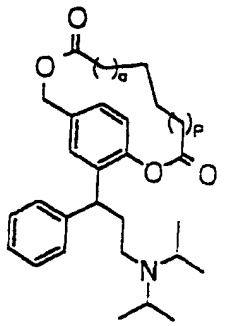
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



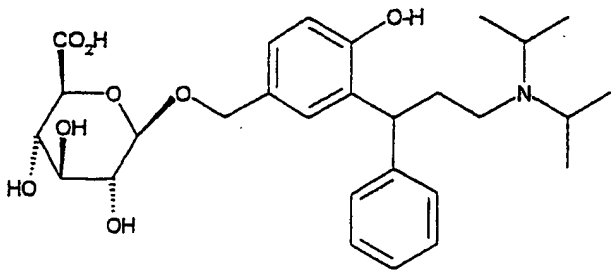
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

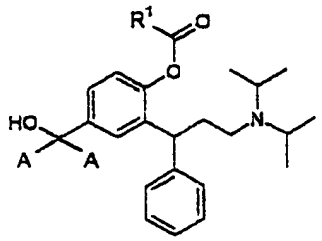


and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

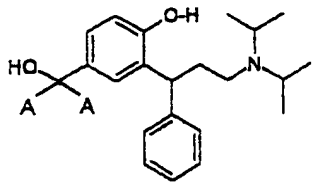
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

A process for the production of phenolic monoesters represented by the general formula II

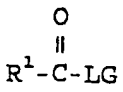


Formula II

as defined above, which comprises treatment of a compound of the formula

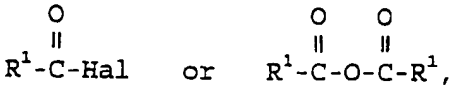


with an equivalent of an acylating agent selected from



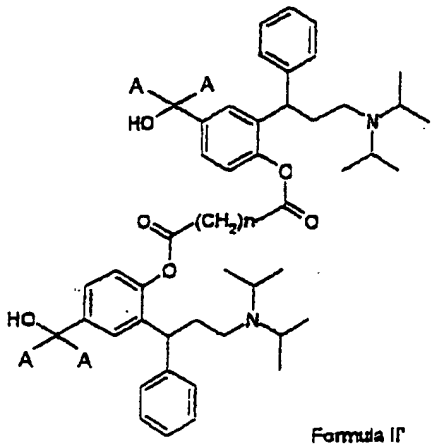
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

Preferably, the acylating agent is selected from



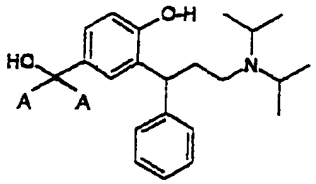
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is as defined above.

A process for the production of phenolic monoesters represented by the general formula II'

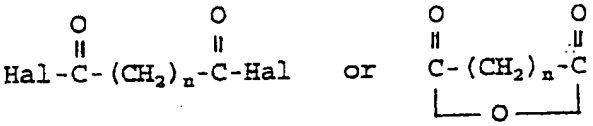


Formula II'

as defined above, which comprises treatment of two equivalents of a compound of the formula

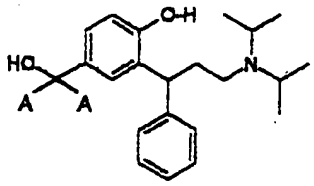


with an acylating agent selected from



wherein Hal represents a halogen atom, preferably a chlorine atom.

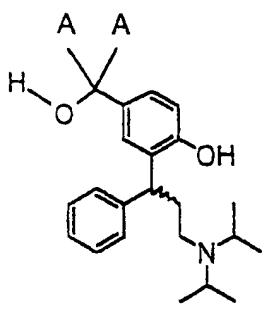
Hence, in these processes, an Intermediate B having the formula



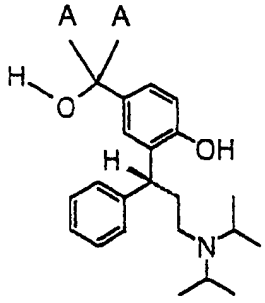
is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n

is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

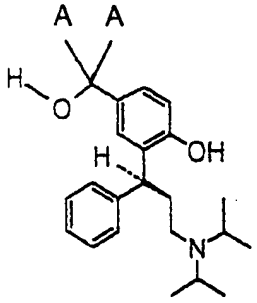
The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



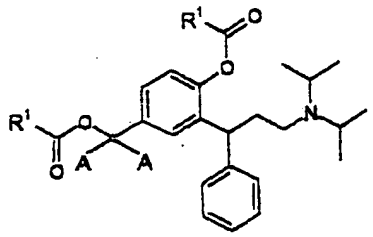
Intermediate R-(+)



Intermediate S-(-)

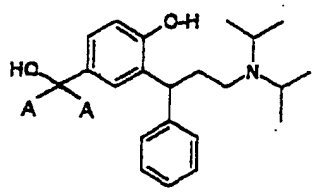
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III



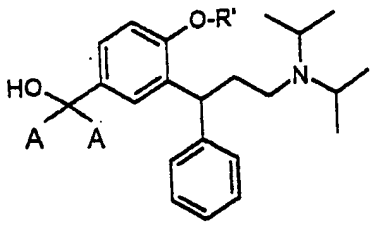
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



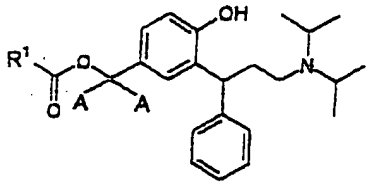
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



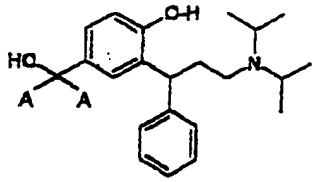
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes represented by the general formula V



Formula V

wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula

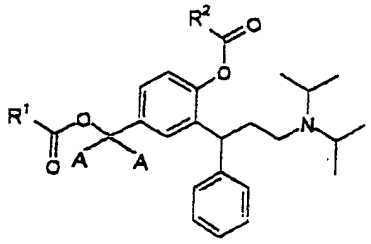


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room tempera-

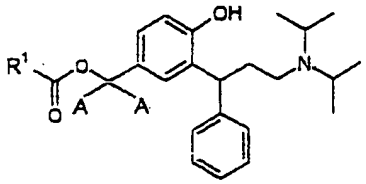
ture and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

The mixed diesters represented by the general formula IV



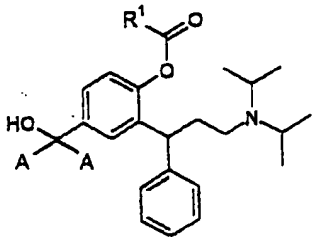
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

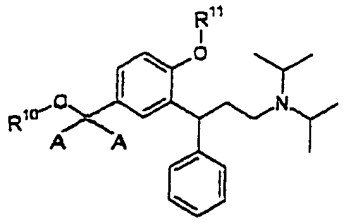


Formula II

as defined hereinbefore.

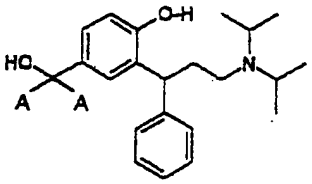
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI



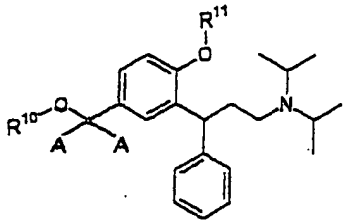
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



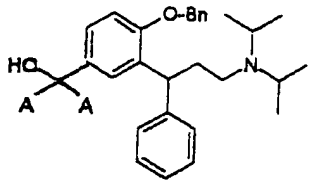
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

A further process for the preparation of ethers represented by the general formula VI

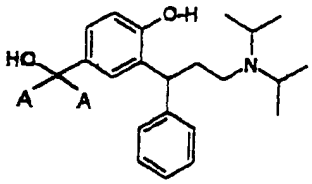


Formula VI

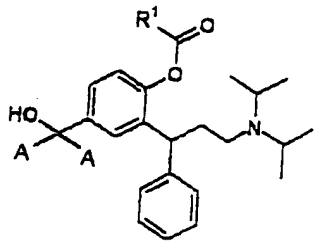
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

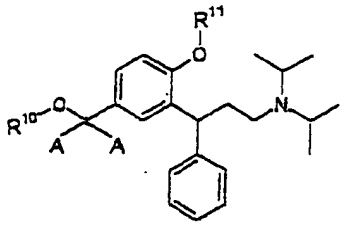


and



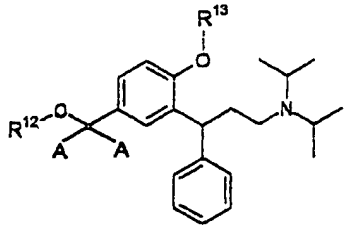
Formula II

or



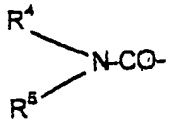
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or



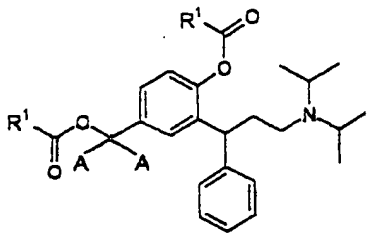
Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or

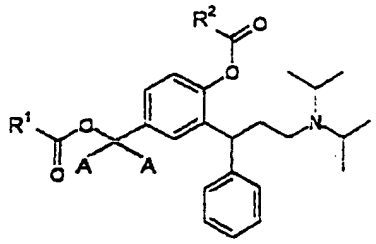


wherein R^4 and R^5 are as defined above

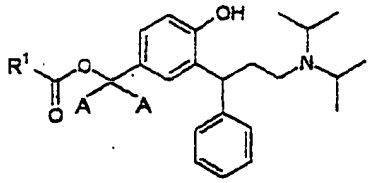
or of benzylic acylates selected from



Formula III



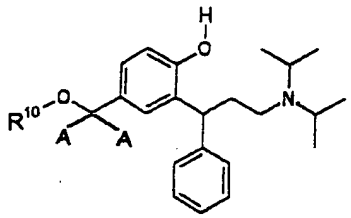
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

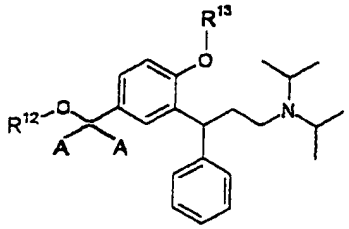


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

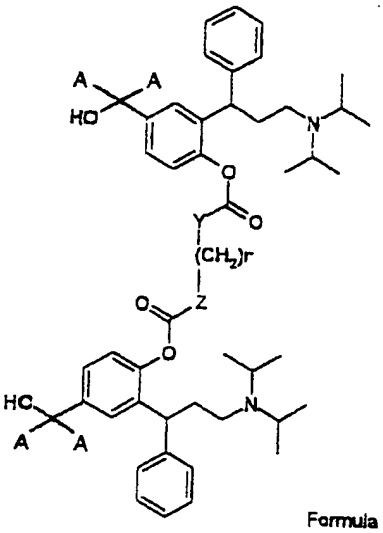
In summary, regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

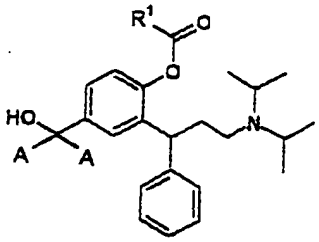


Formula VII

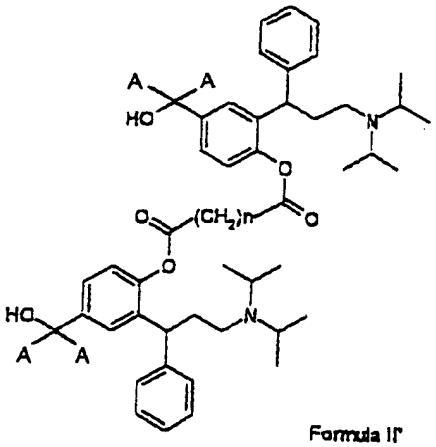


Formula VIII

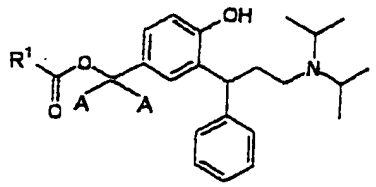
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



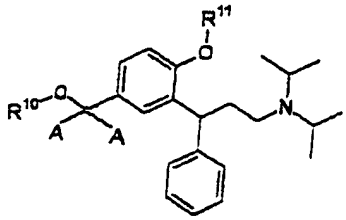
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, R^{10} or R^{11} is hydrogen with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents -C(=O)-Y-R^3, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in

the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^{1}H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.
Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%);(2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).
Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.
Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.
IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.
Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.
Combined liquid chromatography-mass spectrometry (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester

An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at

room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with ethylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline *(±)-6-bromo-4-phenylchroman-2-one*, m.p. 117.8°C, tlc: (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300 ml) and the extract was washed with water (2 x 200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46,

126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* (0,391 g, 0,92 mmol) in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid*, colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$): 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, $M^{+\cdot}$), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr): 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

Alternatively, the crude reaction mixture from the above described synthesis of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly

with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) **Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* (815.6 g, 1.85 mol) and 1S,2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$): 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

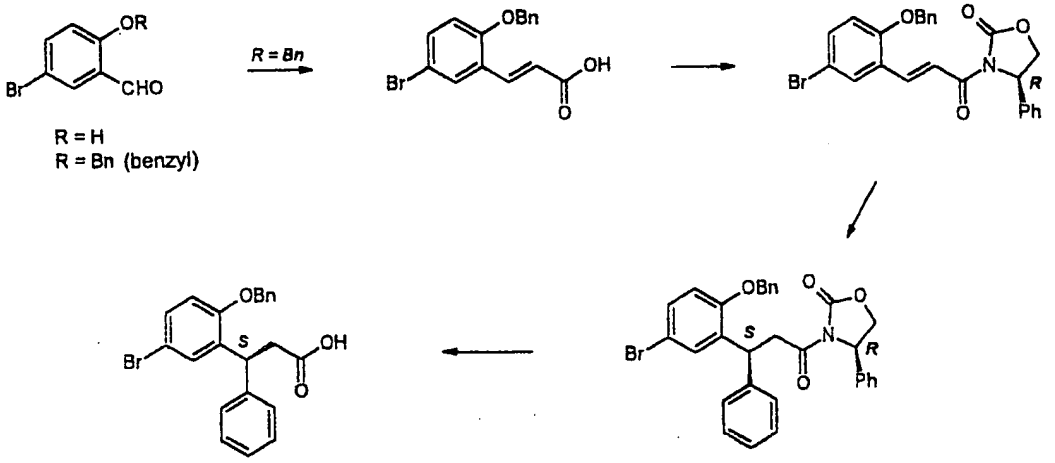
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-

heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$): 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) **Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**



2-Benzyloxy-5-bromobenzaldehyde

To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromo-benzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid

material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one

Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3-[3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

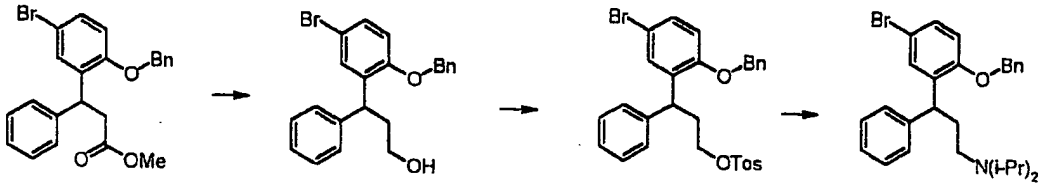
HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ = +21.6 (c = 0.5, MeOH).

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Conjugate organocuprate addition of phenylmagnesiumbromide to *3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystalliza-

tions, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) Synthesis of the R- and S- Enantiomers of Intermediate B

(i) Phenylpropanol Route



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8°C, tlc: (1) 0.47, *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol*. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

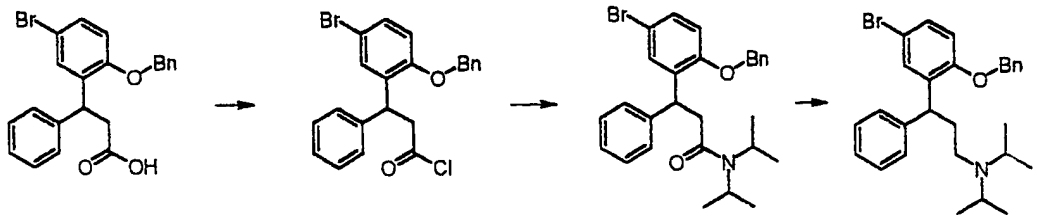
A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *(±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9%

yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route



S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride

Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 g). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temper-

ature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionamide

The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tetrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%) of the title compound as a viscous colourless oil, tlc:(4) 0.86. The NMR spectrum corresponds to the product, obtained from the

tosylate precursor (see above).

S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

The optical purities were determined by chiral HPLC using Chiralpak OD columns.

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

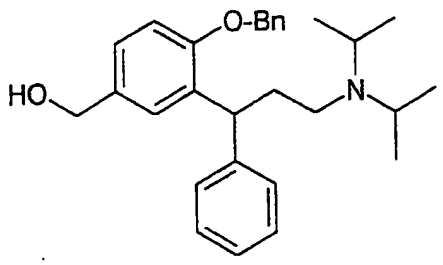
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to

pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol

Intermediate d_2-A (n = 2)

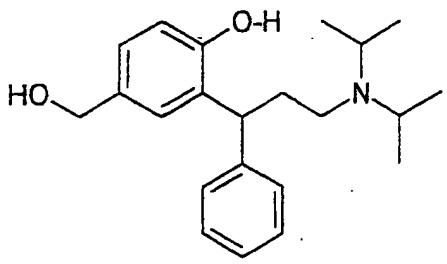
Repetition of the above described reduction of the methyl-ester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Intermediate B (n = 1)

A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, *(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50°C, tlc: (2) 0.15. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38.

Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *S-(-)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6): 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield,

colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).

R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water); NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.

S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

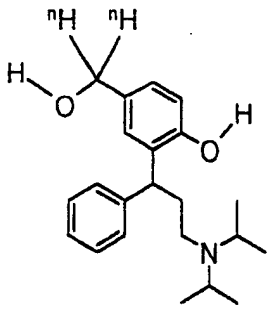
Intermediate d_2-B (n = 2)

A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave

(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol

as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

A solution of the above (±)-[4-benzyloxy-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc:(4) 0.57 (starting material 0.77). NMR ($CDCl_3$): 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



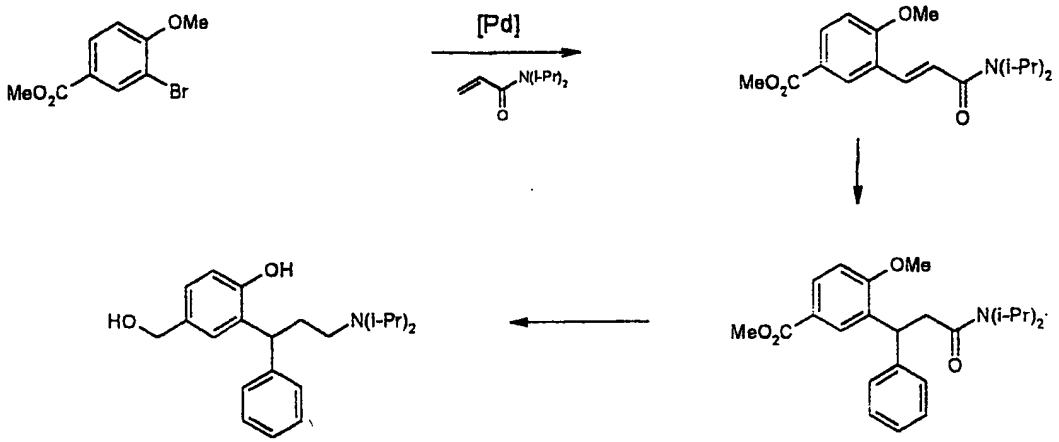
Intermediate d_2-B

n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B



Intermediate B

N,N-Diisopropyl-acrylamide

A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$): 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were

dried before use.

A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40.

NMR (CD_2Cl_2): 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07.

MS (EI, DI, 105°C): 319 ($M^{+\cdot}$, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxy-benzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclo-

hexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave

(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

as a viscous slightly yellow syrup (1.8 g, 44% yield).
NMR (CD_2Cl_2): 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C): 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room tem-

perature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of **S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate** in 33% yield, tlc: (4): 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD): 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ = -26.3 (c = 1.0, methanol).

Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:
(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
S-(+)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids
A stirred solution of (±)-*2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid monochloride for compounds of formula II, 2.50 mmol for compounds

of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.
The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids
Phenolic Monoesters
To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).

The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16,

43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-Cl (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-Cl (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$): 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI

(ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxy-methyl)phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$): 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$): 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%);gradually crystallized upon refrigeration; NMR ($CDCl_3$): 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70, 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 164.99.

*R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-*hydroxymethylphenyl ester
tlc R_f 0.30 (4); colourless syrup
Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform);
NMR ($CDCl_3$): 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81, 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.
LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$): 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
colourless syrup, tlc: (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%), 223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 ($M^{+\cdot}$, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$): 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 ($M^{+\cdot}$, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 ($M^{+\cdot}$, 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$): 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$): 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$): 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 ($M^{+\cdot}$, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$): 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 ($M^{+\cdot}$, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23,

64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.
Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* **37**: 45-58 [1954])

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethylsilyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$)- 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc: R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

(±)-n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76,

148.41, 171.68, 173.40; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR (DMSO-d_6): 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) Mixed diesters

Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Working up and physical properties corresponded to the bases and salts described above.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$): identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$): 17.14, 18.53,

21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropyl-amino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 hrs complete disappearence of the starting material (R_f = 0.45 (3)). The mixture was filtered and then evaporated under high vacuum (< 40°C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2); NMR ($CDCl_3$): 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

Molar equivalents of bases of formula VI (R^{11} = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl

derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%);
hydrochloride: amorphous hygroscopic colourless solid;
m.p. 161°C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol, tlc: R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 444.8 (100%), 398.4 (6%);
hydrochloride: colourless non-hygroscopic crystals, m.p. 158-161°C, NMR (CD_3OD): 15.43, 17.12, 18.82, 33.80, 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethyl-phenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65.
Hydrochloride: colourless crystals, m.p. 140.4°C, tlc (4) 0.61. LC-MS: 383 (6%, $[M-HCl]^{+\cdot}$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28,

39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxy-phenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

(±)-{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-di-methylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropyl-amine, tlc: R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7

(78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$): 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and carbonates

Mono N-substituted carbamates

A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloromethane (20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After

washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64°C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride
Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$): 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72,

130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3); NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 36.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

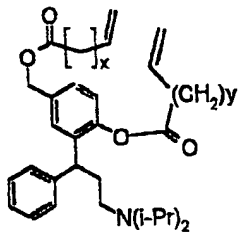
(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N,N-diethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

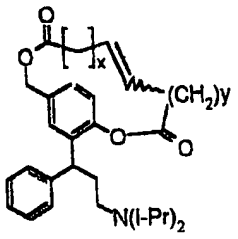
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6); dihydrochloride m.p. 142.5-145.6°C

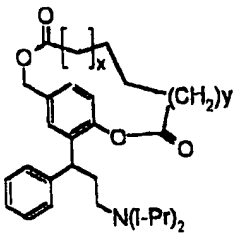
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

g) **Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)**







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy-*

methyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers. NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the

presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.

NMR ($CDCl_3$): 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.

The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate B of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$):

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm

CH resonances of the poly-lactyl chain: 5.10-5.30 ppm

CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.

Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{CH_2}$), 2.40-2.80 ($N\underline{CH_2}$), 3.30-3.50 ($N\underline{CH}$), 4.45-4.55 ($\underline{CH}CH_2$), 4.70-4.80 ($\underline{CH_2}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{CH}$).

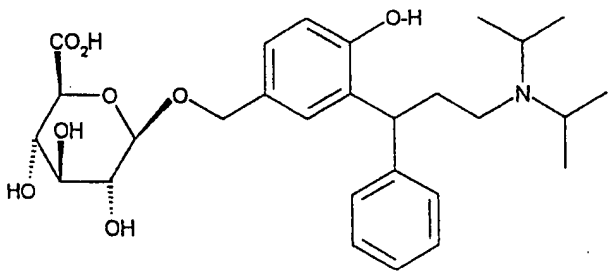
h) **Inorganic ester**

Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester
Hydrochloride

To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$): 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) **Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol**
((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropyl-amino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester*, colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol, sodium salt,

amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated

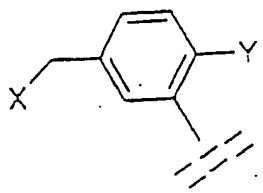
for 2 hrs at 37°C with 40 µM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:
The prodrugs introduced in the assay show the following chemical structure:



chemical structure	X-/-Y	
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate

iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
AcO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 µM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in

a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 μM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 μM) contractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	20
(-)HO-/-OH	680
(+)HO-/-OiBut	57
(+)HO-/-OBz	180
(+)BzO-/-OBz	220
(+)AcO-/-OiBut	240

These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

Different compounds of the invention were tested for their ability to penetrate the human skin (200 μm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV de-

tection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin

Prodrug	Flux rate [$\mu g/cm^2/24hrs$]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

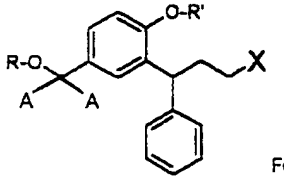
Disubstitution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

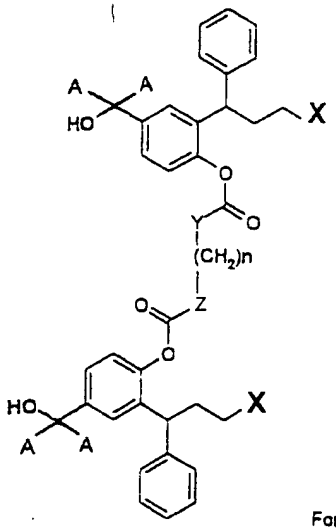
Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



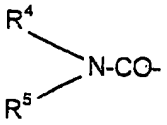
Formula VII'

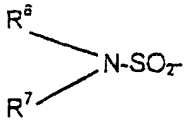
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

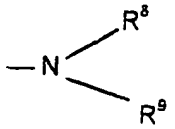
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

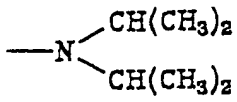
A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

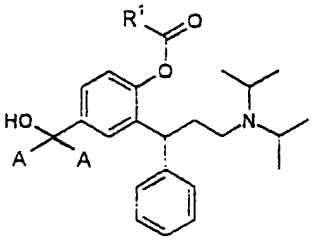
and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

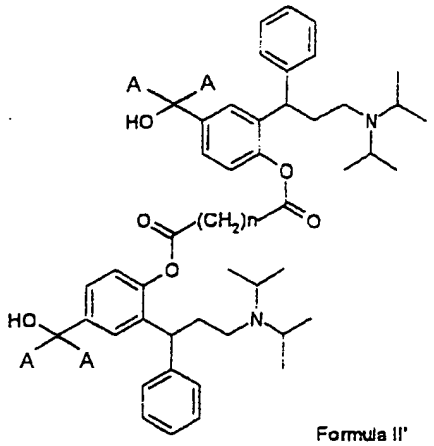
2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is



3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

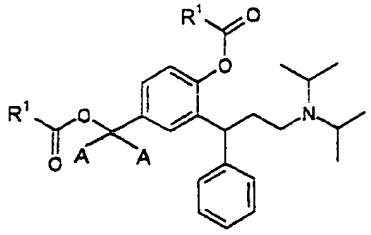
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



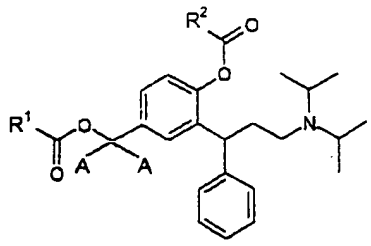
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is defined as in claim 3

and

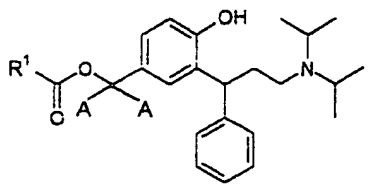
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropyl-amino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



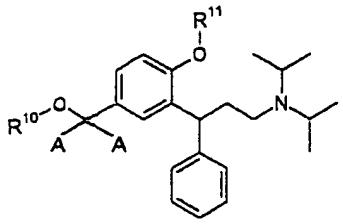
Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:
(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



Formula VI

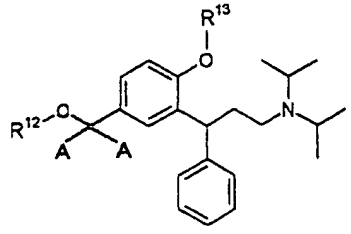
wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethyl-phenol,

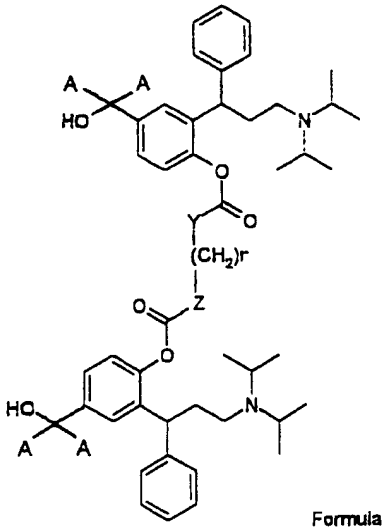
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-tri-methylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII

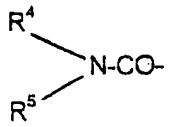


Formula VII



Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

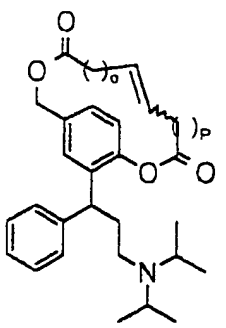
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

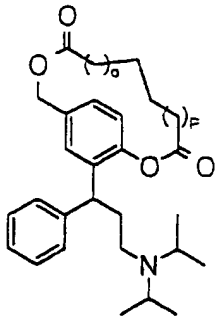
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



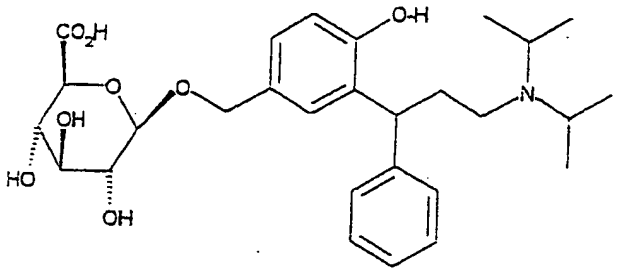
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenyl-propyl)-4-hydroxymethyl-phenol

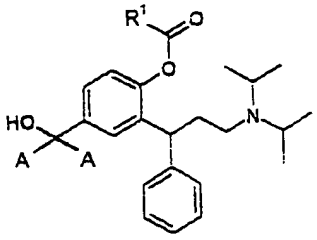
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and

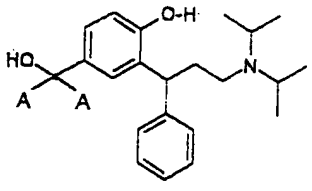
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II

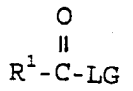


Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

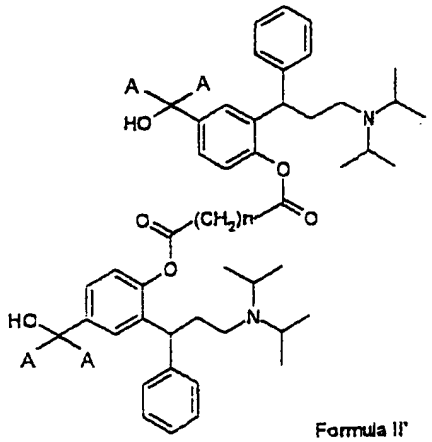


with an equivalent of an acylating agent selected from



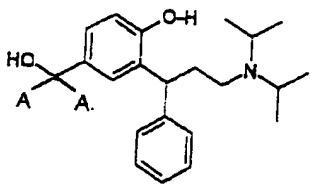
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'

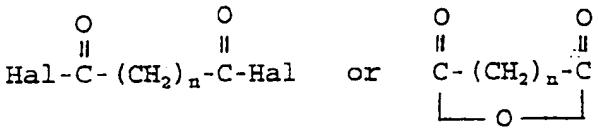


Formula II'

as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula

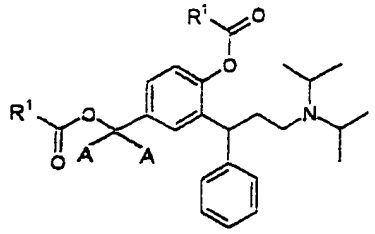


with an acylating agent selected from



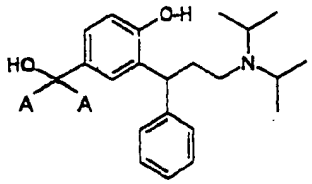
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



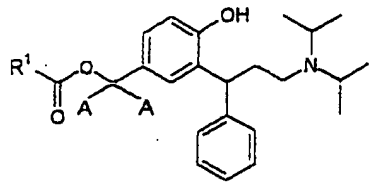
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



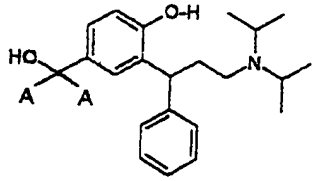
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



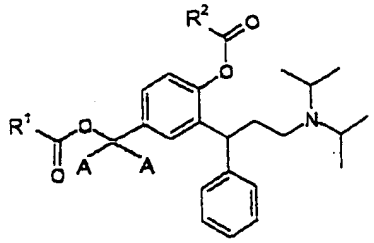
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



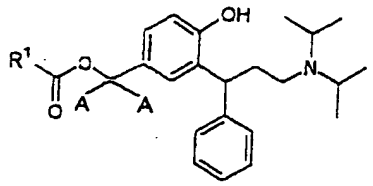
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

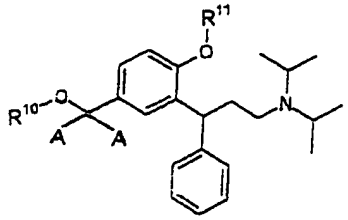
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

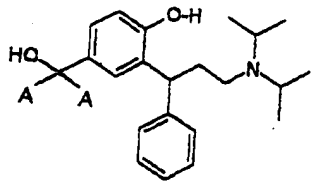
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



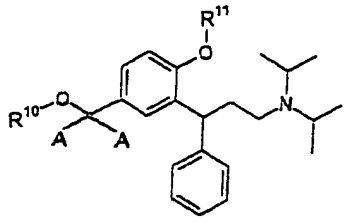
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



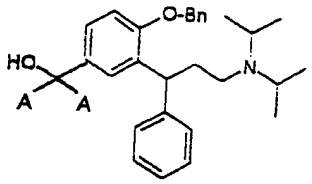
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

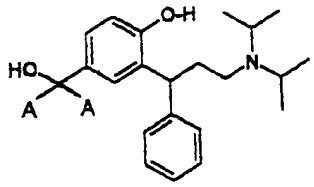


Formula VI

wherein R^{10} and R^{11} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and



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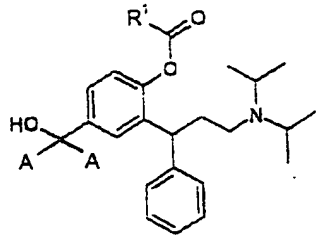
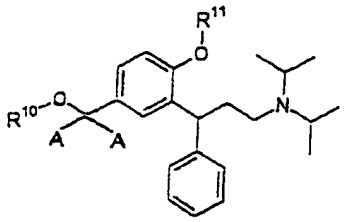


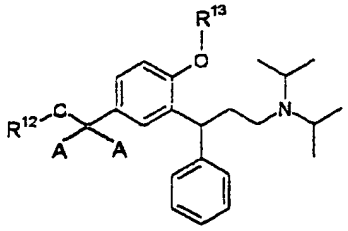
Formula II

or



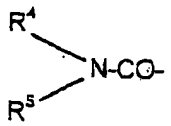
Formula VI

wherein R^{10} is hydrogen or

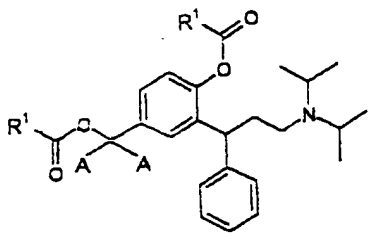


Formula VII

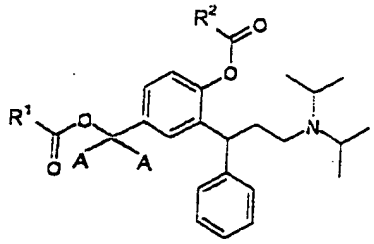
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



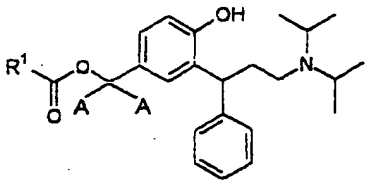
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



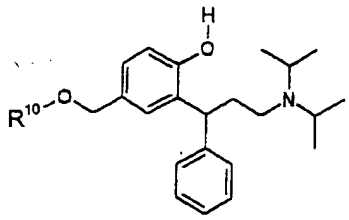
Formula IV



Formula V

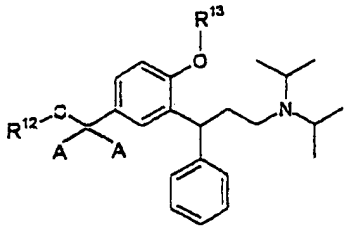
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

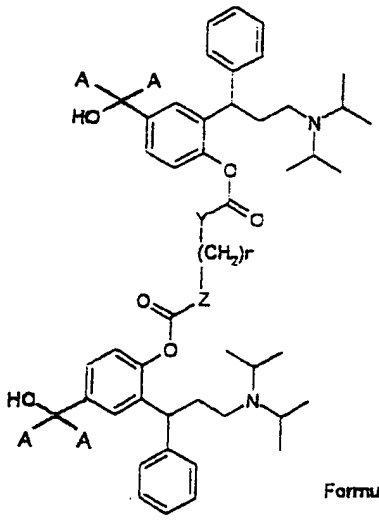


with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

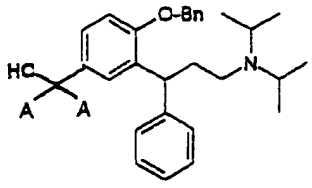


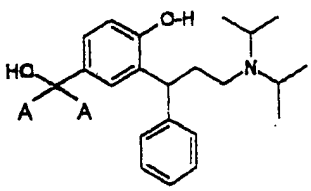
Formula VII

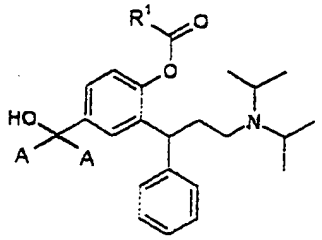


Formula VIII

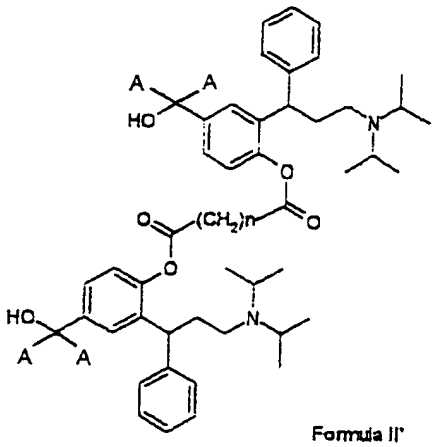
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



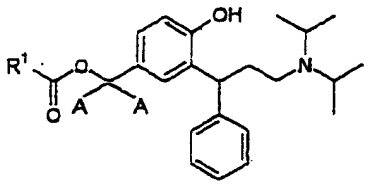




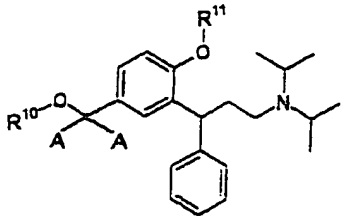
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

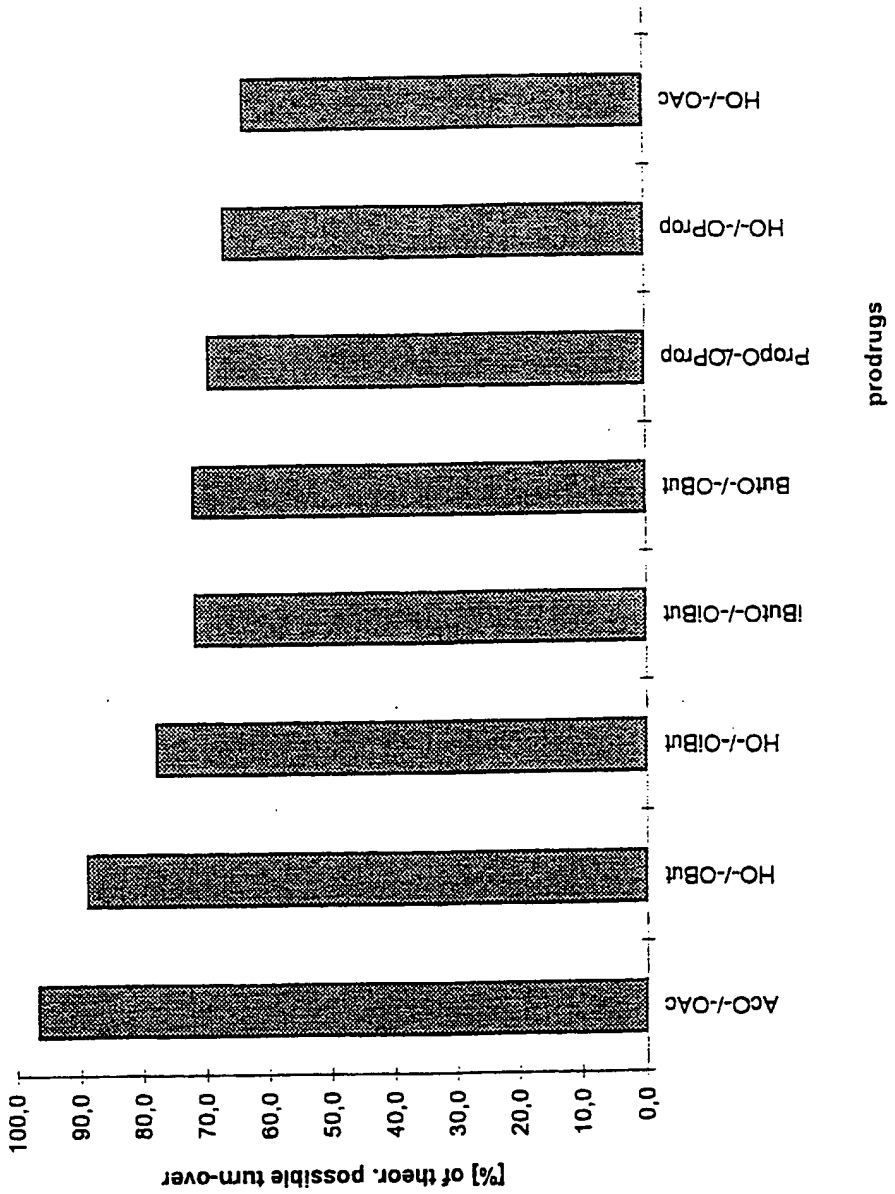
25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

26. A pharmaceutical composition comprising a 3,3-diphenylpropylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

FIG. 1

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h



INTERNATIONAL SEARCH REPORT

Inter. onal Application No
PCT/EP 99/03212

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C1/00 C07C217/62 C07C217/48 C07C219/28 C07C219/22
C07D207/06 C07D295/06 C07C271/08 C07F7/18 C07C307/02
A61K31/135 A61K31/325 A61K31/40 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 (1994-05-26) cited in the application page 12, line 35 - page 13, line 15 ---	1-3,5,9, 25-27
A	WO 89 06644 A (KABIVITRUM AB) 27 July 1989 (1989-07-27) abstract ---	1-3, 25-27
A	LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 cited in the application the whole document -----	1,25-27

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Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1999	26/07/1999

Name and mailing address of the ISA	Authorized officer
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Information on patent family members

Inter. onal Application No
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9803871-4 11 November 1998 (11.11.98) SE

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(74) Agents: WIDÉN, Björn et al.; Pharmacia & Upjohn AB, S-112 87 Stockholm (SE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

(57) Abstract

A method and formulation for treating unstable or overactive urinary bladder, wherein tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, is administered to a patient in a pharmaceutically effective amount thereof through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a controlled rate for at least 24 hours.

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THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

The present invention relates to an improved method of treating unstable or overactive urinary bladder as well as a formulation therefor.

A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Oxybutynin, which chemically is the DL-racemic form of 4-diethylamino-2-butynyl-phenylcyclohexylglycolate, is given orally, usually as a tablet or syrup. Oxybutynin, usually administered as the chloride salt, is metabolized to an active metabolite, N-desethyl-oxybutynin. The drug is rapidly absorbed from the gastrointestinal tract following administration and has a duration of from three to six hours. While the effectiveness of oxybutynin has been well documented, its usefulness is limited by classical antimuscarinic side-effects, particularly dry mouth, which often leads to discontinuation of treatment.

WO 96/12477 discloses a controlled release delivery system for oxybutynin, which delivery system is said not only to be of convenience to the patient by reducing the administration to a once daily regimen, but also to reduce adverse side-effects by limiting the initial peak concentrations of oxybutynin and active metabolite in the blood of the patient.

The alleged relief of side-effects by reducing or eliminating peak concentrations through administration of the controlled release delivery system is, however, contradicted by a later published clinical report, Nilsson, C. G., et al., Neurourology and Urodynamics 16 (1997) 533-542, which describes clinical tests performed with the controlled release delivery system disclosed in WO 96/12477 above. In the clinical tests reported, a 10 mg controlled release oxybutynin tablet was compared with the administration of a conventional (immediate release) 5 mg tablet given twice daily to urge incontinent patients. While high peak levels of the drug obviously were eliminated with the controlled release oxybutynin tablet, no difference in side-effects between the controlled release tablet and the conventional tablet was observed. The advantage of the controlled release tablet thus resided merely in enhancing treatment compliance by its once-a-day dosage rather than also reducing side-effects as stated in WO 96/12477.

Recently, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195-207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647-655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287-295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

According to the present invention it has now surprisingly been found that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

In one aspect, the present invention therefore provides a method of treating unstable or overactive urinary bladder, which method comprises administering to a (mammal) patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a

controlled rate for at least 24 hours. It is preferred that the dosage form formulation is capable of maintaining a substantially constant serum level of the active moiety or moieties for said at least 24 hours.

Overactive urinary bladder encompasses detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency.

As mentioned above, the chemical name of tolterodine is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine. The term "tolterodine-related compound" is meant to encompass the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms thereof.

By the term "active moiety or moities" is meant the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the release profile of the controlled release formulation

should essentially not exhibit any peak values. This may, more sophistically, also be expressed by reference to the "flucuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve) for dosage interval τ, and τ is the length of the dosage interval. Thus, according to the present invention, the controlled release formulation should provide a mean fluctuation index (for n being at least 30) that is usually not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average (blood) serum or plasma levels are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. WO 89/06644. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the

(S)-5-hydroxymethyl metabolite), it may be referred to WO 94/11337. The (S)-enantiomer and its use in the treatment of urinary and gastrointestinal disorders is described in WO 98/03067.

In another aspect, the present invention provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

Still another aspect of the present invention provides the use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides a controlled release of tolterodine or said tolterodine-related compound, or salt thereof at a controlled rate for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

The controlled release formulation is preferably an oral delivery system or a transdermal preparation, such as a transdermal patch, but also other controlled release forms may, of course, be contemplated, such as buccal tablets, rectal suppositories, subcutaneous implants, formulations for intramuscular administration.

An exemplary type of oral controlled release formulation, a specific embodiment of which is described in Example 1 below, is a multi-unit formulation comprising controlled-release beads. Each bead comprises (i) a core unit of a water-soluble, water-swellable or water-insoluble inert material (having a size of about 0.05 to 2 about 2 mm), such as e.g. a sucrose sphere; (ii) a first layer on the core of a substantially water-insoluble (often hydrophilic) polymer (this layer may be omitted in the case

of an insoluble core, such as e.g. of silicon dioxide), (iii) a second layer of a water-soluble polymer having an active ingredient dissolved or dispersed therein, and (iv) a third polymer layer effective for controlled release of the active ingredient (e.g. a water-insoluble polymer in combination with a water-soluble polymer).

In the case of an oral controlled release formulation for once-daily administration, the dosage of tolterodine (or tolterodine related compound) is, for example, 4 mg or 6 mg.

A transdermal patch for tolterodine or tolterodine-related compound is described in our co-pending international application "Transdermally administered tolterodine as antimuscarinic agent for the treatment of overactive bladder" (based on Swedish patent application no. 9802864-0, filed on 27 August 1998), the full disclosure of which is incorporated by reference herein. Illustrative patch formulations are described in Example 2 below.

With the guidance of the disclosure herein, the skilled person may either adapt controlled release administration forms, such as tablets, capsules, patches etc, known in the art, to obtain the objectives of the present invention, or design modified or new controlled release administration forms.

The invention is illustrated by the following Examples, without, however, limiting the scope of the invention in any way. Percentages are by weight, unless otherwise stated. Reference will be made to the accompnaying drawings, in which:

Figure 1 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through (i) an immediate release tablet (2 mg) twice daily as in the prior art, and (ii) a controlled release capsule (4 mg) once daily in accordance with the present invention;

Figure 2 is a diagram showing the variation of the basal salivation (g/min) with time (hours) during 4 hours after administration of (i) a 4 mg tolterodine controlled release capsule in accordance with the present invention, (ii) a prior art tolterodine immediate release tablet, and (iii) placebo; and

Figure 3 is is a bar chart diagram showing patients' individual estimates of experienced dry mouth side effect (no dry mouth, mild, moderate, severe) after administration of tolterodine through (i) a conventional 2 mg immediate release tablet, (ii) controlled release capsules of 4, 6 and 8 mg, respectively, according to the present invention, and (iii) placebo.

EXAMPLE 1

TOLTERODINE ORAL CR CAPSULE AND IR TABLET

Preparation of tolterodine CR capsules 2 mg and 4 mg

A controlled release (CR) capsule containing non-pareil beads coated by (i) an ethylcellulose layer, (ii) a tolterodine/HPMC layer, and (iii) a sustained release ethylcellulose/HPMC layer was prepared as follows:

1200 g of (starch-containing) sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated with the following three coating solutions:

- (1) a Surelease® sealcoating solution prepared by mixing 788 g of Surelease® with 563 g of purified water (Surelease® is an aqueous filmcoating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil; manufactured by Colorcon, Inc., West Point, PA, U.S.A.);
- (2) a suspension prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of Hypromellose, 5cP (hydroxypropylmethyl cellulose (HPMC)); and

- (3) a sustained release coating solution prepared by mixing 29 g of Hypromellose, 5 cP, with 375 g of purified water, and then mixing with 695 g of Surelease®.

After drying, the coated spheres were filled into hard gelatin capsule shells (size 3, white/white) to obtain 2 mg and 4 mg capsules, respectively, of the composition (filling mass for 2 mg capsule, 169-207 mg/capsule):

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	69 mg	137 mg
Surelease®	21 mg	42 mg
Hypromellose, 5cP	2.0 mg	4.1 mg

Tolterodine L-tartrate IR tablets 2 mg

Commercially available tolterodine L-tartate 2 mg tablets for immediate release (IR) (Detrusitol®, Pharmacia & Upjohn AB, Sweden) were used. The tablets had the following composition:

Core

Tolterodine L-tartrate	2.0 mg
cellulose, microcrystalline	53.4 mg
calcium hydrogen phosphate dihydrate	18.0 mg
sodium starch glycollate	6.0 mg
magnesium stearate	0.4 mg
colloidal anhydrous silica	0.2 mg

Coating

Methylhydroxypropyl cellulose	1.5 mg
cellulose, microcrystalline	0.3 mg
stearic acid	0.6 mg
titanum dioxide E 171	0.6 mg

PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

A clinical trial was performed in patients with overactive bladder to determine the pharmacodynamic and pharmacokinetic effects of different daily doses of (i) the above described tolterodine controlled release capsule (below referred to as TOD), compared with (ii) the above described tolterodine immediate release tablet (below referred to as TIR), and (iii) a placebo capsule (containing sugar spheres only). The trial was performed as a double-blind, double dummy, cross-over trial in 60 patients for three one week periods and six treatments (2, 4, 6 and 8 mg TOD once daily, 2 mg TIR twice daily, and placebo). All patients were randomised to three out of six treatments, meaning that 30 patients were subjected to each of the treatments. Pharmacodynamic and pharmacokinetic measurements were performed on day seven in each treatment period. The determinations included measurements of (i) serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time, (ii) salivation (dry mouth), and (iii) residual urine volumes.

Serum concentrations of tolterodine and main metabolite

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136). Figure 1 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily, and, on the other hand, the administration of a 2 mg TIR tablet

twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI = (Cmax - Cmin)/AUCτ/τ, where τ is the length of the dosage interval and AUCτ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.40 (95% CI 1.95-2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59-0.78) for the TOD capsule.

Salivation (dry mouth)

Salivation was measured using dental cotton rolls applied in the mouth for 3 x 2 minutes. Measurements were performed before breakfast and thereafter after each blood sample on day seven in each treatment period. Based on all measurements after dosing, the mean salivation during 12 hours was calculated. The basal salivation at steady state was measured after treatment with (i) 4 mg TOD capsule, (ii) 2 mg TIR tablet, and (iii) placebo. The results are presented in Figure 2. As can be seen in the Figure, the salivation is substantially constant during the period shown for the TOD capsule, whereas a considerable reduction in salivation (i.e. drier mouth) is obtained with the TIR tablet.

While Fig. 2 shows the total salivation as measured, the degree of salivation, or dry mouth, was also determined, based on the patient's estimate of experienced intensity of the phenomenon. The results for 2 mg TIR tablet b.i.d., 4 mg TOD capsule, 6 mg TOD capsule and 8 mg TOD capsule, are presented in bar chart form in Figure 3.

The four bars for each dosage represent, from left to right in the figure, no dry mouth, mild, moderate, and severe, respectively.

As apparent from Fig. 2, the dry mouth intensity for the TIR 2 mg b.i.d. tablet is clearly higher than that of the TOD 4 mg capsule, and about twice that dosage, i.e. TOD 8 mg, is required to match the adverse dry mouth effects of the TIR 2 mg b.i.d. tablet.

The results from the salivation determinations thus show that flattening of the concentration peaks of the "active moiety" (i.e. tolterodine plus 5-HM) leads to a substantial reduction of the undesired dry mouth effect.

Residual urine volume

Residual volume is the volume of urine left in the bladder immediately after voiding. Measuring residual volume offers a method of assessing the effect of antimuscarinic treatment on the bladder. In fact, it offers a measure of efficacy (change in residual volume) as well as safety (urinary retention, i.e. inability to pass urine). Efficacy may thus be measured as the mean residual volume per unit of time, and safety as any case where the residual urine exceeds a fixed level. The mean residual volume per micturition was measured by a non-invasive (ultrasonic) method for placebo, TIR tablet 2 mg b.i.d., and for capsules TOD 2 mg, TOD 4 mg, TOD 6 mg, and TOD 8 mg.

The results are presented in Tables 1 and 2 below. Table 1 shows the mean residual volume per micturition, and Table 2 shows the maximum residual volume during 12 hours.

The results presented clearly demonstrate that the TOD capsule dosages are as efficacious as the corresponding TIR b.i.d dosages, and also that the TOD dose may be increased up to 8 mg daily and still be safe with regard to urinary retention.

Table 1

Mean Residual Volume per micturition (ml)

	Placebo	TIR 2mg b.i.d	TOD 2mg	TOD 4mg	TOD 6mg	TOD 8mg
Estimated mean	29	62	40	59	69	77
95% confidence interval	12 to 46	45 to 79	26 to 55	51 to 66	60 to 78	65 to 89
Estimated difference vs. IR			-22	-4	7	14
			-44 to 1	-23 to 15	-13 to 26	-7 to 36

Table 2

Maximum Residual Volume during 12 hours

	Placebo	TIR 2mg b.i.d	TOD 2mg	TOD 4mg	TOD 6mg	TOD 8mg
Median value (ml)	46	72	45	55	87	77
min-max	5-267	10-316	0-192	0-349	0-360	0-390

The results from the clinical trial described above demonstrate that a flatter serum concentration of active moiety (tolterodine plus 5-HM) not only does not lead to a loss of efficacy or to untoward side-effects, primarily urinary retention, but, importantly, also provides for a reduced dry mouth effect (unaffected or less reduced salivation).

EXAMPLE 2

TOLTERODINE TRANSDERMAL PATCH FORMULATION

Tolterodine-releasing patches were prepared as follows:

System 1 (drug-in-adhesive, acrylate)

5 g of tolterodine base were dissolved in 11 g of ethanol and added to 20 g of Durotak 387-2287 (National Starch & Chemical, U.S.A.). The drug gel was coated onto a backing membrane (Scotchpak 1012; 3M Corp., U.S.A.) by using a coating equipment (RK Print Coat Instr. Ltd, Type KCC 202 control coater). The wet layer thickness was 400 µm. The laminate was dried for 20 min. at RT and then for 30 min. at 40°C. A polyester release liner (S 2016; Rexam Release) was laminated onto the dried drug gel. The sheet was cut into patches and stored at 2-8°C until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,5 mg/cm².

System 2 (multi-laminate, acrylate)

5 g of tolterodine base were dissolved in 10 ml of ethanol. A mix of 6,4 g of Eudragit RL 100 (Röhm GmbH Chemische Fabrik, Germany) and 6,4 of ethanol and a mix of 2,6 g of Polyvidone 90 (BASF, Germany) and 10,2 g of ethanol were added to the solution of tolterodine base in ethanol. Finally, 4 g of propylene glycol were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment above. The wet layer thickness was 400 µm. The laminate was then dried at 40°C for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80°C for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2-8°C until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,0 mg/cm².

System 3 (multi-laminate, water-based acrylate)

1 g of tolterodine base was mixed with Tween 80 (Merck) by heating to 60 - 70°C. 1,8 g of triethylacetate and 1,3 g of dem. water was added to the mix. The final mix was then added to 25 g of Eudragit RL 30 D (Röhm GmbH Chemische Fabrik, Germany). Finally, 180 mg of 1 N NaOH

were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment. The wet layer thickness was 400 µm. The laminate was dried at 40°C for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80°C for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2-8°C until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 0,5 mg/cm².

CLAIMS

1. A method of treating unstable or overactive urinary bladder, wherein the method comprises administering to a patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a controlled rate for at least 24 hours.

2. The method according to claim 1, wherein the formulation is capable of maintaining a substantially constant serum level of the active moiety or moieties for said at least 24 hours.

3. The method according to claim 2, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

4. The method according to claim 1, 2 or 3, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

5. The method according to claim 1, 2 or 3, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum

level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

6. The method according to any one of claims 1 to 5, wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

7. The method according to any one of claims 1 to 5, wherein the controlled release formulation is a transdermal preparation, preferably a transdermal patch.

8. The method according to any one of claims 1 to 7, wherein tolterodine is administered.

9. A pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

10. The formulation according to claim 9, which provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as $FI = (Cmax - Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

11. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of unbound

tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

12. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

13. The formulation according to any one of claims 9 to 12, which is a capsule or tablet for oral administration once daily.

14. The formulation according to any one of claims 1 to 12, which is a transdermal preparation, preferably a transdermal patch.

15. The formulation according to any one of claims 9 to 14, which provides controlled release of tolterodine.

16. Use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

17. The use according to claim 16, wherein a formulation according to any one of claims 10 to 15 is manufactured.

18. A method for providing a continuous plasma concentration of tolterodine-related active moiety in a patient, wherein the method comprises administering a

dosage form formulation comprising tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, that is administered over at least 24 hours to the patient at a controlled and sustained rate to provide the desired plasma active moiety concentration.

19. The method according to claim 18, wherein the dosage form formulation is administered orally.

AMENDED CLAIMS

[received by the International Bureau on 10 February 2000 (10.02.00);
original claims 1-19 replaced by new claims 1-17 (3 pages)]

1. A method of treating unstable or overactive urinary bladder, wherein the method comprises administering to a patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through a controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or moieties for at least 24 hours.

2. The method according to claim 1, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as $FI = (Cmax - Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

3. The method according to claim 1 or 2, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

4. The method according to claim 1, 2 or 3, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

5. The method according to any one of claims 1 to 4, wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

6. The method according to any one of claims 1 to 4, wherein the controlled release formulation is a transdermal preparation, preferably a transdermal patch.

7. The method according to any one of claims 1 to 6, wherein tolterodine is administered.

8. The method according to any one of claims 1 to 6, wherein urinary incontinence is treated.

9. A pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

10. The formulation according to claim 9, which provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as $FI = (Cmax - Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

11. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of

unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

12. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

13. The formulation according to any one of claims 9 to 12, which is a capsule or tablet for oral administration once daily.

14. The formulation according to any one of claims 1 to 12, which is a transdermal preparation, preferably a transdermal patch.

15. The formulation according to any one of claims 9 to 14, which provides controlled release of tolterodine.

16. Use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

17. The use according to claim 16, wherein a formulation according to any one of claims 10 to 15 is manufactured.

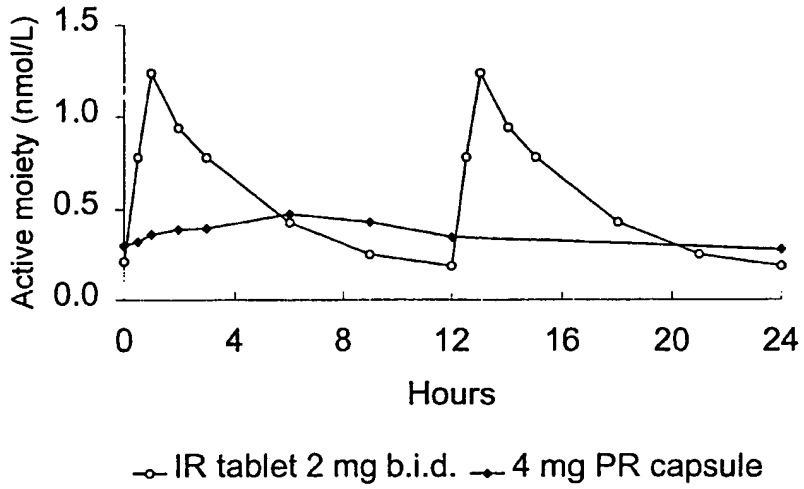

FIG. 1

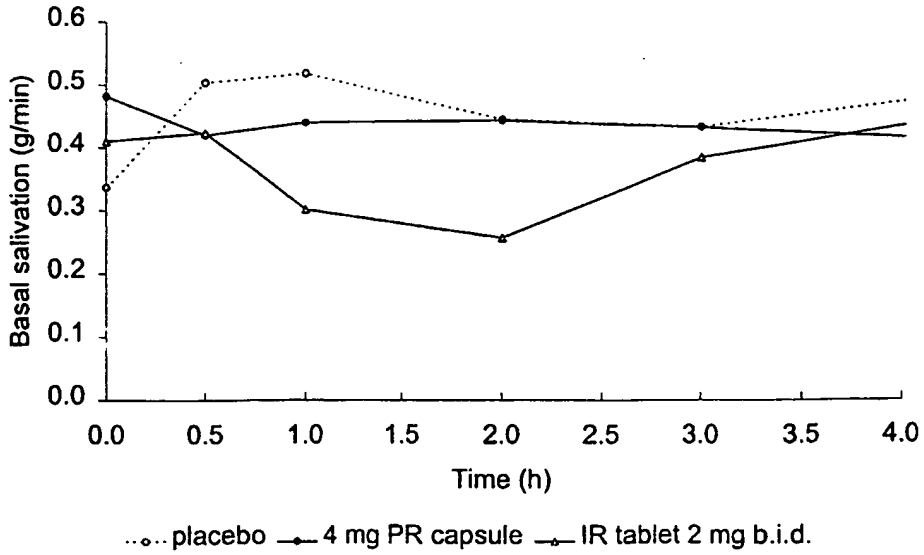

FIG. 2

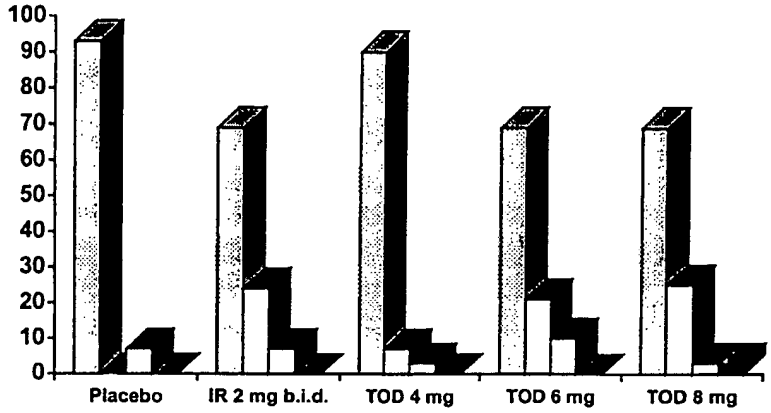

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01463

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/22, A61K 9/52, A61K 9/70, A61K 31/135, A61P 13/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9803067 A1 (ÅBERG, GUNNAR), 29 January 1998 (29.01.98), abstract, second paragraph on page 4, third paragraph on page 5 and claims 12 and 13	1-19
A	WO 9811888 A1 (AMERICAN HOME PRODUCTS CORPORATION), 26 March 1998 (26.03.98), page 3, line 5; page 3, line 20 - line 25	1-19
A	WO 9612477 A1 (LEIRAS OY), 2 May 1996 (02.05.96)	1-19
A	WO 9323025 A1 (ALZA CORPORATION), 25 November 1993 (25.11.93)	1-5,7-12, 14-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 1999	19 January 2000 (19.01.00)
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson / MR Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01463

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-8, 18-19
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01463

Remark: Claims 1-8,18-19 are directed to methods of treatment of the human or animal body by terapy methods practised on the human or animal body/Rule 39.1(iv) Nevertheless a search has been executed for these claims. The search has been based on the alleged effects of the copositions.

INTERNATIONAL SEARCH REPORT

02/12/99

International application No.
PCT/SE 99/01463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803067 A1	29/01/98	AU 3725997 A	10/02/98
		CA 2259012 A	29/01/98
		EP 0924983 A	30/06/99
WO 9811888 A1	26/03/98	AU 4421697 A	14/04/98
		EP 0927034 A	07/07/99
WO 9612477 A1	02/05/96	AU 7994694 A	15/05/96
WO 9323025 A1	25/11/93	AT 185694 T	15/11/99
		AU 666735 B	22/02/96
		AU 4247393 A	13/12/93
		CA 2132865 A	25/11/93
		DE 69326848 D	00/00/00
		EP 0767659 A,B	16/04/97
		FI 945311 A	11/11/94
		JP 8502952 T	02/04/96
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		ZA 9303349 A	15/06/94

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A1

(11) International Publication Number: **WO 00/27364**

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Published
With international search report.

(54) Title: NEW CONTROLLED RELEASE BEAD, A METHOD OF PRODUCING THE SAME AND MULTIPLE UNIT FORMULATION COMPRISING IT

(57) Abstract

A controlled release bead comprises: (i) a core unit of a substantially water-soluble or water-swellable inert material; (ii) a first layer on the core unit of a substantially water-insoluble polymer; (iii) a second layer covering the first layer and containing an active ingredient; and (iv) a third layer of polymer on the second layer effective for controlled release of the active ingredient, wherein the first layer is adapted to control water penetration into the core. A method of producing the controlled release bead is also disclosed.

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NEW CONTROLLED RELEASE BEAD, A METHOD OF PRODUCING THE SAME AND MULTIPLE UNIT FORMULATION COMPRISING IT

The present invention relates to pharmaceutical controlled release beads comprising a drug, to a formulation containing said controlled release beads, and to a method of preparing said beads.

A common type of controlled release beads comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer.

An example of such controlled release beads is described in US-A-5,783,215 where each bead comprises (i) a core unit of a soluble or insoluble inert material, (ii) a first layer on the core unit comprising an active ingredient dispersed in a hydrophilic polymer, (iii) an optional second layer of hydrophilic polymer covering the first layer, and (iv) an outermost membrane layer effective for controlled release of the active ingredient.

In the above and similar controlled release beads it is not uncommon to apply a "sealcoat" in the form of a small amount (e.g. 1-3%) of a water-soluble polymer, such as hydroxypropylmethyl cellulose (HPMC) or polyvinylpyrrolidone (PVP), between the inert core and the layer containing the active ingredient. The purpose thereof is generally to isolate the drug from the core surface in the event that a drug-core chemical interaction is possible, and/or to smooth the surface of the inert core such that the surface area is more consistent from lot to lot to thereby improve the coating quality when the drug layer and the controlled release membrane layers are applied.

According to the present invention, it has now surprisingly been found that by applying a relatively thick layer of a water-insoluble polymer to the inert core as a sealcoat, several advantages may be obtained in addition to those mentioned above.

Firstly, in case of a soluble core like one of sugar, for example, the amount of time that the solution within the bead would be saturated with respect to drug may be maximized. Thus, by preventing the soluble core from being a reservoir for drug dissolution, the relative time that a saturated solution would remain within the bead during the release period can be increased considerably. This means that a substantially longer zero order drug release phase (the phase when the drug release rate is essentially

constant) will be obtained (and less in the undesirable declining release rate phase). In other words, generally, the use of a thick sealcoat layer will permit the drug release profile to be altered in a predictable fashion, in particular for drugs with a moderate to high water solubility. Also, without drug migrating into the sealcoat, all drug will get released.

Secondly, the potential influence of the core material on drug release, in particular osmotic pressure or swelling of the core material which could potentially cause internal pressure and film rupture, may be minimized.

Thirdly, the substantial initial lag phase (no or very low amount of drug release early) that is generally observed with the prior art controlled release beads, especially for slower release formulations where the water influx is slower, may be substantially reduced or eliminated relatively independently of the steady state release rate.

Therefore, in a first aspect, the present invention provides a controlled release bead comprising:

(i) a core unit of a substantially water-soluble or water-swellable inert material having;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-

thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

Usually, the first layer (ii) above constitutes more than about 2% (w/w) of the final bead composition, preferably more than about 3% (w/w), e.g. from about 3% to about 80% (w/w).

The amount of the second layer (ii) above usually constitutes from about 0.05 to about 60 % (w/w), preferably from about 0.1 to about 30 % (w/w) of the final bead composition.

The amount of the third layer (iv) above usually constitutes from about 1 to about 50 % (w/w), preferably from about 2 to about 25 % (w/w) of the final bead composition.

The core unit typically has a size in the range of from about 0.05 to about 2 mm.

In a second aspect, the present invention provides a multiple unit formulation comprising said controlled release beads, such as a capsule or a tablet.

The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. Especially, the beads are spheres of sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (latex or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

A wide variety of therapeutically active agents may be used in conjuction with the present invention. While the therapeutic agent usually is a low or medium dose drug, also high-dose drugs may be contemplated for use in the present invention. The therapeutic agent is preferably a soluble or moderately water-soluble drug (e.g. having a solubility corresponding to from less than 1 to about 30 ml of water per gram of solute at a temperature between 15 °C and 25 °C).

The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer,

or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

In a third aspect, the present invention provides a method for producing the controlled release beads and formulation, respectively. This method comprises the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

Optionally, the method comprises the further step of applying one or more additional polymer layers to the core as has been mentioned above.

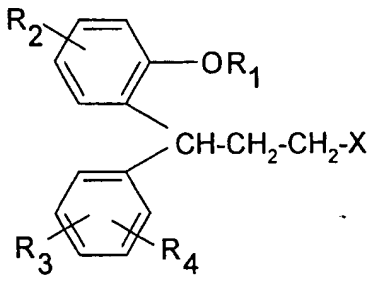
The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets.

The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30-80°C, for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35°C before stopping the process.

The pharmaceutical formulation of the invention may be administered orally.

An exemplary class of compounds which may be used as active ingredients in the present invention comprises the 3,3-diphenylpropylamines disclosed in US-A-5,382,600, US-A-5,559,269 and US-A-5,686,464 (the entire diclosures of which are incorporated by reference herein) and having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. An exemplary specific compound is tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, prodrug forms and pharmaceutically acceptable salts thereof.

Useful analogues to the above compounds are disclosed in WO 98/43942 (the full diclosure of which is incorporated by reference herein).

The above as well as the latter compounds have anti-cholinergic activity and may be used for treating, *inter alia*, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial

cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The compounds also have spasmolytic activity and may be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

Specifically, the beads and multiple unit formulation, respectively, according to the present invention have proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urge incontinence, urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine. A salient feature of tolterodine is that it has considerably less side-effects than the previously conventionally used drug, oxybutynin, especially regarding the propensity to cause dry mouth.

When tolterodine is the active ingredient in the controlled release bead, the fraction of active ingredient that is released in vitro is preferably not more than about 30% after 1 hour, from about 40 to about 85% after 3 hours, and not less than about 80% after 7 hours.

Administration of the controlled release formulation according to the present invention permits a well controlled release of tolterodine, and thereby a substantially constant serum level of active moiety or moieties to be maintained in the patient for at least 24 hours.

By the term "active moiety or moities" is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations

of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite)

are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. the above-mentioned US-A-5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned US-A-5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

The invention will now be described in more detail by the following non-limiting Examples. Reference will be made to the accompanying drawings, wherein:

Fig. 1 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with different sealcoat thicknesses; and

Fig. 2 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with 14 % (w/w) and 0 % (w/w) seal coat, respectively. The polymer composition in the third layer of the beads with 0 % sealcoat has been adjusted in order to produce approximately similar initial drug release as from beads with 14 % sealcoat.

EXAMPLE 1

An exemplary bead containing tolterodine L-tartrate as active ingredient has the following structure:

Core:	Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73 % w/w of the final bead; purpose: coating substrate;
First layer:	Surelease® "sealcoat" (Surelease® is an aqueous film-coating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12 % w/w of the final bead;

purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;

Second layer: Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3 % w/w of the final bead; ratio of Tolterodine:HPMC is 5:1;
purpose: drug supply;

Third layer: Surelease®/HPMC; comprises about 12 % w/w of the final bead; ratio of Surelease®:HPMC is 6:1;
purpose: drug release rate control;

Beads with a three-layer coating having the above characteristics were prepared as follows:

1200 g of sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40°C with the following three coating liquids:

- (1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;
- (2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and
- (3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

After tray drying for 3 hours at 70°C, the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	68.6 mg	137.2 mg
Surelease®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer : HPMC; comprises about 1 % w/w of the final bead; purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Study of effect of sealcoat thickness

The effect of the sealcoat thickness on drug release was tested as follows.

Four lots of 20-25 mesh beads were prepared that contained (i) a Surelease® sealcoat layer at 0, 2, 10 or 14% level, (ii) an HPMC/drug (tolterodine L-tartrate) layer at 4% level (drug:HPMC ratio =5:4), (iii) a Surelease®/HPMC layer at 10% level (Surelease®:HPMC ratio = 6:1 ratio), and (iv) a final HPMC layer at 1%. These were prepared essentially as described above and cured 1 hr at 70 °C.

Note that the coating level for layer (i) is expressed relative to the sum of the core plus sealcoat while coating levels for layers (ii-iv) are expressed relative to the final coated bead weight.

A fifth lot of beads was also manufactured identical to the 0% sealcoat lot described above except that the third coating layer was modified (increase in the Surelease®: HPMC layer from a 6:1 to a 11:1) such that the initial drug release rate was similar to the 14% sealcoat formulation described above.

The in vitro drug release at 37°C in phosphate buffer pH 6.8 with addition of 0.22M potassium chloride was measured. The USP dissolution test apparatus 1 was used. The results are shown in the diagrams in Fig. 1 and 2. As shown in Fig. 1, as the sealcoat layer gets thicker, the drug release rate both decreases and becomes more zero-order.

Fig. 2 shows the comparison of the 0% sealcoat formulation (11:1 Surelease®: HPMC) to the 14% sealcoat (6:1 the Surelease®: HPMC). It can be seen that, after a slight lag period observed by the 0% sealcoated beads, the initial drug release rates are similar. However, after approximately 15-20% of the drug is released, the release rate from beads with 0 % sealcoat beads falls while release rate from the 14% sealcoat remains extremely zero order. Indeed, for the 0 % sealcoat beads the release rate between 45-60% is only approximately half of the initial (first 20 %) release rate. Comparatively, for the 14% sealcoat lot, the release rate between 45-60% range is identical to the rate over the first 20%.

In an analogous manner to the procedure described in Example 1 above, other exemplary bead formulations containing tolterodine L-tartrate as the active ingredient were prepared as described in Examples 2 and 3 below.

EXAMPLE 2

400 g of sugar spheres (20-25 mesh, Edward Mendell Co, USA) were charged into a top-spray fluid bed coater (Nica, Sweden) and coated with Surelease® and thereafter cured in a drying cabinet at 70°C for 5 hours.

A solution of tolterodine-L-tartrate and hydroxypropyl cellulose (HPC) in water was sprayed onto the coated cores.

The spheres obtained were then coated with a mixture of ethylcellulose, hydroxypropylcellulose and triethylcitrate (plasticizer). The coating materials were dissolved in a mixture of dichlormethane and ethanol.

The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	75.7
Surelease®	13
Tolterodine L-tartrate	4.9
HPC	1.5
Ethylcellulose	4.3
Triethyl citrate	0.6

The obtained spheres showed extended release of tolterodine L-tartrate over at least 10 hours. The release rate was essentially constant.

EXAMPLE 3

4800 g of sugar spheres (18-20 mesh, Mendell, USA) were coated in a Wurster fluid bed with Surelease® to a theoretical weight gain of 10 % and thereafter cured in a drying cabinet at 60°C for 6 hours.

A solution of tolterodine L-tartrate and hydroxypropylmethyl cellulose (HPMC) in water was sprayed onto 1200 g of the cured sphere cores.

1000 g of the obtained spheres were then coated by spraying with an aqueous dispersion of a cross-linked latex of hydroxyl-end blocked polydimethylsiloxan (PDMS, Dow Corning; USA) and colloidal silica (Dow Corning, USA) to a theoretical weight gain of 15 %.

The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	76
Surelease®	7.8
Tolterodine L-tartrate	2.8
HPMC	0.4
PDMS	8.7
Colloidal silica	4.3

The obtained spheres showed extended release of tolterodine L-tartrate over at least 11 hours. The release rate was nearly constant.

While the invention has been described above with reference to specific embodiments thereof, it is not restricted thereto in any way whatsoever. On the contrary, as will be understood by those skilled in the art, various changes, modifications, substitutions and omissions can be made without departing from the basic concept of the invention as defined in the claims which follow.

CLAIMS

1. A controlled release bead comprising:

(i) a core unit of a substantially water-soluble or water-swellable inert material;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer of polymer on the second layer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

2. The bead according to claim 1, wherein the amount of polymer in said first layer is sufficient to substantially retard water penetration into the core.

3. The bead according to claim 1 or 2, wherein the thickness of said first layer is sufficient to affect the drug release rate from the bead.

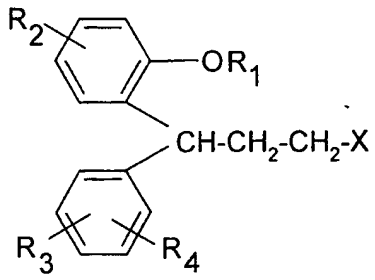
4. The bead according to claim 1, 2 or 3, wherein the amount of the first layer constitutes more than 2% (w/w), preferably more than 3% (w/w) of the final bead composition.

5. The bead according to any one of claims 1 to 4, wherein the amount of said second layer usually constitutes from about 0.05 to about 60 % (w/w), preferably from about 0.1 to about 30 % (w/w) of the final bead composition.

6. The bead according to any one of claims 1 to 5, wherein the amount of said third layer usually constitutes from about 1 to about 50 % (w/w), preferably from about 2 to about 25 % (w/w) of the final bead composition.

7. The bead according to any one of claims 1 to 6, wherein said third polymer layer is coated with a fourth layer of a water-soluble polymer or an additional functional coating.

8. The bead according to any one of claims 1 to 7, wherein said active ingredient is selected from compounds having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

9. The bead according to claim 8, wherein said active ingredient is selected from tolterodine, the 5-hydroxymethyl metabolite of tolterodine, the (S)-enantiomer of tolterodine, the 5-hydroxymethyl metabolite of the (S)-enantiomer of tolterodine, the racemate of tolterodine, and prodrug forms and pharmacologically acceptable salts thereof.

10. The bead according to claim 9, wherein said active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

11. The bead according to claim 10, wherein the fraction of active ingredient that is released in vitro is not more than about 30% after 1 hour, from about 40 to about 85% after 3 hours, and not less than about 80% after 7 hours.

12. The bead according to any one of claims 1 to 11, wherein the polymer material of said first layer comprises ethyl cellulose.

13. The bead according to any one of claims 1 to 12, wherein said second layer comprises hydroxypropylmethyl cellulose as binder.

14. The bead according to any one of claims 1 to 13, wherein the polymer material of said third layer comprises a combination of hydroxypropylmethyl cellulose and ethyl cellulose.

15. The bead according to any one of claims 1 to 14, wherein the core unit has a size of about 0.05 to about 2 mm.

16. A multiple unit formulation comprising a controlled release bead according to any one of claims 1 to 15.

17. The multiple unit formulation according to claim 16 which is a capsule.

18. A method of producing a controlled release bead, which method comprises the steps of:

a) providing a core unit of a substantially water-soluble or water-swellable materia;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first is selected to provide a layer thickness that permits control of water penetration into the core.

19. A method for treating overactive bladder, which comprises administering a therapeutically effective amount of beads according to any one of claims 8 to 15.

20. The method according to claim 19, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

21. A method for treating nocturia, which comprises administering a therapeutically effective amount of beads according to any one of claims 8 to 15.

22. The method according to claim 21, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

23. A method for treating gastrointestinal disorders, which comprises administering a therapeutically effective amount of beads according to any one of claims 8 to 15.

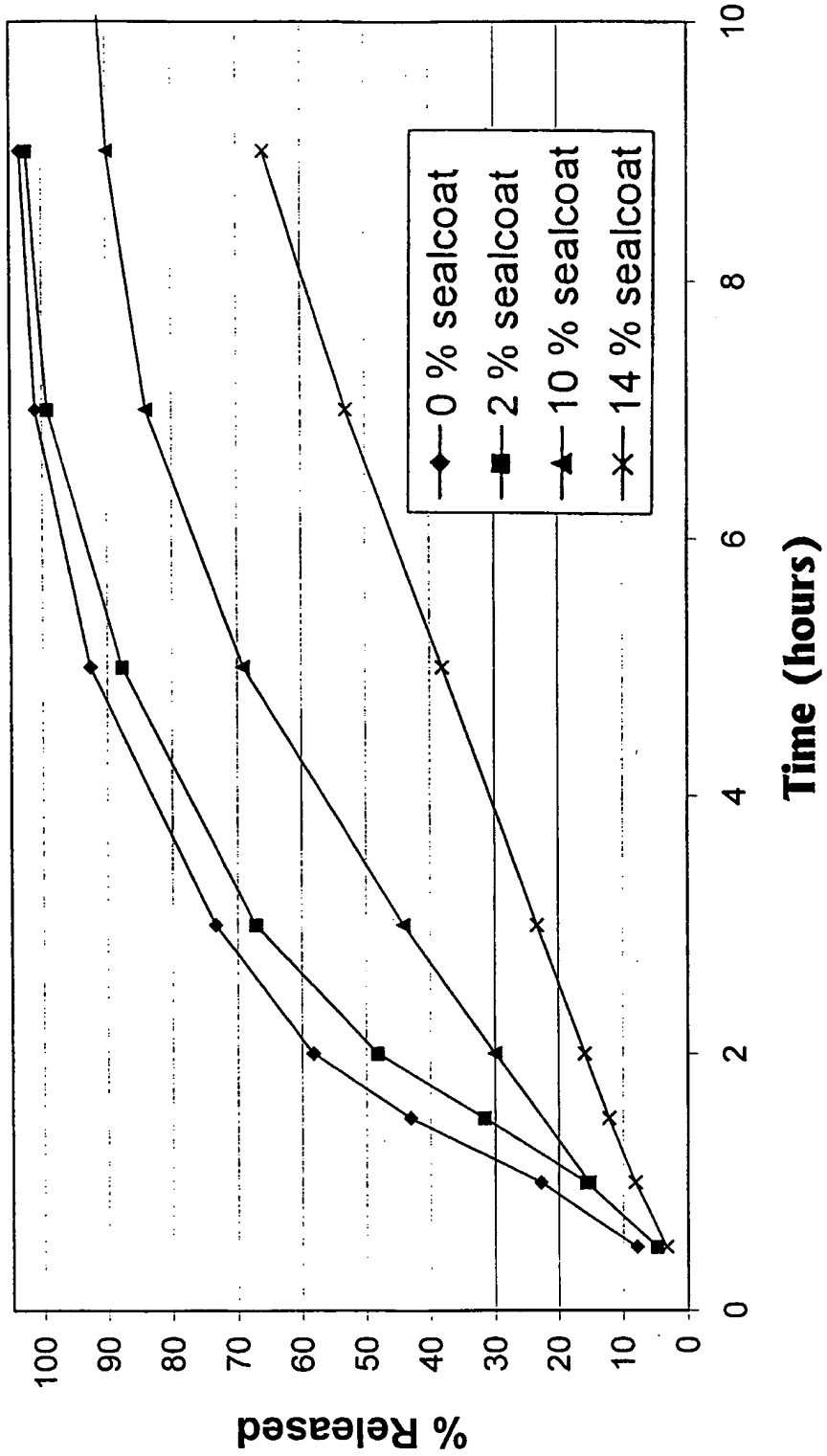


FIG. 1

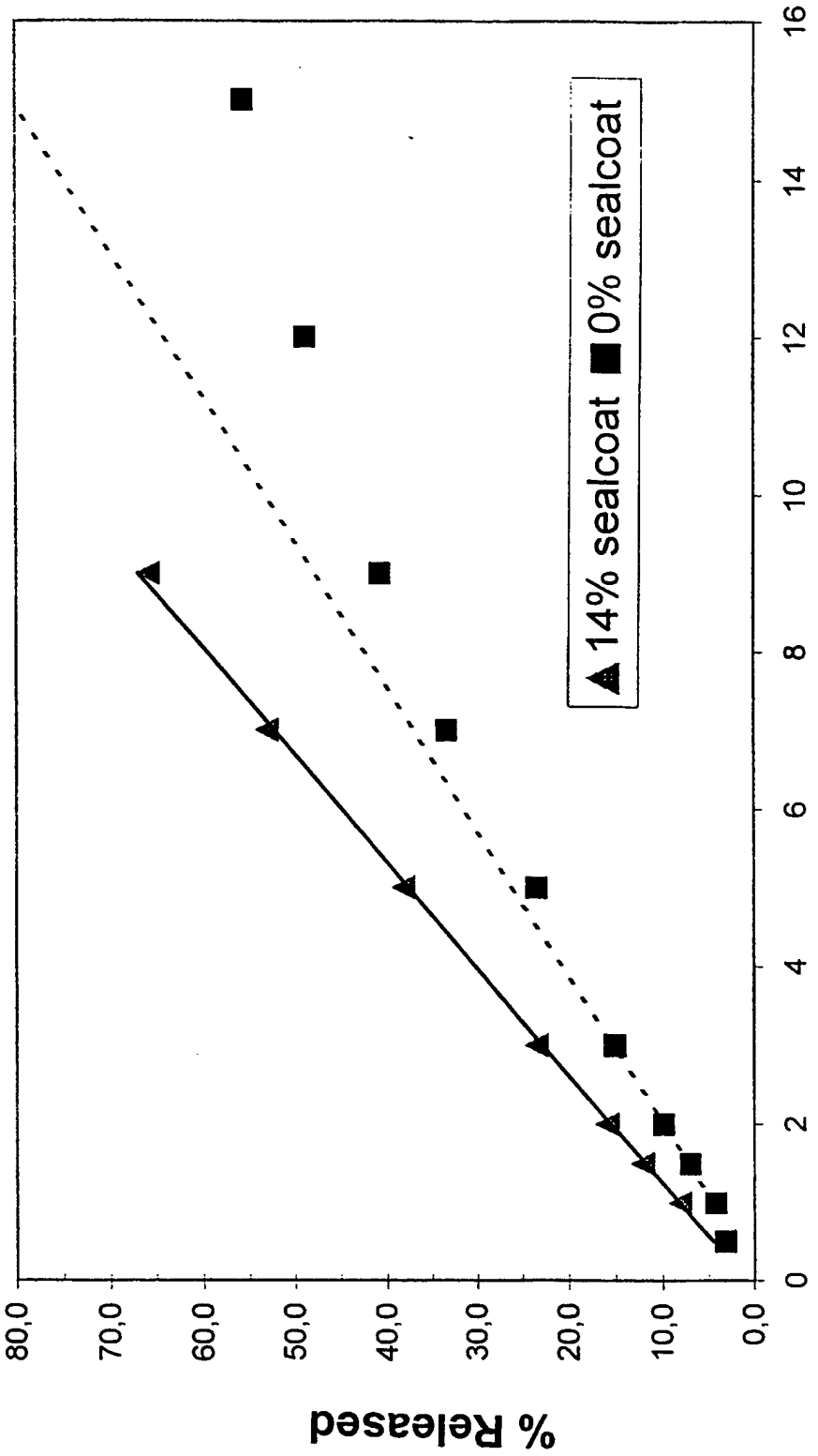


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02052

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/16, A61K 9/26, A61K 9/58, A61K 31/135, A61P 13/10, A61P 1/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9601621 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96) --	1-23
A	WO 9629992 A1 (ANDRX PHARMACEUTICALS, INC.), 3 October 1996 (03.10.96) --	1-23
A	EP 0061217 A2 (PHARMATEC S.P.A.), 29 Sept 1982 (29.09.82) -- --------	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 February 2000	25 -02- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02052

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-23
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 19-23 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1 (iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 99/02052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601621 A1	25/01/96	AU 700949 B	14/01/99
		AU 2993695 A	09/02/96
		BR 9506026 A	14/10/97
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		HU 9600575 D	00/00/00
		IL 114448 D	00/00/00
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		NZ 289947 A	28/07/98
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		US 5567441 A	22/10/96
		US 5834023 A	10/11/98
EP 0061217 A2	29/09/82	DK 121382 A	20/09/82
		IT 1144911 B	29/10/86
		IT 8120578 D	00/00/00

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Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL FORMULATION CONTAINING TOLTERODINE AND ITS USE

(57) Abstract: The invention relates to a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours. The invention also relates to the use of the pharmaceutical formulation for treating overactive bladder and gastrointestinal disorders.

WO 01/34139 A1

Pharmaceutical formulation containing tolterodine and its use.

The present invention relates to a pharmaceutical formulation for administering tolterodine or a tolterodine-related compound, and to the medical use of such a formulation.

A substantial part (5-10%) of the adult population suffers from overactive or unstable urinary bladder, often also referred to as urinary incontinence. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. The prevalence of overactive bladder, particularly of so-called urge incontinence, increases with age. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Recently, however, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195-207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647-655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287-295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While,

as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

Our co-pending international application PCT/SE99/01463 relates to the administration of tolterodine and tolterodine-related compounds through a controlled release formulation and is based on the finding that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

Our above-mentioned PCT/SE99/01463 discloses treatment of overactive bladder by the administration of a controlled release formulation that delivers tolterodine, a tolterodine-related compound, or a pharmacologically acceptable salt thereof such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

The present invention is based on the unexpected observation that a substantially constant serum level of the active moiety or moieties for 24 hours may be obtained through oral administration of a controlled release pharmaceutical formulation that releases the major content of active compound in less than about 18 hours, and more particularly that the formulation has an in vitro release of not less than about 80 % after 18 hours at the conditions specified below.

In one aspect, the present invention therefore provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation

exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

A second aspect of the invention relates to the use of the pharmaceutical formulation for treating a disorder or disease selected from overactive bladder (including i.a. urinary incontinence and nocturia) and gastrointestinal disorders.

A third aspect of the invention relates to the use of tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, for the preparation of the pharmaceutical formulation of the above first aspect of the invention.

Preferably, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released is not less than about 80 % after 15 hours, especially not less than about 80 % after 12 hours.

On the other hand, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after 1 hour is preferably not more than about 50 %, especially not more than about 30%.

The fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after three hours is preferably from about 30 to 95 %, especially from about 40 to about 85 %.

It may be preferred that after 7 hours, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 50 %, especially not less than about 80 %.

In an exemplary in vitro release profile for the pharmacutical formulation, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50 % after 1 hour, from about 30 to about 95 % after 3 hours, and more than about 50 % after 7 hours.

The in vitro release measurement conditions referred to above are those for a drug release test that utilizes the United States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deareated phosphate buffer at pH 6.8 and 37°C, where the phosphate buffer solution is prepared as described on pages 2049-2050 in USP 23. The phosphate buffer nominally contains 0.05 M phosphate.

By the term "active moiety or moities" it is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any substantial peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite) are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

The formulation of the present invention is not restricted to any particular type of formulation. Thus, various types of controlled or sustained release type formulations may be used for embodying the present invention, such as, for example, osmotic tablets, gel matrix tablets, coated beads, etc.

A common type of controlled release formulation that may be used for the purposes of the present invention comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer. A "sealcoat" may be provided between the inert core and the layer containing the active ingredient. When the core is of a water-soluble or water-swellable inert material, the sealcoat is preferably in the form of a relatively thick layer of a water-insoluble polymer. Such a controlled release bead may thus comprise:

(i) a core unit of a substantially water-soluble or water-swellable inert material;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein the first layer is adapted to control water penetration into the core.

The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-

thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

Usually, the first layer (ii) above constitutes more than about 2% (w/w) of the final bead composition, preferably more than about 3% (w/w), e.g. from about 3% to about 80% (w/w).

The amount of the second layer (ii) above usually constitutes from about 0.05 to about 60 % (w/w), preferably from about 0.1 to about 30 % (w/w) of the final bead composition.

The amount of the third layer (iv) above usually constitutes from about 1 to about 50 % (w/w), preferably from about 2 to about 25 % (w/w) of the final bead composition.

The core unit typically has a size in the range of from about 0.05 to about 2 mm.

The controlled release beads may be provided in a multiple unit formulation, such as a capsule or a tablet.

The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. The cores may be spheres of materials such as sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (dispersed or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

The above controlled release beads and formulation, respectively may be produced by a method comprising the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

Optionally, one or more additional polymer layers are applied to the core as has been mentioned above.

The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets.

The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30-80°C, for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35°C before stopping the process.

As mentioned above, the pharmaceutical formulation according to the present invention may be used for treating, *inter alia*, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The formulation may also be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

The pharmaceutical formulation according to the present invention has proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urinary incontinence (urge incontinence), urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. the above-mentioned US-A-5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned US-A-5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

The invention will now be described in more detail by the following non-limiting Examples. Reference will be made to the accompanying drawings, wherein:

Fig. 1 is a diagram showing the fraction of tolterodine L-tartrate released in vitro versus time for 2 and 4 mg controlled release capsules according to the Example below; and

Fig. 2 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through a prolonged release (PR) capsule (4 mg) according to the Example below once daily. The corresponding variation with a prior art immediate release (IR) tablet (2 mg) twice daily is also shown.

EXAMPLE

Preparation of controlled release beads and capsules

An exemplary bead formulation containing tolterodine L-tartrate as active ingredient has the following structure:

Core:	Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73 % w/w of the final bead; purpose: coating substrate;
First layer:	Surelease® "sealcoat" (Surelease® is an aqueous film-coating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12 % w/w of the final bead; purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;
Second layer:	Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3 % w/w of the final bead; ratio of Tolterodine:HPMC is 5:1; purpose: drug supply;
Third layer:	Surelease®/HPMC; comprises about 12 % w/w of the final bead; ratio of Surelease®:HPMC is 6:1; purpose: drug release rate control;

Beads with a three-layer coating having the above characteristics were prepared as follows:

1200 g of sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40°C with the following three coating liquids:

- (1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;
- (2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and
- (3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

After tray drying for 3 hours at 70°C, the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	68.6 mg	137.2 mg
Surelease®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer : HPMC; comprises about 1 % w/w of the final bead;
purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Drug in vitro release study

A drug-release test which utilizes the USP Apparatus 1 (rotating basket) at 100 rpm with 1000 mL of deaerated phosphate buffer prepared at pH 6.8, was used to study the in vitro release at 37°C of the two three-layered beads-containing 2 and 4 mg capsules prepared above. The buffer was identical to that used for the Buffer Stage testing of Delayed-release dosage forms described in USP 23 General Chapter 724, and nominally contains 0.05 M phosphate and 0.075 M chloride. The results are shown in Fig. 1. As can be seen therein, about 90 % of the tolterodine tartrate had been released from both capsules after 12 hours.

Pharmacokinetic study – Determination of serum concentrations of tolterodine and main metabolite

A clinical trial was performed in patients with overactive bladder to determine the pharmacokinetic effects of a (i) a once daily dose of a 4 mg tolterodine controlled release capsule (below referred to as TOD) as described above, and (ii) two doses daily of a tolterodine immediate release tablet (below referred to as TIR), described below. 30 patients were subjected to each of the treatments. The measurements were performed on day seven in each treatment period and included measurements of serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time.

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136). Figure 2 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily (PR capsule in Fig. 2), and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus

providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI = (Cmax - Cmin)/AUCτ/τ, where τ is the length of the dosage interval and AUCτ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.29 (95% CI 1.95-2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59-0.78) for the TOD capsule.

While the invention has been described above with reference to specific embodiments thereof, it is not restricted thereto in any way whatsoever. On the contrary, as will be understood by those skilled in the art, various changes, modifications, substitutions and omissions can be made without departing from the basic concept of the invention as defined in the claims which follow. Thus, for example, other sustained release formulations may be used.

CLAIMS

1. A pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, which formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

2. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80 % after 15 hours.

3. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80 % after 12 hours.

4. The formulation according to claim 1, 2 or 3, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50 % after 1 hour.

5. The formulation according to claim 4, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 30 % after 1 hour.

6. The formulation according to claim any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 30 to about 95 % after 3 hours.

7. The formulation according to any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 40 to about 85 % after 3 hours.

8. The formulation according to any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 50 % after 7 hours.

9. The formulation according to any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 80 % after 7 hours.

10. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not more than about 50 % after 1 hour, from about 30 to about 95 % after 3 hours, and not less than about 50 % after 7 hours.

11. The formulation according to any one of the preceding claims, wherein the in vitro release is measured by a drug release test which utilizes the United States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deareated phosphate buffer at pH 6.8 and 37 °C, where the phosphate buffer solution is prepared as described on pages 2049-2050 of USP 23, and nominally contains 0.05 M phosphate.

12. The formulation according to any one of the preceding claims, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

13. The formulation according to any one of the preceding claims, which comprises tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a salt thereof.

14. The formulation according to any one of the preceding claims, which comprises tolterodine, or a salt thereof.

15. The formulation according to claim 14 or 15, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

16. The formulation according to claim 14 or 15, wherein and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

17. A method for treating overactive bladder, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

18. A method for treating urinary incontinence, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

19. A method for treating nocturia, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

20. A method for treating gastrointestinal disorders, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

21. Use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for

treating a disorder selected from overactive urinary bladder, including urinary incontinence, nocturia and gastrointestinal disorders, which formulation exhibits a controlled in vitro release of tolterodine, a tolterodine-related compound or pharmacologically acceptable salt thereof, in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

22. A method for orally administering tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, to a patient to maintain a substantially constant serum level of the active moiety or moieties for 24 hours, which method comprises administering a pharmaceutical formulation containing tolterodine, a tolterodine-related compound or a salt thereof, which formulation exhibits a controlled in vitro release in phosphate buffer at pH 6.8 of tolterodine, tolterodine-related compound or salt thereof of not less than about 80 % after 18 hours.

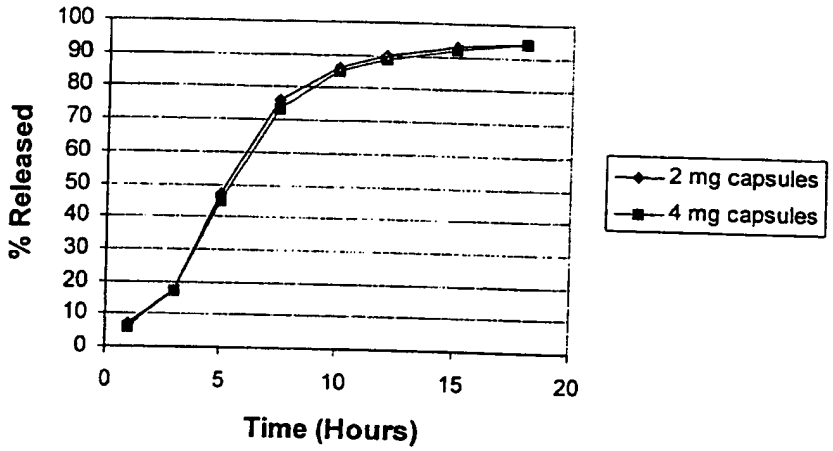
100
90
80
70
60
50
40
30
20
10
0
% Released
0
5
10
15
20
Time (Hours)
2 mg capsules
4 mg capsules

FIG. 1

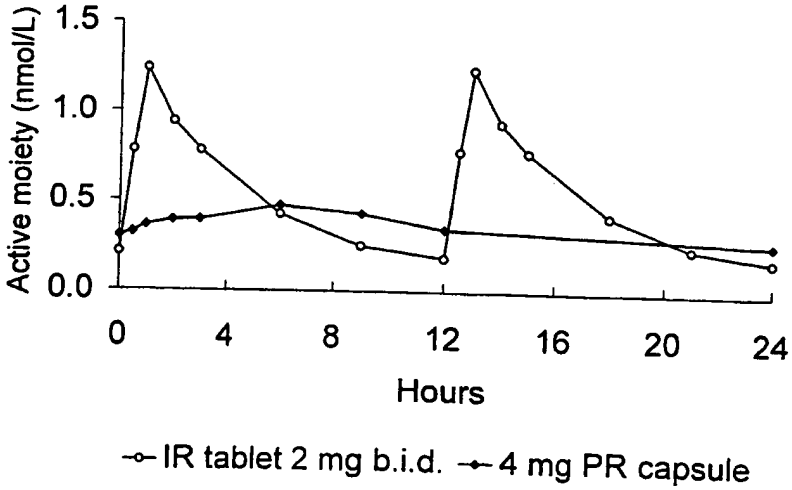
1.5
1.0
0.5
0.0
Active moiety (nmol/L)
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02061

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/135, A61K 9/16, A61K 9/26, A61P 13/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0012069 A1 (PHARMACIA & UPJOHN AB), 9 March 2000 (09.03.00), see page 7, lines 22-30 --	1-22
P,X	WO 0027364 A1 (PHARMACIA & UPJOHN AB), 18 May 2000 (18.05.00) --	1-22
A	WO 9803067 A1 (ABERG, GUNNAR), 29 January 1998 (29.01.98) -- --------	1-22

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2001	29 -03- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02061

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-20, 22
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02061

Claims 17-20, 22 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/02061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0012069 A1	09/03/00	AP 200001823 D	00/00/00
		AU 5891899 A	21/03/00
		AU 5891999 A	21/03/00
		EP 1039882 A	04/10/00
		NO 20002977 A	09/06/00
		SE 9802864 D	00/00/00
		WO 0012070 A	09/03/00
		AU 1436600 A	29/05/00
		SE 9803871 D	00/00/00
		WO 0027364 A	18/05/00
WO 0027364 A1	18/05/00	AP 200001823 D	00/00/00
		AU 1436600 A	29/05/00
		AU 5891899 A	21/03/00
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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention provides a solid pharmaceutical composition, e.g. in form of a tablet, powder or capsule, comprising e.g. a cyclosporin.

Pharmaceutical Compositions

The present invention relates to novel galenic compositions, in particular novel galenic compositions comprising a poorly water-soluble drug, e.g. a cyclosporin.

Cyclosporins present highly specific difficulties in relation to administration generally and galenic composition in particular, including in particular problems of stability, drug bioavailability, and variability in inter- and intra-patient dose response.

In order to meet these and related difficulties, in GB patent publication no. 2 222 770 and no. 2 257 359, galenic compositions are disclosed comprising a cyclosporin as active ingredient and which take the form of, inter alia, an emulsion, e.g. microemulsion, or emulsion, e.g. microemulsion, pre-concentrate. Microemulsion pre-concentrates have been developed for commercial use under the trademark Neoral® which may be orally administered in the form of drink solutions or soft gelatine capsules.

There remains a need for formulations comprising a poorly water-soluble drug, e.g. cyclosporin, that can be orally administered in solid form, e.g. tablet, powder or capsules, which is stable and exhibit consistent and effective absorption. Conveniently, the tablets or capsules are of a volume that allows convenient administration, e.g. easy swallowing.

The poorly water soluble drug preferably is a lipophilic drug, e.g. a cyclosporin. The term "poorly water soluble", as used herein, is understood to mean a solubility in water at 20°C of less than 1, e.g. 0.01, % weight/volume, e.g. a sparingly soluble to very slightly soluble drug as described in Remington: The Science and Practice of Pharmacy, 19th Edition, Ed. A.R. Gennaro, Mack Publishing Company, US, 1995, vol. 1, p 195.

Cyclosporins to which the present invention applies are any of those having pharmaceutical utility, e.g. as immunosuppressive agents, anti-parasitic agents and agents for the reversal of multi-drug resistance, as known and described in the art, in particular Cyclosporin A (also known as Ciclosporin), Cyclosporin G, [O-(2-hydroxyethyl)-(D)Ser]^{8}-Ciclosporin, and [3'-dehydroxy-3'-keto-MeBmt]^{1}-[Val]^{2}-Ciclosporin. Cyclosporin A is preferred.

In one aspect the present invention provides a composition according to the present invention wherein the cyclosporin is Cyclosporin A.

In accordance with the present invention it has now surprisingly been found that particularly suitable galenic compositions containing a poorly water-soluble drug, e.g. a cyclosporin, having particularly interesting bioavailability characteristics and reduced variability in inter- and intra-subject bioavailability parameters, e.g. in the form of tablets, capsules or powder, are obtainable using a solid polymer and/or a solid surfactant.

The present invention provides in one aspect a solid pharmaceutical composition, e.g. in form of a tablet, a powder or a capsule, comprising
(1) a poorly water soluble drug, e.g. a cyclosporin, and
(2) a polymer which is solid at room temperature.

The polymer is preferably one which can exist in the form of a, e.g. flowable, powder, having a melting point of e.g. above 40°C, preferably having a melting point and/or a glass transition temperature of above about 80°C.

In accordance with the present invention, it has surprisingly been found that suitable cyclosporin-containing compositions and compositions containing other poorly water-soluble drugs may be obtained based on polymers (2) which are solid at room temperature. The polymer is for example a pH dependent or non-pH dependent polymer. The polymer preferably is a hydrophilic polymer. Conveniently one or a mixture of polymers may be used.

Suitable pH-independent polymers include

2.1 polyvinyl pyrrolidone. A preferred example may be PVP K30, having an approx. molecular weight of 50 000 Daltons, or PVP K12, having an approx. molecular weight of 2 500 Daltons, as known and commercially available under the trade name Kollidon® or Plasdone® (Fiedler, "Lexikon der Hilfsstoffe fÜr Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), 1, , p.1256);

2.2 cellulose derivatives such as hydroxypropylmethylcellulose, preferably having a molecular weight of from 10 000 to 1 500 000 Daltons, as known and commercially available under the trade names Pharmacoat® or Methocel® (Fiedler, loc. cit., p.790). A

preferred example may be as known and commercially available under the name HPMC 3 cP.

Suitable pH-dependent polymers include:

2.3 cellulose derivatives such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate or cellulose acetate phthalate. Preferably, hydroxypropylmethylcellulose phthalate may be used as known and commercially available, e.g. from Shin-Etsu, under the name HPMCP HP50, having a viscosity of 190±20 cP, a methoxy content of 20.0-25.0%, hydroxypropyl content of 5.0-10.0%, and a carboxybenzoyl content of 20.0-24.0%, or HPMCP HP55, having a viscosity of 240±20 cP, a methoxy content of 18.0-22.0%, hydroxypropyl content of 4.0-9.0%, and a carboxybenzoyl content of 27.0-35.0% (Fiedler, loc. cit., p.762). Preferably, hydroxypropylmethylcellulose acetate succinate (HPMCAS) may be used as known and commercially available, e.g. from Shin-Etsu. Preferably, cellulose acetate phthalate may be used as known and commercially available, e.g. from Eastman Chemical Company, US, under the trade name C-A-P.

2.4 poly(meth)acrylates, preferably having a molecular weight from about 100 000 to about 400 000 Daltons. Preferably, the polymer is a copolymer which is resistant to gastric juice and soluble in intestinal juices, e.g. a copolymer formed from monomers selected from the group consisting of methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters, or e.g. a copolymer formed from butyl methacrylate, (2-dimethylaminoethyl)methacrylate, and methyl methacrylate, e.g. as those known and commercially available under the trade mark Eudragit® from Röhm Pharma GmbH. Especially preferred polymers are the 1:1 copolymer formed from monomers selected from the group consisting of methacrylic acid and methacrylic acid lower alkyl esters, such as the 1:1 copolymer formed from methacrylic acid and methyl methacrylate, available under the trade mark Eudragit® L, e.g. Eudragit® L100, having a molecular weight of about 135 000 Daltons, and the 1:1 copolymer of methacrylic acid and acrylic acid ethyl ester as known and commercially available under the trade mark Eudragit® L100-55, having a molecular weight of about 250 000 Daltons, and the 1:2:1 copolymer formed from butyl methacrylate, (2-dimethylaminoethyl)methacrylate, and methyl methacrylate, available under the trade mark Eudragit® E, having a molecular weight of about 150 000 Daltons.

Although any pharmaceutically acceptable components selected from the group of polymers specified above may be used in the composition of the invention, certain components are preferred. These include polyvinyl pyrrolidones, e.g. PVP K12/K30, hydroxypropylmethyl-cellulose phthalates, e.g. HPMCP HP50/55, or 1:1 copolymers formed from methacrylic acid and methyl methacrylate, e.g. Eudragit® L100 and L 100-55. Conveniently, one or a mixture of these polymers may be used.

pH-Dependent polymers preferably dissolve at a pH of below about 6, e.g. below about 5.

In the pharmaceutical compositions of the present invention, in a further alternative aspect the constitutional ratio of poorly water-soluble drug (e.g. cyclosporin) : polymer may be from about (10 to 50) : (90 to 50), e.g. 10 : 90, 20 : 80, 30 : 70, or 50 : 50.

The present invention provides in another aspect a solid pharmaceutical composition, e.g. in form of a tablet, a powder or a capsule, comprising
(1) a poorly water soluble drug, e.g. cyclosporin, and
(3) a surfactant which is solid at room temperature.

The present invention provides in a further aspect a solid pharmaceutical composition, e.g. in form of a tablet, a powder or a capsule, consisting of or consisting essentially of
(1) a poorly water-soluble drug, e.g. cyclosporin, and
(3) a surfactant, which is solid at room temperature.

The surfactant (3) is preferably one which can exist in the form of a, e.g. flowable, powder, having a melting point of e.g. above 40°C.

The surfactant (3) is for example nonionic, ionic or amphoteric surfactant. Preferably, the surfactants have solubilizing power for the poorly water-soluble drug, e.g. cyclosporins. In one embodiment the invention provides a composition as described above wherein the surfactant is ionic, e.g. surfactants such as listed below under (3.5). In another embodiment the invention provides a composition as described above wherein the surfactant is nonionic, e.g. surfactants such as listed below under (3.1)-(3.4) and (3.6)-(3.12).

Conveniently one or a mixture of the following surfactants may be used:

3.1 polyoxyethylene alkyl ethers; preferably the alkyl ethers are of C_{12} to C_{18} alcohols. Preferably the polymer number is from about 2 to about 150, e.g. about 5 to about 150. Preferably the polymers are polyoxyethylene glycol ethers. Preferred examples include polyoxyl 2-, 10- or 20-cetyl ether or polyoxyl 23-lauryl ether, or polyoxyl 20-oleyl ether, or polyoxyl 2-, 10-, 20- or 100-stearyl ether, as known and commercially available e.g. under the trade mark Brij® from Uniqema. An especially preferred product of this class is e.g. Brij® 35 (polyoxyl 23 lauryl ether), Brij® 58, Brij® 78P (polyoxyl 20 stearyl ether), or Brij® 98 (polyoxyl 20 oleyl ether) and polyethoxylated (20) cetyl ether, e.g. Nikkol® BC-20 TX, (H. Fiedler, loc. cit., pp. 259; "Handbook of Pharmaceutical Excipients", 2nd Edition, Editors A. Wade and P. J. Weller (1994), Joint publication of American Pharmaceutical Association, Washington, USA and The Pharmaceutical Press, London, England, page 367).

Similar products which may also be used are polyoxyethylene-polyoxypropylene-alkyl ethers, e.g. polyoxyethylene-polyoxypropylene- ethers of C_{12} to C_{18} alcohols, e.g. polyoxyethylen-20-polyoxypropylene-4-cetylether which is known and commercially available under the trade mark Nikkol PBC® 34, from e.g. Nikko Chemicals Co., Ltd. (Fiedler, loc. cit., vol. 2, pp. 1239).

3.2 polyethoxylated fatty acid esters. Preferably the molecular weight is from about 600 to about 18 000 Daltons. Preferably the polymerization number is from about 8 to about 400. Preferably the fatty acid is of 12 to 20 carbon atoms, e.g. stearic acid, e.g. of the type known and commercially available under the trade name Myrj® from Uniqema (Fiedler, loc. cit., vol. 2, pp. 1042). An especially preferred product of this class is Myrj® 52 having a D^{25} of about 1.1, a melting point of about 40 to 44°C, an HLB value of about 16.9, an acid value of about 0 to 1 and a saponification no. of about 25 to 35, or Myrj® 53, or Myrj® 59 (polyethyleneglycol-100-stearate), e.g. from Uniqema.

3.3 polyethoxylated sorbitan monostearates, e.g. as known and commercially available under the trade name Tween® 61 from Uniqema (Fiedler, loc. cit., vol. 2, pp. 1616).

3.4 polyethoxylated distearates, e.g. as known and commercially available under the trade name Atlas® G 1821 from Uniqema (Fiedler, loc. cit., vol. 2, pp. 206), or Nikko® CDS-6000P from Nikko Chemicals Co., Ltd.

3.5 anionic surfactants, e.g. those based on an alkali metal salt (e.g. of sodium);

3.5.1 sodium alkyl sulfates e.g. sodium C_8-C_{18}alkyl sulfates, e.g. sodium C_{10}-C_{18}alkyl sulfates, e.g. sodium lauryl sulfate, which is also known as sodium dodecyl sulfate and which is commercially available, e.g. under the trade name Texapon K12® from Henkel KGaA (Fiedler, loc. cit., vol. 2, pp. 1551);

3.5.2 sodium alkyl sulfonates, e.g. sodium C_8-C_{18}alkyl sulfonates, e.g. sodium C_{10}-C_{18}alkyl sulfonates;

3.5.3 sodium alkyl aryl sulfonates, e.g. sodium C_8-C_{18}alkyl aryl sulfonates, e.g. sodium C_{10}-C_{18}alkyl aryl sulfonates, wherein aryl is e.g. benzyl, phenyl and the like;

3.5.4 sodium alkyl phosphate e.g. sodium C_8-C_{18}alkyl phosphate, e.g. sodium C_{10}-C_{18}alkyl phosphate, e.g. sodium lauryl phosphate, or e.g. potassium cetyl phosphate, available under the trade name of AMPHISOL K from Hoffmann La Roche Ltd.;

3.5.5. sodium stearoyl lactylate (sodium-O-stearyllactate), e.g. as known and commercially available under the name SSL P55 VEG from Danisco; or

3.5.6 sodium (C_4-C_{12}) fatty acid salts e.g. sodium caprinate (Fiedler, loc. cit., vol. 2, pp. 1051).

3.6 polyoxyethylene(POE)-polyoxypropylene(POP)-polyoxyethylene(POE) surfactants, e.g. poloxamers, e.g. poloxamer 188, as known and commercially available under the tradename of Pluronic® F 68 from BASF or Synperonic® PE/F 68 from Uniqema, or e.g. poloxamer 407 as known and commercially available under tradename Pluronic® F 127 from BASF or Synperonic PE/F 127 from Uniqema.

3.7 vitamin E based surfactants, e.g. as known and commercially available under the name Vitamin E TPGS (polyethoxylated tocopherol succinate) from e.g. Eastman Kodak.

3.8 sucrose esters, e.g. sucrose stearate or sucrose palmitate.

3.9 monoglyceride based food emulsifiers, e.g. as known and commercially available under the trade name Panodan® AM VEG from Danisco (Fiedler, loc. cit., vol. 2, pp. 1139), or citric acid esters of monoglyceride, e.g. Citrem® LC VEG from Danisco.

3.10 polyethoxylated hydrogenated castor oil, e.g. as known and commercially available under the trade name Cremophor® RH 60 from BASF (Fiedler, loc. cit.; vol. 2, pp. 394), which has a saponification value of about 40 to 50, an acid value less than about 1, an iodine value of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, an n_D^{60} of about 1.453 to 1.457 and an HLB of about 15 to 17.

3.11 polyethylene glycol (PEG) sterol ethers having, e.g. from 5 to 35 [CH_2-CH_2-O] units, e.g. 20 to 30 units, also in combination with polyoxethylene alkyl ethers. Preferably the polymer is as known and commercially available under the trade name Solulan® C24 (Choleth 24 (and) Ceteth 24) from Amerchol (Fiedler, loc. cit., vol. 2, pp. 1413), or Forlan® C-24 (Choleth 24 (and) Ceteth 24) from R.I.T.A. Corp. (Fiedler, loc. cit., vol. 2, pp. 647)

Similar products which may also be used are those which are known and commercially available under the trade name Nikkol® BPS-30 (polyethoxylated 30 phytosterol) or Nikkol® BPSH-25 (polyethoxylated 25 phytostanol), from e.g. Nikko Chemicals Co., Ltd.

3.12 lecithins, e.g. soy bean phospholipid, e.g. as known and commercially available under the trade name Lipoid® S75 from Lipoid; or egg phospholipid, e.g. as known and commercially available under the trade name Phospholipon® 90 from Nattermann (Fiedler, loc. cit., vol. 2, pp. 1185)

It is to be appreciated that surfactants may be complex mixtures containing side products or unreacted starting products involved in the preparation thereof, e.g. surfactants made by polyoxyethylation may contain another side product, e.g. polyethylene glycol.

In the compositions of the present invention, a surfactant having a hydrophilic-lipophilic balance (HLB) value of 8 to 40, e.g. 8 to 17, is preferred. The surfactant selected preferably has a hydrophilic-lipophilic balance (HLB) of at least 10. The HLB value is preferably the mean HLB value. Preferably, the surfactant is a polyethylene glycol (PEG) sterol ether having from 5 to 35 [CH_2-CH_2-O] units, e.g. Solulan® C24, a polyethoxylated fatty acid ester, e.g. Myrj® 59, a polyoxyethylene alkyl ether, e.g. Brij® 78P, sodium caprinate, or sodium stearoyl lactylate SSL P55.

In a further alternative embodiment, in the pharmaceutical compositions of the present invention consisting of or consisting essentially of (1) a drug and (3) a surfactant, the constitutional ratio of drug (e.g. cyclosporin) : surfactant may be e.g. from about 1 : 0.1 to 20, preferably from about 1 : 0.1 to 9.

Preferably in the pharmaceutical compositions of the present invention consisting of or consisting essentially of (1) a drug and (3) a surfactant, the surfactant may be selected from the group consisting of surfactants (3.1), (3.2), (3.5) and (3.11). More preferably, the surfactant is a polyethylene glycol (PEG) sterol ether having from 5 to 35 [CH_2-CH_2-O] units, e.g. Solulan® C24, a polyethoxylated fatty acid ester, e.g. Myrj® 59, a polyoxyethylene alkyl ether, e.g. Brij® 78P, sodium caprinate or sodium stearoyl lactate SSL P55. Even more preferably, the surfactant is sodium caprinate or sodium stearoyl lactate SSL P55.

The surfactant may be present in an amount by weight of e.g. 1% up to about 90%, e.g. 10 to 70%, by weight of the composition.

Compositions comprising anionic surfactants, e.g. sodium caprinate or sodium stearoyl lactate SSL P55, preferably are enteric coated. The enteric coating may be applied to tablets and/or to granules, pellets, powders or particles which may be further compressed to tablets.

The term "enteric coating", as used herein, comprises any pharmaceutically acceptable coating preventing the release of the poorly water-soluble drug in the stomach and sufficiently disintegrating in the intestinal tract, e.g. by contact with juices of a pH of about 5, approximately neutral or alkaline intestine juices, to allow the resorption of the active agent through the walls of the intestinal tract. Preferably, the poorly water-soluble drug, e.g. cyclosporin, is released at a pH of about 5. In vitro tests for determining whether or not a coating is classified as an enteric coating is known in the art.

More specifically, the term "enteric coating", as used herein, refers to a coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38°C and preferably thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH_2PO_4 buffered solution of pH 6.8.

The enteric coating may be applied as described e.g. in Remington's Pharmaceutical Sciences, 18th Edition, Ed.: Alfonso R. Gennaro, Easton, PA : Mack, 1990, Bauer K., Lehmann K., Osterwald H., Überzogene Arzneiformen, 1988, Wissensch. VG, Stuttgart, the contents of which are incorporated herein.

Preferably, the release of the poorly water-soluble drug is not prolonged by the enteric coating.

In another embodiment, the compositions of the invention, e.g. in form of a tablet, a powder or a capsule, comprise

(1) a poorly water soluble drug, e.g. a cyclosporin,

(2) a polymer which is solid at room temperature, and

(3) a surfactant, e.g. a nonionic or ionic or amphoteric surfactant.

The surfactant may be selected from the group (3.1) to (3.12) mentioned above.
Preferably a non-ionic surfactant may be used. More preferably, the surfactant may be selected from the group consisting of surfactants (3.1), (3.2), and (3.11). Even more preferably, the surfactant is a polyethylene glycol (PEG) sterol ether having from 5 to 35 [CH_2-CH_2-O] units, e.g. Solulan® C24, a polyethoxylated fatty acid ester, e.g. Myrj® 59, and a polyoxyethylene alkyl ether, e.g. Brij® 78P.

In a further aspect the present invention provides the compositions of the invention, e.g. in form of a tablet, a powder or a capsule, comprising

(1) a poorly water soluble drug, e.g. a cyclosporin,

(2) a polymer which is solid at room temperature, and

(3) a surfactant, which e.g. is solid at room temperature, e.g. a surfactant which can exist in the form of a, e.g. flowable, powder and having a melting point of e.g. above 40°C.

In the pharmaceutical composition of the present invention comprising (1) a poorly water soluble drug, e.g. a cyclosporin, (2) a polymer which is solid at room temperature, and (3) a surfactant, the amount of the surfactant may be up to about 50%, e.g. up to about 40%, e.g. up to about 20% by weight, e.g. 1 to 15% by weight, preferably from about 2 to 10, in particular about 3 to 7% by weight based on the total weight of the composition comprising the poorly water-soluble drug, e.g. cyclosporin, the polymer and the surfactant. Preferably,

the ratio of surfactant : drug (e.g. cyclosporin) is 1 : 0.5 to 50, e.g. 1 : 1 to 40, e.g. 1 : 2 to 20. Preferably these three components comprise at least 95, or 95% of the composition.

A preferred embodiment comprises cyclosporin compositions comprising a polymer (2) which is solid at room temperature, and a surfactant (3) which is solid at room temperature.

In a further aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule comprising
(1) a poorly water soluble drug, e.g. a cyclosporin,
(2) a polymer,
(3) optionally a surfactant and
(4) a carrier.

In another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule consisting of or consisting essentially of
(1) a poorly water soluble drug, e.g. a cyclosporin,
(3) a surfactant and
(4) a carrier.

Preferably as a carrier is present e.g.:

4.1 a water-soluble or water-insoluble saccharide such as lactose or mannitol;

4.2 microcrystalline cellulose, e.g. as known and commercially available under the trade name Avicel® from FMC Corporation; or

4.3 colloidal silicon dioxide, e.g. as known and commercially available under the trade name Aerosil®;

4.4 anhydrous calcium phosphate, e.g. as known and commercially available under the trade name Fujicalin®, or anhydrous dicalcium phosphate, e.g. as known and commercially available under the trade name A-TAB® from Rhodia.

A mixture of carriers may be present.

Any carrier, if present, is generally present in an amount of up to about 50%, e.g. 0.5 to 50%, e.g. 10 to 40%, e.g. 15 to 40% by weight, preferably from about 20 to about 30% by

weight based on the total weight of the composition comprising the drug, e.g. cyclosporin, the polymer and/or surfactant and the carrier.

The surfactant is preferably present in an amount of 20 to 50% by weight of the composition, for example about 30% by weight of the composition comprising the drug, e.g. cyclosporin, polymer and/or the surfactant and the carrier.

In another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule comprising

(1) a poorly water soluble drug, e.g. a cyclosporin, e.g. cyclosporin A,
(2) a polymer,
(3) optionally a surfactant,
(4) optionally a carrier, and
(5) optionally a disintegrant.

In yet another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule consisting of or consisting essentially of
(i) a poorly water soluble drug (1), e.g. a cyclosporin, e.g. cyclosporin A,
(ii) a surfactant (3),
(iii) a carrier (4), and/or a disintegrant (5).

Suitable disintegrants include e.g.

5.1 natural starches, such as
5.1.1 maize starch, potato starch, and the like,
5.1.2 directly compressible starches, e.g. Sta-rx® 1500, modified starches, e.g. carboxymethyl starches and sodium starch glycolate, available as Primojel®, Explotab®, Explosol®, and
5.1.3 starch derivatives such as amylose;
5.2 crosslinked polyvinylpyrrolidones, e.g. crospovidones, e.g. Polyplasdone® XL and Kollidon® CL;
5.3 alginic acid or sodium alginate;
5.4 methacrylic acid-divinylbenzene copolymer salts, e.g. Amberlite® IRP-88; and
5.5 cross-linked sodium carboxymethylcellulose, available as e.g. Ac-di-sol®, Primellose®, Pharmacel® XL, Explocel®, and Nymcel® ZSX, or

5.6 a mixture of thereof.

The disintegrant or disintegrants may be present in an amount of 1 to 50%, e.g. 5 to 40% by weight based on the total weight of the composition.

In a further aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule comprising
(1) a poorly water soluble drug, e.g. a cyclosporin, e.g. cyclosporin A,
(2) a polymer,
(3) optionally a surfactant,
(4) optionally a carrier,
(5) optionally a disintegrant, and
(6) optionally a lubricant, e.g. magnesium stearate.

In yet another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule consisting of or consisting essentially of
(i) a poorly water soluble drug (1), e.g. a cyclosporin, e.g. cyclosporin A,
(ii) a surfactant (3),
(iii) a carrier (4), a disintegrant (5) and/or a lubricant (6), e.g. magnesium stearate.

Lubricants may be present in a total amount of up to about 5% by weight, e.g. 2%, e.g. 1% by weight based on the total weight of the composition.

The pharmaceutical composition may also include further additives or ingredients, for example antioxidants, such as ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols, and/or preserving agents. In a further alternative aspect these additives or ingredients may comprise about 0.05 to 1% by weight of the total weight of the composition. The pharmaceutical composition may also include sweetening or flavoring agents in an amount of from e.g. 0.1 to e.g up to about 2.5 or 5% by weight based on the total weight of the composition.

Details of excipients of the invention are described in e.g. Fiedler, H. P., loc cit; "Handbook of Pharmaceutical Excipients", loc cit; or may be obtained from the relevant manufacturers, the contents of which are hereby incorporated by reference.

Preferably the compositions of the present invention do not contain any organic hydrophilic component. Under "organic hydrophilic component" is to be understood any hydrophilic component or any hydrophilic co-component as described in the above mentioned British patent application no. 2 222 770. Such hydrophilic components excluded may comprise no added hydrophilic component such as water soluble components and/or ethanol, propylene glycol or water. Naturally it will be appreciated that small amounts of organic hydrophilic components e.g. which have no significant effect, may be tolerated, e.g. as a result of impurities such as less than 3% by weight of the composition.

Preferably the compositions of the present invention do not contain any lipophilic component. Under "lipophilic component" is to be understood any lipophilic component as described in the above mentioned British patent application no. 2 222 770. Such lipophilic components excluded comprise no added lipophilic component such as glyceryl fatty acid ester. Naturally it will be appreciated that small amounts of lipophilic components e.g. which have no significant effect, may be tolerated, e.g. as a result of impurities such as less than 3% by weight of the composition.

Accordingly, in one aspect the present invention provides a composition as described above which is free, e.g. substantially free, from an organic hydrophilic component and/or a lipophilic component. In one group of compositions of the present invention there is no glyceryl fatty acid present.

The drug, e.g. cyclosporin, may be present in an amount by weight of up to about 50% by weight of the composition. The drug is preferably present in an amount of e.g. 1 to 50%, e.g. 15 to 40% by weight of the composition, for example about 20% by weight of the composition comprising the drug, e.g. cyclosporin, the polymer and/or the surfactant. Yet, the tablets or capsules are of a volume that allows convenient administration, e.g. easy swallowing.

In one aspect, upon dilution with an aqueous medium the compositions of the present invention may form, e.g. to an substantial amount, e.g. to the extent of 60% or more, e.g. 85% or more, e.g. more than 90, 95 or 99%, fine particles of, e.g. substantially amorphous,

poorly water-soluble drug, e.g. cyclosporin. By "substantially amorphous " is meant more than 90%, e.g. more than 95%, preferably about or more than 99% in amorphous form.

Preferably, upon dilution with an aqueous medium, for example water, for example on dilution of 1:1 to 1:300, e.g. 1:5 to 1:100, e.g. 1:10 to 1:100, or in the gastric juices after oral application, the compositions of the present invention, comprising (1) a poorly water soluble drug, e.g. a cyclosporin, (2) a polymer and/or (3) a surfactant, spontaneously substantially form fine particles, e.g. solid particles of substantially amorphous poorly water-soluble drug, e.g. cyclosporin, e.g. of a range of from 50 nm to 20 000 nm, e.g. from 50 nm to 10 000 nm, e.g. from 50 nm to 2000 nm, e.g. as measured by conventional methods, e.g. light diffraction techniques, e.g. based on a Mastersizer. Conveniently, there is a narrow size distribution.

In another aspect, upon dilution with an aqueous medium the compositions of the present invention comprising (1) a poorly water soluble drug, e.g. cyclosporin, (3) a surfactant which is solid at room temperature, may form a system which is a mixture of substantially solubilized drug, e.g. about 10 to 100%, preferably about 10 to 80%, e.g. 30 to 40%, more preferably 40 to 70% of the total drug and particulate drug, e.g. about 0 to 90%, preferably about 20 to 90%, e.g. 60 to 70%, more preferably 30 to 60% of the total drug. The constitutional ratio of drug : surfactant may be preferably 1 : 0.1, or 1 : 0.25, or 1 : 0.5, or 1 : 1, or 1 : 2, or 1 : 4, or 1 : 9. Preferably, the drug is cyclosporin, e.g. cyclosporin A.

In yet a further aspect the present invention provides compositions which upon dilution with an aqueous medium form a system wherein the poorly water-soluble drug, e.g. cyclosporin, e.g. Cyclosporin A, substantially is solubilized, e.g. is solubilized to an extent of about 90% of total drug or more, e.g. more than about 95%. It has been found that surprisingly low drug (e.g. cyclosporin) : nonionic surfactant ratios of e.g. about 1 : 5.3 to 6.6, may be used to completely solubilize the drug, e.g. cyclosporin, when one of the nonionic surfactants as specified above, e.g. Choleth 24 (and) Ceteth 24, e.g. Solulan® C24 or Forlan® C-24; or polyethoxylated (30) phytosterol, e.g. Nikkol® BPS-30; or polyethoxylated (25) phytostanol, e.g. Nikkol® BPSH-25; or polyethoxylated (20) stearyl ether, e.g. Brij® 78P; or polyethoyxlated (20) cetyl ether, e.g. Nikkol® BC-20 TX, is used. Particularly suitable are polyethoxylated (30) phytosterol, e.g. Nikkol® BPS-30; or polyethoxylated (25) phytostanol, e.g. Nikkol® BPSH-25; or polyethoxylated (20) stearyl ether, e.g. Brij® 78P.

The amount of poorly water-soluble drug, e.g. cyclosporin, which can be solubilized may be analyzed by centrifugation followed by HPLC for the distribution of drug, e.g. cyclosporin, between the solubilized and particulate phase.

The state of the particles may be analyzed by X-ray and the particle size distribution may be analyzed e.g. by laser light scattering or electron microscopy.

The compositions of this invention may produce on contact with water stable e.g. particulate systems, e.g. for up to one day or longer, e.g. one day. Preferably the systems remain stable for more than 5 hours.

In one aspect the present invention provides a composition, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant, which is in form of a solid dispersion.

In a further alternative aspect the present invention provides a composition according to the present invention comprising (2) a polymer wherein the poorly water-soluble drug, e.g. cyclosporin, is encapsulated in a polymeric matrix, e.g. in form of microparticles.

The compositions of the invention may be prepared by working up active agent with the excipients. The following processes A to H are contemplated.

A. In one aspect the compositions of the present invention in form of a solid dispersion comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant may be obtained by

(i) dissolving, suspending or dispersing the drug, e.g. cyclosporin, and polymer, if present, in a solvent or solvent mixture,

(ii) adding the surfactant, if present, to the drug/solvent or drug/polymer/solvent mixture,

(iii) evaporating the solvent and co-precipitating the drug, e.g. cyclosporin, with the polymer and/or the surfactant,

(iv) drying the resulting residue, e.g. under reduced pressure, milling and sieving the particles.

The solvent of (i) may be a single solvent or a mixture of solvents. Suitable solvents for use according to the present invention may be organic solvents such as an alcohol, e.g. methanol, ethanol, or isopropanol; an ester, e.g. ethylacetate; an ether, e.g. diethylether; a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. dichloromethane. Preferably a solvent mixture of ethanol/acetone having a weight ratio of ethanol : acetone of between about 1:10 to about 10:1, e.g. 1:5 to 5:1 may be used.

B. In another aspect the compositions of the present invention in form of a solid dispersion comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant may be obtained by

(i) dissolving, suspending or dispersing the drug, e.g. cyclosporin, and surfactant, if present, in a solvent or solvent mixture and optionally adding small amounts of water, if necessary,

(ii) adding the polymer, if present, to the drug/solvent or drug/surfactant/solvent mixture,

(iii) evaporating the solvent and co-precipitating the drug, e.g. cyclosporin, with the surfactant and/or the polymer,

(iv) drying the resulting residue, e.g. under reduced pressure, milling and sieving the particles.

The solvent of (i) may be a single solvent or a mixture of solvents. Suitable solvents for use according to the present invention may be organic solvents such as an alcohol, e.g. methanol, ethanol, or isopropanol; an ester, e.g. ethylacetate; an ether, e.g. diethylether; a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. dichloromethane. Preferably a solvent mixture of ethanol/acetone having a weight ratio of ethanol : acetone of between about 1:10 to about 10:1, e.g. 1:5 to 5:1 may be used.

C. Alternatively, the solid dispersions of the invention, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant, may be prepared by spray-drying techniques. A solution or dispersion as formed above is dispersed through a nozzle at an inlet temperature of about 50 to about 130°C into a chamber. The solvent is evaporated through the nozzle, and finely dispersed particles are collected.

D. In a further alternative embodiment of the present invention the solid dispersion, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a

surfactant, may be prepared by spray-drying the solution or dispersion as formed above onto (4) a carrier in the fluid bed.

The particles typically have a mean particle size of less than about 2 mm, e.g. 1 mm, e.g. 0.5 mm, as measured e.g. by light microscopy.

E. The compositions of the present invention wherein the poorly water-soluble drug, e.g. cyclosporin, is encapsulated in a polymeric matrix, e.g. in form of microparticles, may be prepared e.g. according to a process comprising the following steps:

(i) preparation of an internal organic phase comprising

(ia) dissolving the polymer in an organic solvent or solvent mixture. The solvent may be a single solvent or a mixture of solvents. Suitable solvents for use according to the present invention may be organic solvents such as a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. methylene chloride. Preferably a solvent mixture of methylene chloride/acetone having a weight ratio of methylene chloride : acetone of between about 1:10 to about 10:1, e.g. 1:5 to 5:1, preferably 1:1, may be used,

(ib) adding the poorly water-soluble drug, e.g. cyclosporin, to the polymer solution, and optionally

(ic) adding a surfactant to the solution obtained by step (ib),

(ii) preparation of an external aqueous phase comprising

(iia) preparing a buffer, e.g. acetate buffer,

(iib) dissolving gelatin or polyvinylalcohol (PVA) in water, and

(iic) mixing the solution obtained by step (iib) with the solution obtained by step (iia) to obtain e.g. a 0.5% gelatin solution in the buffer,

(iii) mixing the internal organic phase, e.g. brought at 20 ml/min with a gear pump, with the external aqueous phase, e.g. brought at 400 ml/min with a gear pump, e.g. in a ratio of internal phase to external phase of about 1 : 10 to about 1 : 40, preferably about 1 : 20, with a device creating high shear forces, e.g. with a static mixer, to form e.g. an oil/water emulsion, and

(iv) hardening the microparticles by solvent evaporation, washing for excipients removal and collecting the microparticles.

The microparticles typically have a mean particle size of less than about 350 microns, e.g. about 1 to about 180 microns, as measured e.g. by scanning electron microscopy.

In order to e.g. increase flowability of the final microparticle powder, the obtained microparticles may be further worked up by adding an aqueous solution of a carrier, e.g. lactose, and lyophilization or spray drying of the resulting suspension to obtain a, e.g. flowable, powder.

F. In one embodiment the compositions of the invention, in form of solid dispersions, comprising a surfactant are obtained by

(i) preparation of an organic preconcentrate comprising dissolving the surfactant in an organic solvent or a mixture of solvents, e.g. ethanol, adding the poorly water-soluble drug, e.g. cyclosporin, and stirring until dissolved,

(ii) diluting or delivering the organic preconcentrate obtained in step (i) to a mixer, e.g. a magnetic stirrer or a static mixer, together with an aqueous solution, optionally comprising a carrier, e.g. lactose, and

(iii) spray-drying the mixture or, if no carrier is present in step (ii), spray-drying the diluted preconcentrate obtained in step (ii) onto a carrier, e.g. lactose, e.g. in the fluid bed.

G. In yet a further embodiment of the present invention the compositions of the invention, in form of solid dispersions, comprising a surfactant (3) are prepared by

(i) dissolving the surfactant, e.g. ionic surfactant, the cycloysporin and optionally a carrier e.g. lactose in water, and

(ii) spray-drying the aqueous solution

H. In yet a further alternative embodiment of the present invention the compositions of the invention, in form of solid dispersions, comprising a surfactant (3) are prepared by

(i) dissolving the poorly water-soluble drug, e.g. cyclosporin, in an organic solvent, e.g. propylene glycol, to obtain e.g. a 40% solution of poorly water-soluble drug, e.g. cyclosporin, in propylene glycol,

(ii) mixing the solution obtained in step (i) with a molten surfactant,

(iii) optionally mixing or granulating the mixture obtained in step (ii) with a carrier, e.g. lactose; or microcrystalline cellulose, or colloidal silicon dioxide; or anhydrous calcium phosphate, and

(iv) cooling the mixture obtained in step (ii) or (iii) to obtain a solid composition.

The solid dispersions obtained by processes F to H preferably do not contain any polymer (2).

Other excipients may be added at any stage, preferably however after the powder is formed.

The resulting mixtures of any of the processes F to H described above may be dried, milled and sieved to obtain a fine, e.g. flowable, powder.

The compositions of the invention in powder form, e.g. particles, e.g. solid dispersion particles or microparticles, may be compressed to tablets.

The particles, e.g. solid dispersion particles or microparticles, may be combined with one or more flow enhancers, e.g. colloidal silicon dioxide, and/or one or more solid surfactants as specified above, e.g. sodium lauryl sulfate, e.g. in a total amount of enhancers and/or surfactants of up to about 70% by weight, e.g. 20 to 60% by weight, in particular 40 to 50% by weight based on the total weight of the composition.

If present in the compositions, the filler or a mixture of fillers, the disintegrants or a mixture of disintegrants, the lubricants or a mixture of lubricants, the flow enhancers or a mixture of flow enhancers, the additional surfactant or surfactants may be added to the drug/polymer/solvent mixture, the drug/surfactant/solvent mixture, the drug/polymer/surfactant/solvent mixture or, preferably, to the outer tabletting phase.

In one aspect of the invention the outer tabletting phase may comprise one or more solid surfactants as specified above, e.g. sodium lauryl sulfate, instead or in addition to adding a surfactant to the drug/polymer/solvent mixture in the preparation process of the solid dispersion particles or microparticles, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and optionally (3) a surfactant, as hereinabove described.

The outer tabletting phase may comprise e.g. spray-dried lactose/microcrystalline cellulose mixtures, dicalcium phosphate anhydrous or a mixture of α-lactose monohydrate and microcrystalline cellulose, e.g. Microcelac® 100, e.g. to achieve tablet compositions with a suitable average hardness and a short disintegration time.

Microcelac® 100 is a spray-dried compound consisting of 75% α-lactose monohydrate and 25% microcrystalline cellulose produced by Meggle.

Accordingly, in one embodiment, the present invention provides tablet compositions with an average hardness of e.g. from 60 N to 200 N, preferably 80 N to 110 N, and/or a disintegration time of e.g. below about 10 min, preferably below 1 min, wherein the outer tabletting phase comprises e.g. lactose/microcrystalline cellulose mixtures, dicalcium phosphate anhydrous or α-lactose monohydrate/microcrystalline cellulose mixtures.

Preferably, the compositions comprise α-lactose monohydrate/microcrystalline cellulose mixtures, e.g. Microcelac® 100, in an amount of e.g. about 10 to 80%, e.g. about 10 to 60% by weight based on the total weight of the composition or dicalcium phosphate anhydrous in an amount of e.g. about 10 to 80%, e.g. about 10 to 60% by weight based on the total weight of the composition.

Preferably, compositions comprising HPMCP comprise α-lactose monohydrate/microcrystalline cellulose mixtures, e.g. Microcelac®. Preferably, compositons comprising PVP comprise dicalcium phosphate anhydrous.

Applicants have found that surprisingly high drug loadings may be obtained in accordance with the present invention, e.g. drug loadings up to 70%, e.g. from about 20 to about 60%, in particular about 30 to 50% by weight based on the total weight of the particles, e.g. solid dispersion particles or microparticles, or e.g. drug loadings of up to 40%, e.g. about 20% by weight based on total weight of the final composition.

The compositions, e.g. those in the examples hereinafter, show good stability characteristics as indicated by standard stability trials, e.g. no poorly water-soluble drug, e.g. cyclosporin, crystallization (as determined by differential scanning calorimetry) or degradation, having e.g. a shelf life stability of up to one, two or three years, and even longer. The compositions

of this invention may produce stable particulate systems upon dilution with aqueous media, e.g. for up to one day or longer, e.g. one day.

The pharmaceutical compositions of the invention exhibit especially advantageous properties when administered orally; for example in terms of consistency and high level of bioavailability obtained in standard bioavailability trials. These trials are performed in animals e.g. rats or dogs or healthy volunteers using HPLC or a specific or nonspecific monoclonal kit to determine the level of the drug substance, e.g. cyclosporin in the blood. For example, the compositions of Examples 1 to 15 administered p.o. to dogs may give surprisingly high C_{max} and AUC(0-24h) values as detected by a radioimmunoassay (RIA) method using a specific monoclonal antibody and within e.g. 60 to 120%, preferably 90 to 120%, of that of Neoral®.

In one aspect the present invention provides a method of orally administering a pharmaceutical composition, said method comprising orally administering to a patient in need of poorly water-soluble drug, e.g. cyclosporin, therapy a composition according to the present invention.

Pharmacokinetic parameters, for example absorption and blood levels, also become surprisingly more predictable and problems in administration with erratic absorption may be eliminated or reduced. Additionally the pharmaceutical compositions are effective with biosurfactants or tenside materials, for example bile salts, being present in the gastro-intestinal tract. That is, the pharmaceutical compositions of the present invention are fully dispersible in aqueous systems comprising such natural tensides and thus capable of providing particulate systems in situ which are stable. The function of the pharmaceutical compositions upon oral administration remain substantially independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual.

The pharmaceutical compositions of the invention release the poorly water-soluble drug, e.g. cyclosporin, to the extent of e.g. about above 80% over a 60 minute period, e.g. about 75% in a 15 minute period, as measured by standard in vitro dissolution studies, e.g. at pH 6.8 or 1 using the paddle method.

The compositions of this invention show reduced variability in inter- and intra-patient dose response.

In one aspect the present invention provides a method of reducing the variability of bioavailability levels of a poorly water-soluble drug, e.g. cyclosporin, for patients during poorly water-soluble drug, e.g. cyclosporin, therapy, said method comprising orally administering an oral pharmaceutical composition according to the present invention.

The utility of all the pharmaceutical compositions of the present invention may be observed in standard clinical tests in, for example, known indications of drug dosages giving equivalent blood levels of drug; for example using dosages in the range of 2.5 mg to 1000 mg of drug per day for a 75 kilogram mammal, e.g. adult and in standard animal models. The increased bioavailability of the drug provided by the compositions may be observed in standard animal tests and in clinical trials, e.g. as described above.

The optimal dosage of drug to be administered to a particular patient may be considered carefully as individual response to and metabolism of the drug, e.g. cyclosporin, may vary, e.g. by monitoring the blood serum levels of the drug by radioimmunoassay (RIA), enzyme linked immunosorbent assay (ELISA), or other appropriate conventional means. Poorly water-soluble drug, e.g. cyclosporin, dosages may be 25 to 1000 mg per day (preferably 50 mg to 500 mg).

The pharmaceutical composition, e.g. in form of a tablet or a powder suitable for tablet formation, will suitably contain between 10 and 100 mg of the drug, for example 10, 15, 20, 25, 50, or 100 mg. Such unit dosage forms are suitable for administration 1 to 5 times daily depending upon the particular purpose of therapy, the phase of therapy and the like.

The pharmaceutical compositions of the invention are useful for the same indications as the poorly water soluble drugs. The pharmaceutical compositions comprising a cyclosporin are particularly useful for:

a) treatment and/or prevention of organ, cell or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants. The pharmaceutical compositions are also indicated for the

prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation;

b) treatment and/or prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronic progrediente and arthritis deformans) and rheumatic diseases; and

c) treatment and/or prevention of psoriasis.

Pharmaceutical compositions of the invention, e.g. comprising cyclosporin, may be used alone or together with other immunosuppressants, immunomodulatory or anti-inflammatory drugs. For example, they may be used in combination with everolimus, sirolimus, tacrolimus, pimecrolimus, mycophenolic acid, mycophenolate sodium, mycophenolate mofetil, an accelerating lymphocyte homing agent, e.g. FTY720, corticosteroids, or the like.

Therefore in a further aspect the present invention provides

i. a pharmaceutical composition, e.g. comprising cyclosporin, as defined above for use in the treatment and/or prevention of organ, cell or tissue transplant rejection, prevention of graft-versus-host disease, treatment and/or prevention of autoimmune disease and of inflammatory conditions, and treatment and/or prevention of psoriasis;

ii. a method of treating and/or preventing organ, cell or tissue transplant rejection, preventing graft-versus-host disease, treating and/or preventing autoimmune disease and inflammatory conditions, and treating and/or preventing psoriasis, comprising administering a composition of the present invention, e.g. comprising cyclosporin, to a patient in the need thereof;

iii. the use of a composition of the present invention, e.g. comprising cyclosporin, in the preparation of a medicament for the treatment and/or prevention of organ, cell or tissue transplant rejection, prevention of graft-versus-host disease, treatment and/or prevention of autoimmune disease and of inflammatory conditions, and treatment and/or prevention of psoriasis; or

iv. a method as defined above comprising co-administering a composition of the present invention, e.g. comprising cyclosporin, and a second drug substance, said second drug substance being e.g. an immunosuppressant, an immunomodulatory or an anti-inflammatory drug.

Following is a description by way of example only of compositions of this invention. Unless otherwise indicated, components are shown in % by weight based on each composition. The examples illustrate compositions useful for example in the prevention of transplant rejection or for the treatment of autoimmune disease, on administration of from 1 to 5 unit dosages/day at a dose of 2 to 5 mg/kg per day. The examples are described with particular reference to Cyclosporin A but equivalent compositions may be obtained employing any cyclosporin or other poorly water-soluble drug.

Example 1 to 7:

Preparation of solid dispersion compositions

Compositions of examples 1 to 7 in amount as indicated in Table 1 are made up by dissolving Cyclosporin A in an ethanol/acetone mixture, adding the polymer, surfactant, if present, and carrier medium, if present, of Table 1, mixing until homogenously dispersed, evaporation of the solvents, and drying, milling and sieving the resulting residue.

Table 1

COMPONENT	Ex 1	Ex 2	Ex 3	Ex 4	Ex 5	Ex 6	Ex 7
Cyclosporin A	21%	30%	30%	40%	20%	25%	30%
PVP K30	-	67%	-	-	-	72%	-
HPMCP HP50	-	-	67%	55%	75%	-	63%
Eudragit® L100-55	50%	-	-	-	-	-	-
Solulan®	-	3%		-	-	3%	-
Myrj® 59	-	-	3%	5%	5%	-	-
Brij® 78P	-	-	-	-	-	-	7%
Lactose	25%	-	-	-	-	-	-
Crospovidone	4%	-	-	-	-	-	-

Example 8 and 9:

Preparation of microparticule compositions

Compositions of example 8 and 9 in amounts as indicated in Table 2 are made up by dissolving HPMCP HP50 in methylene chloride/acetone, adding Cyclosporin A and Brij® 78P or Myrj®59, respectively; delivering the polymer system to a mixer together with a buffered

gelatin solution; evaporation of the solvent, washing for excipients removal and collecting the microparticles.

Table 2

COMPONENT	Ex 8	Ex 9
Cyclosporin A	30%	40%
HPMCP HP50	63%	55%
Brij® 78P	7%	-
Myrj® 59	-	5%

Other examples may be made by replacing Eudragit® L100-55 or HPMCP HP50 by any of the polymers specified above or by replacing Brij® 78P by any of the surfactants specified above.

Example 10:

Compositions of example 10 in amounts as indicated in Table 3 are made up by dissolving the surfactant and the cyclosporin and suspending the carrier in ethanol, stirring to obtain a homogenous suspension, and evaporation of the solvent under reduced pressure.

The resulting powder is milled and sieved. After dilution with water at a ratio of 1+100 at 37°C the distribution of Cyclosporin A between solubilized and particulate phase is analyzed by centrifugation followed by HPLC. The results show a mixture of solubilized (35%) and particulate (65%) cyclosporin A. Particle sizes of up to about 12.5 microns are measured by a light microscope.

Table 3:

quantity given in wt-%

COMPONENTS	Ex. 10	Ex. 11	Ex. 12
Cyclosporin A	25%	30%	25%
Brij® 78P	50%	-	-
Sodium stearyl lactylate P55	-	30%	-
Sodium caprinate	-	-	37%
Lactose	25%	40%	38%

Example 11:

Compositions of example 11 in amounts as indicated in Table 3 are made up by dissolving the surfactant in ethanol, adding the cyclosporin, stirring to obtain a solution, delivering the organic preconcentrate to a mixer together with an aqueous solution of lactose, and spray-drying the mixture to obtain a fine powder.

The resulting powder is diluted with water at a ratio of 1+100 at 37°C and the distribution of Cyclosporin A between solubilized and particulate phase is analyzed by centrifugation followed by HPLC. The results show a mixture of solubilized (29%) and particulate 71% cyclosporin A. Particle sizes of up to about 2.5 microns are measured by a light microscope.

Example 12:

Compositions example 12 in amounts as indicated in Table 3 are made up by dissolving the surfactant, the cyclosporin, and the carrier in water, and spray-drying the aqueous solution to obtain a fine powder.

The resulting powder is diluted with water at a weight ratio of 1+7 at 37°C and the distribution of Cyclosporin A between solubilized and particulate phase is analyzed by centrifugation followed by HPLC. The results show a mixture of solubilized (72%) and particulate (28%) cyclosporin A.

Other examples may be made by replacing Brij® 78P, or sodium stearoyl lactylate P55, or sodium caprinate by any of the surfactants specified above.

Other examples may be made by replacing lactose by any of the carriers specified above.

Example 13 and 14:

Preparation of tablets based on solid dispersion particles

Compositions of examples 13 and 14 in amount as indicated in Table 4 are made up by dissolving Cyclosporin A in an ethanol/acetone mixture, adding the polymer, surfactant, if present, and carrier medium, if present, of Table 4, mixing until homogenously dispersed, evaporation of the solvents, and drying, milling and sieving the resulting residue. The

resulting particles are mixed with the additional excipients and directly compressed to flat tablets.

The tablets have a hardness (compression force), a disintegration time and dissolution rates as indicated in Table 5.

Table 4

COMPONENT	Ex 13	Ex 14	Ex. 15
Cyclosporin A	16.7%	14.3%	20%
PVP K30	-	41.2%	-
HPMCP HP50	22.9%	-	27.5%
Solulan®	-	1.7%	-
Myrj® 59	2.1%	-	2.5%
Crospovidone	20%	30%	20%
Microcelac 100	37.5%	-	29.2%
dicalcium phosphate anhydrous	-	12%	-
magnesium stearate	0.5%	0.5%	0.5%
Aerosil 200	0.3%	0.3%	0.3%

Table 5

	Ex 13	Ex 14	Ex. 15
average hardness in N	91	94	95
disintegration time in minutes	< 1	< 8	< 1
tablet diameter in mm	10	11	9
tablet weight in mg	300	350	250
dissolution rate after 15 min	80%	90%	89%
dissolution rate after 60 min	92%	94%	90%

Example 15

Preparation of tablets based on microparticules

Compositions of example 15 in amounts as indicated in Table 4 are made up by dissolving HPMCP HP50 in methylene chloride/acetone, adding Cyclosporin A and Myrj®59; delivering the polymer system to a mixer together with a buffered gelatin solution; evaporation of the

solvent, washing for excipients removal and collecting the microparticles. The resulting particles are mixed with the additional excipients and directly compressed to flat tablets.
The tablets have a hardness (compression force), a disintegration time and dissolution rates as indicated in Table 5.

Example 16

Single oral doses of 50 mg cyclosporin A per animal of composition of example 1,8, 10, 11 and 12 filled in a hard gelatin capsule size 1, corresponding to about 5 mg/kg were given to fasted dogs (n = 8) using a two-block latin square design with a one-week interval between administrations. The nominal doses of cyclosporin A in mg/kg body weight are listed in Table 6.
Blood (about 1 ml each) was collected from the cephalic or jugular vein at 0 min (= pre-dose), and 10 min, 30 min, 45 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours post dose. The EDTA blood samples were stored frozen below -18°C until bioanalysis.
Cyclosporin A blood concentrations were determined by a radioimmunoassay (RIA) method.

The pharmacokinetic parameters C_{max} (highest observed concentration in blood); t_{max} (time to reach C_{max}); and AUC(0-24h) (area under the plasma concentration-time curve from 0 to 24 h, calculated by the linear trapezoidal rule, wherein concentrations below the limit of quantitation (LOQ) were taken as 'zero'), are listed in Table 6.

Table 6:

	Composition of						
	Ex. 1	Ex. 8	Ex. 10	Ex. 11	Ex. 12	Ex. 6	Ex. 13
Actual dose CyA [mg/kg]	4.89	4.93	4.05	4.14	4.07	3.45	4.67
AUC(0-24h) [(ng/ml)·h]	1893	1973	935	894	576	2646	3436
C_{max} [ng/ml]	394	441	223	195	136	428	635
t_{max} [h]	1.69	1.28	1.57	1.86	2.57	1.13	1.53

Example 17

Single oral doses of 50 mg cyclosporin A per animal of composition of example 6 in form of a suspension in water, corresponding to about 2.5 - 4 mg/kgwere given to fasted dogs (n =

10) using a two-block latin square design with a one-week interval between administrations. The nominal doses of cyclosporin A in mg/kg body weight are listed in Table 6.

Blood (about 1 ml each) was collected from the jugular vein at 0 min (= pre-dose), and 10 min, 30 min, 45 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours post dose. The EDTA blood samples were stored frozen below -18°C until bioanalysis.

Cyclosporin A blood concentrations were determined by a radioimmunoassay (RIA) method.

The pharmacokinetic parameters C_{max} (highest observed concentration in blood); t_{max} (time to reach C_{max}); and AUC(0-24h) (area under the plasma concentration-time curve from 0 to 24 h, calculated by the linear trapezoidal rule, wherein concentrations below the limit of quantitation (LOQ) were taken as 'zero'), are listed in Table 6.

Example 18

Single oral doses of 50 mg cyclosporin A per animal of tablet compositions of example 13 corresponding to about 5 mg/kg were given to fasted dogs (n = 7) using a two-block latin square design with a one-week interval between administrations. The nominal doses of cyclosporin A in mg/kg body weight are listed in Table 6.

Blood (about 3 ml each) was collected from the cephalic vein at 0 min (= pre-dose), and 10 min, 30 min, 45 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours post dose. The EDTA blood samples were stored frozen below -18°C until bioanalysis.

Cyclosporin A blood concentrations were determined by a radioimmunoassay (RIA) method.

The pharmacokinetic parameters C_{max} (highest observed concentration in blood); t_{max} (time to reach C_{max}); and AUC(0-24h) (area under the plasma concentration-time curve from 0 to 24 h, calculated by the linear trapezoidal rule, wherein concentrations below the limit of quantitation (LOQ) were taken as 'zero'), are listed in Table 6.

Claims

1. A solid pharmaceutical composition comprising
   (1) a poorly water soluble drug,
   (2) a polymer which is solid at room temperature, and
   (3) a surfactant which is solid at room temperature and which has a HLB value of between 8 and 17.
2. A composition according to claim 1 wherein the ratio of surfactant : drug is 1 : 1 to 40.
3. A composition according to claim 1 or 2 wherein the surfactant is selected from poly-oxyethylene alkyl ethers, polyethoxylated fatty acid esters or polyethylene glycol (PEG) sterol ethers.
4. A composition according to any preceding claim wherein the polymer is selected from polyvinyl pyrrolidone; cellulose derivatives such as hydroxypropylmethylcellulose or such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate and cellulose acetate phthalate; and poly(meth)acrylates.
5. A solid pharmaceutical composition comprising
   (1) a poorly water soluble drug,
   (2) a polymer which is solid at room temperature, and
   (3) an anionic surfactant which is solid at room temperature.
6. A composition according to claim 5 wherein the anionic surfactant is sodium caprinate or sodium stearoyl lactate.
7. A composition according to claim 5 or 6 which is enteric coated.
8. A composition according to any preceding claim wherein the composition is in form of a solid dispersion.
9. A composition according to claim 1 to 7 wherein the drug is encapsulated in a polymeric matrix.
10. A composition according to any preceding claim wherein the poorly water soluble drug is cyclosporin A.
11. A composition according to any preceding claim wherein the composition is substantially free of a hydrophilic component.
12. A composition according to any preceding claim wherein the composition is substantially free of a lipophilic component.
13. A composition according to any preceding claim which upon dilution with an aqueous medium forms a system wherein the poorly water-soluble drug substantially is in the form of fine particles.

14. A composition according to any one of claims 1 to 12 which upon dilution with an aqueous medium forms a system which is a mixture of solubilized drug and particulate drug.

15. A composition according to any one of claims 1 to 12 which upon dilution with an aqueous medium forms a system wherein the poorly water-soluble drug substantially is solubilized.

16. Use of a composition as claimed in any one of claims 1 to 15 in the manufacture of a medicament for the treatment of autoimmune diseases or for the use as an immunosuppressant.

17. A process for the production of a composition according to claim 8 which process comprises

(i) dissolving, suspending or dispersing the drug and polymer, if present, in a solvent or solvent mixture,

(ii) adding the surfactant, if present, to the drug/solvent or drug/polymer/solvent mixture,

(iii) evaporating the solvent and co-precipitating the drug with the polymer and/or the surfactant,

(iv) drying the resulting residue, milling and sieving the particles.

18. A process for the production of a composition according to claim 9 which process comprises

(i) preparation of an internal organic phase comprising the drug, the polymer, optionally the surfactant, and an organic solvent,

(ii) preparation of an external aqueous phase comprising a buffered gelatin solution,

(iii) mixing the internal organic phase with the external aqeous phase,

(iv) hardening the microparticles by solvent evaporation.

19. A solid pharmaceutical composition comprising

(1) Cyclosporin A, and

(2) a polymer which is solid at room temperature.

20. A solid pharmaceutical composition comprising

(1) a cyclosporin and

(3) a surfactant which is solid at room temperature.

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORIN

(57) Abstract: A solid pharmaceutical composition, e.g. in form of a tablet, powder or capsule, comprising 1) a poorly water soluble drug, e.g. cyclosporin, 2) a polymer which is solid at room temperature, and 3) a surfactant which is solid at room temperature and which has an HLB value of between 8 and 17.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K38/13 A61P37/06

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, PASCAL, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rodriguez-Palmero, M

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INTERNATIONAL SEARCH REPORT

Int. ›nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

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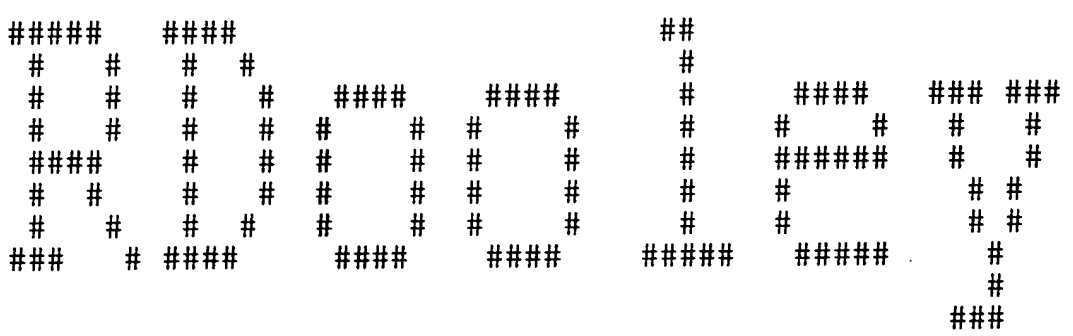

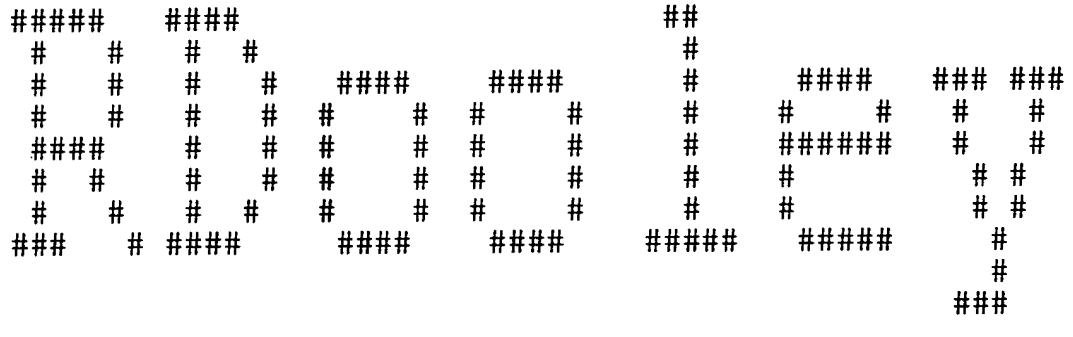

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Job Number: 749

I, _____, hereby declare as follows:

1. I submit this declaration in opposition to Defendants' Motion for Summary Judgment of Invalidity Under 35 U.S.C. §§ 102 and 112. Goss International Americas, Inc. has retained me as an expert witness in connection with this litigation. A true and correct copy of my Rebuttal Expert Report dated ____, is attached as Exhibit 1.

2. I am...

3. I have reviewed...

4. The specifications of U.S. Patent Nos. 6,374,734 B1 and 6,386,100 B1, ("the '734 Patent" and "the '100 Patent," respectively), describe a printing blanket having a "cylindrical outer surface which is continuous and free of gaps to promote smooth rolling engagement with the cylindrical outer surface of the printing plate 41 on the plate cylinder 22. The absence of gaps in the smooth cylindrical outer surface 40 of the printing blanket 18 eliminates bumps or vibrations as compared to having a gap which rolls into and out of engagement with the surface of the printing plate 41 on the plated cylinder 22." (HWS 078090, lines 54-62 and HWS 078106, lines 34-43, respectively). In my technical opinion, a person of ordinary skill in the art in 1997, reading the '734 Patent and the '100 Patent (filed November, 11, 1997, and March 11, 1997, respectively), would understand the specification to describe a tubular blanket which eliminates bumps and vibrations associated with prior printing blanket designs by remaining in constant contact with the printing plate during use.

5. Additionally, the '734 and '100 Patents both describe as an advantage of the invention that the gapless printing blanket "provides smooth and vibration free rolling engagement between the printing blanket and the printing plate and between the printing blanket and an impression cylinder." (HWS 078089, lines16-19 and HWS 078105, lines 6-9, respectively). A person of ordinary skill in the art reading this specification would understand it to describe a tubular printing blanket which eliminates vibrations by remaining in constant contact with the printing plate and an impression cylinder.

6. A person of ordinary skill in the art would understand that a tubular printing blanket could remain in constant contact with the printing plate if the tubular printing blanket was gapless. In my understanding, this is one practical example of the structure of the tubular printing blanket disclosed in the '734 and '100 Patents. However, it is my opinion that a person of ordinary skill in the art would recognize that the advantages associated with this invention could similarly be attained by alternate structures.

7. A person of ordinary skill in the art would also understand that this tubular printing blanket could also include gaps, seams, or adhesives and still remain in constant contact with the printing plate. This alternative embodiment would likewise create a smooth cylinder surface, which would eliminate bumps or vibrations.

8. Additionally, U.S. Patent No. 6,739,251 B2 (filed February 8, 2002) has an identical specification to the '734 and '100 Patents. It is also my opinion that a person of ordinary skill in the art reading the U.S. Patent No. 6,739,251 B2 ("the '251 Patent") on its filing date in 2002 would likewise understand the specification to describe a tubular blanket which remains in

constant contact with the printing plate, thereby eliminating bumps and vibrations associated with prior printing blanket designs.

9. In addition to the knowledge that a person skilled in the art would have individually possessed in 1997, one skilled in the art in 1997 would also have knowledge of U.S. Patent Application No. 07/417,587 ("the '587 Application"), filed on October 4, 1989. The '587 Application was published in both Canada and Europe before the filing of U.S. Application No. 07/699,668 ("the '668 Application") on May 14, 1991. Accordingly, a person of ordinary skill in the art, reading the '668 Application and all later-filed related applications (including the '734, '100, and '251 Patents), would have knowledge of the '587 Application and the invention described therein.

10. The '587 Application explicitly disclosed two different methods for making the tubular blanket. The first method included vulcanizing strips of the outer rubber layer to form a solid body which enclosed the metal sleeve. Alternatively, the '587 Application disclosed that the blanket "could be made in a flat planar piece of material which is then wrapped around sleeve 80 and adhered thereto. The opposite ends of the piece of material would abut each other." (HWS 000179). As the '587 Application also disclosed, the smooth cylindrical outer surface of the blanket "eliminates bumps or vibrations as compared to having a gap which rolls in and out of engagement" with the surface of the printing plate. (HWS 000167). It is my technical opinion that a person of ordinary skill in the art in 1989, reading the '587 Application, would understand the '587 Application's specification to describe a tubular blanket which remains in constant contact with the printing plate, thereby eliminating bumps and vibrations associated with prior printing blanket designs. Accordingly, a person of ordinary skill in the art, reading any of the later-filed patents (the '668, '734, '100, and '251 Patents) on their filing date, would undoubtedly understand that a tubular printing blanket made of a flat panel, wrapped around the blanket sleeve with the ends abutting each other, could eliminate the common problem of vibrations and bumps in the same way as a blanket with a solid outer layer.

11. A person of ordinary skill in the art in 1997 would have also known of U.S. Patent No. 5,351,615 (filed May 25, 1993, issued October 4, 1994). U.S. Patent No. 5,351,615 ("the '615 Patent") describes a blanket composed of a carrier plate and rubber layer. "Beginning and end of the carrier plate and of the rubber layer are connected to each other in such a way that the outer circumferential surface of the blanket is continuous and without gaps." (G127512, lines14-18). Additionally, this specification provides that "means for reproducibly positioning the seam connecting the beginning and the end of the blanket are provided." (G127512, lines 21-23). The '615 Patent cites the objective of preventing "printing quality losses due to vibration loads as a result of impacts at the groove..." (2:8-9). Accordingly, a person of ordinary skill in the art reading the '734 and '100 Patents in light of the '615 Patent would necessarily be aware of the possibility of creating a vibrationless interaction between the printing plate and a blanket that includes a seam. This also holds true for the same person reading the '251 Patent in 2002.

12. A person of ordinary skill in the art reading the '251 Patent in 2002 would have also known of U.S. Patent No. 6,148,725 (filed July 16, 1997, issued November 21, 2000). U.S. Patent No. 6,148,725 ("the '725 Patent") describes a rubber cylindrical sleeve comprised of multiple layers, many of which may contain a joint location. "[T]o form a continuous compressible layer....oppositely located free ends (not shown) of the compressible sheet material

are spliced together or otherwise joined using known joinery means to form a joint location 8." (G 127520, lines 53-58). However, the outermost layer "is configured as a longitudinally continuous tube or cylinder having no joints or seams." (G 127520, lines 65-67). Accordingly, a person if ordinary skill in the art reading the '251 Patent in 2002 would be made further aware of the possibility for creating a rubber cylinder sleeve that does not "adversely impact the print quality" (G 127519, line 30) similar to other cylinder sleeves with connection seams on the outermost layer, while the cylinder sleeve contains seams.

13. Therefore, one skilled in the art would necessarily have comprehended the invention described in the '734, '100, and '251 Patents to describe tubular printing blankets.

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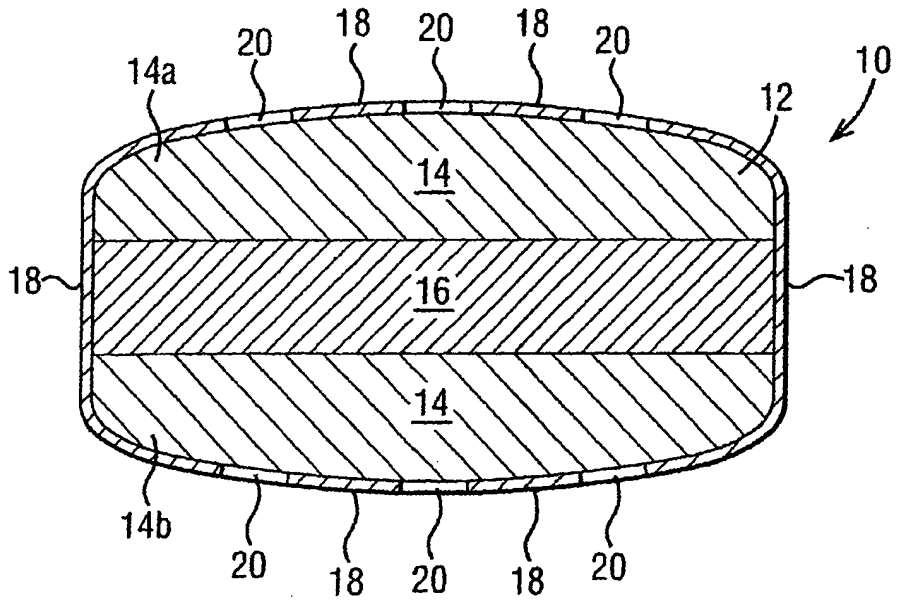
[Continued on next page]

(54) Title: HYDROGEL-DRIVEN DRUG DOSAGE FORM



(57) Abstract: A controlled release dosage form has a coated core with the core comprising a drug-containing composition and a water-swellable composition, each occupying separate regions within the core. The coating around the core is water-permeable, water-insoluble and has at least one delivery port therethrough. A variety of geometric arrangements are disclosed.

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HYDROGEL-DRIVEN DRUG DOSAGE FORM

BACKGROUND OF THE INVENTION

The present invention relates to a dosage form that provides a controlled release of a beneficial agent, or drug, to an environment of use.

Osmotic and hydrogel-driven drug delivery devices for the release of a drug have been known in the art for some time. Exemplary dosage forms have included a tablet comprising a semipermeable wall surrounding a compartment containing the drug and a layer of swellable hydrogel, with the drug being delivered through a passageway in the semipermeable wall by swelling of the hydrogel, as described in U.S. Patent No. 4,327,725; another tablet comprising a wall permeable to an exterior fluid but impermeable to the drug, the wall surrounding a compartment containing two osmotic agents, two expandable polymers and the drug, as described in U.S. Patent No. 4,612,008; drug dispersed in a swellable hydrogel matrix core that releases the drug by diffusion into the environment of use, as described in U.S. Patent No. 4,624,848; a hydrogel reservoir containing a multiplicity of tiny pills wherein each tiny pill consists of a wall surrounding a drug core, as described in U.S. Patent No. 4,851,232; and a two-layered tablet wherein one layer is drug mixed with a hydrogel and the other layer is a hydrogel, as described in U.S. Patent No. 5,516,527.

While the conventional dosage forms described above are functional, nonetheless such dosage forms suffer from a variety of drawbacks. A controlled release dosage form should ideally deliver substantially all of the drug from the dosage form to the environment of use. However, a common problem encountered by osmotic and hydrogel-driven dosage forms, particularly when the drug has low aqueous solubility, is that residual drug is left in the tablet interior after the hydrogel or other swellable material has completely swelled. This residual drug is not available for absorption and, accordingly, such dosage forms require increased amounts of drug to compensate for the failure of the system to release all of the drug into the environment of use.

In addition, the controlled release dosage form must operate within certain size constraints, and yet be capable of delivering most or all of the drug to the environment of use. Dosage forms, particulary for humans, are limited in size, and are usually less than 1 gram, more preferably less than 700 mg in weight. However, for some types of drugs, the dose amount may make up to half or even more of the weight of the dosage form. The water-swellable materials that provide the delivery of the drug must in instances where the dose is high be capable of

providing a highly efficient delivery of the drug, since very little of the dosage form may be available for the swellable material or other excipients.

In addition, it is often desired that the dosage form begin extruding drug relatively quickly upon entering the use environment. However, many delivery systems exhibit a time lag before extruding drug. This can be particularly problematic when the drug has low aqueous solubility or is hydrophobic. Several techniques have been proposed to reduce the time lag, but each has its own drawback. One technique has been to provide high-permeabilitiy coatings by utilizing thin coatings around the dosage form. While this technique provides a quicker uptake of fluid, the thin coating lacks strength and often bursts in use or provides insufficient protection to the dosage form which becomes susceptible to damage during handling. Yet another technique has involved providing pores or one or more passageways that communicate with the water-swellable materials, but this often leads to unacceptable amounts of residual drug. Another technique involves coating the dosage form with an immediate release drug formulation, but this requires additional processing steps and provides a dosage form with two different release rates, which may be undesirable.

Yet another problem encountered with conventional osmotic and hydrogel-driven drug delivery systems is that such dosage forms often require the presence of osmagents. Osmagents are selected such that they generate an osmotic pressure gradient across the barrier of the surrounding coating. The osmotic pressure gradient drives the permeation of water into the tablet and the resulting buildup of sufficient hydrostatic pressure, which forces the drug through the delivery port. These osmagents increase the weight of the dosage form, thus limiting the amount of drug which may be contained in the dosage form. In addition, the presence of additional ingredients in the dosage form, such as osmagents, increases the costs of manufacture due to the need to insure uniform concentrations of the ingredients throughout the dosage form, and may have other drawbacks such as adverse effects on compression properties and on drug stability.

Very little has been done to investigate the delivery of drugs from dosage forms having different arrangements of materials. Dosage forms of the prior art generally fall into one of three arrangements. The first is the conventional bi-layer design, which is characterized by a drug-containing layer and a water-swellable layer. Exemplary of these devices is Wong, et al., U.S. Patent No. 4,612,008.

Yet another arrangement consists of a water-swellable layer surrounded by a drug-containing composition. Such a device is shown in Curatolo, U.S. Patent No. 5,792,471.

Yet another arrangement is shown by McClelland et al., U.S. Patent No. 5,120,548, which discloses a controlled release delivery device containing swelling modulators blended within swellable polymers.

Nevertheless, there is still a need in the art for a controlled release dosage form that results in a highly efficient delivery of drug to an environment of use with very little residual drug, that allows large drug loading so as to minimize the dosage size, that begins releasing drug soon after entering the environment of use, and that limits the number of necessary ingredients. These needs and others which will become apparent to one skilled in the art are met by the present invention, which is summarized and described in detail below.

BRIEF SUMMARY OF THE INVENTION

The various aspects of the invention each provide a controlled release drug dosage form for delivery of at least one drug. A first aspect of the invention provides a controlled release drug dosage form comprising a core and a coating around the core. The core comprises a first drug-containing composition, a second drug containing composition, and a water-swellable composition, each occupying separate regions within the core. The water-swellable composition is located between the first and second drug-containing compositions. The coating is water-permeable, water-insoluble, and has at least one delivery port for communication with the first drug-containing composition and at least one additional delivery port for communication with the second drug-containing composition.

A second aspect of the invention provides a controlled release drug dosage form comprising a core and a coating around said core. The core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core. The drug-containing composition surrounds the water-swellable composition. The drug-containing composition comprises a low-solubility drug and a drug-entraining agent. The water-swellable composition comprises a swelling agent. The coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

A third aspect of the invention provides a controlled release drug dosage form comprising a core and a coating. The core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within the core. The water-swellable composition comprises a plurality of granules. The drug-containing composition comprises a drug and a drug-entraining agent. The water-swellable composition comprises a swelling agent. The coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

A fourth aspect of the invention provides a controlled release drug dosage form comprising a core and a coating. The core is substantially homogeneous throughout and comprises a mixture of a drug, a drug-entraining agent, a fluidizing agent, and a swelling agent. The coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

This invention further provides a method of treating a disease or condition amenable to treatment with a pharmaceutical agent which is administered in a controlled release (*i.e.*, sustained release or delayed release) dosage form, comprising administering to a person in need of such treatment a controlled release dosage form according to any of the four aspects disclosed above, said dosage form comprising an effective amount of said pharmaceutical agent.

The amount of a particular compound which is administered will necessarily be varied according to principles well known in the art taking into account factors such as the particular compound of interest, the severity of the disease or condition being remediated and the size and age of the patient. In general, the compound will be administered so that an effective dose is received, an "effective dose" being determined from safe and efficacious ranges of administration already known for the particular compound of interest. Alternatively, an effective amount can be determined by the attending physician.

The methods of treatment disclosed above are not limited by or to any particular disease or indication, and the scope of such methods is intended to be broad, such methods of treatment including, but not being limited to, any of the classes of compounds or specific compounds disclosed hereinbelow.

The various aspects of the present invention have one or more of the following advantages. The dosage forms of the present invention are capable of delivering greater amounts of drug to the desired environment of use with greater efficiency using smaller amounts of swelling materials, and also result in lower amounts of residual drug than do conventional compositions. The compositions are also capable of higher drug loading compared with conventional compositions. In addition, the compositions begin delivering drug to the environment of use more quickly than do conventional dosage forms. The dosage forms are capable of rapidly delivering a drug without the coating failing due to rupture as a result of excessive pressure within the core when the dosage form is introduced into an environment of use.

In addition, the various embodiments provide at least one manufacturing advantage relative to the bi-layer design, in that the location of the delivery port is not as important, as discussed below. In addition, for the aspect comprising a homogeneous core, that embodiment eliminates processing associated

with forming separate layers.

The foregoing and other objectives, features, and advantages of the invention will be more readily understood upon consideration of the following detailed description of the invention, taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWING

FIGS. 1-4 are schematic drawings of cross sections of exemplary embodiments of dosage forms of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a controlled release dosage form that is specifically designed to provide controlled release of at least one drug primarily by imbibition of water and extrusion of drug from the dosage form as opposed to primarily by diffusion. Referring now to the figures, wherein like numerals refer to like elements, FIGS. 1-4 depict schematically four exemplary dosage form arrangements. FIG. 1 depicts a "tri-layer" tablet; FIG. 2 depicts a "concentric core" tablet; FIG. 3 depicts a "granular core" tablet; and FIG. 4 depicts a "homogeneous core" tablet. Certain features common to all of the exemplary embodiments may be understood by first considering FIG. 1 which shows an exemplary tri-layer dosage form 10 having a core 12 comprising drug-containing composition(s) 14 and a water-swellable composition 16. The drug-containing composition(s) and the water-swellable composition occupy separate regions in the core. By "separate regions" is meant that the two compositions occupy separate volumes, such that the two are not substantially mixed together. Of course, a small amount of intermixing of the compositions may occur where the compositions come in contact with each other, for example, at the interface between two layers. A coating 18 surrounds the core 12 and is water-permeable, water-insoluble and has one or more delivery ports 20 therethrough. In use, the core 12 imbibes water through the coating 18 from the environment of use such as the gastrointestinal ("GI") tract of a mammal. The imbibed water causes the water-swellable composition 16 to swell, thereby increasing the pressure within the core 12. The imbibed water also increases the fluidity of the drug-containing composition. The pressure difference between the core 12 and the environment of use drives the release of the fluidized drug-containing composition(s) 14. Because the coating 18 remains intact, the drug-containing composition(s) 14 are extruded out of the core 12 through the delivery port(s) 20 into the environment of use. Because the water-swellable composition 16 contains no drug, almost all of the drug is extruded through the delivery port(s) 20, leaving very little residual drug.

The dosage form of the present invention releases the drug to an environment of use primarily by "extrusion" rather than by diffusion. The term "extrusion" as used herein is intended to convey an expulsion or forcing out of some or all of the drug through one or more delivery ports or pores in the coating to the exterior of the dosage form by hydrostatic forces, to be distinguished from delivery by a diffusion mechanism or by erosion of the mass of the device. The drug may be released primarily by extrusion either in the form of a suspension of solids in aqueous solution or the drug may be in solution, to the extent dissolution has taken place in the core 12.

Reference to the "release" of drug as used herein means (1) transport of drug from the interior of the dosage form to its exterior such that it contacts fluid within a mammal (*e.g.*, a mammal's GI tract) following delivery or (2) transport of drug from the interior of the dosage form such that it contacts a test medium for evaluation of the dosage form by an *in vitro* test as described below. Reference to a "use environment" can thus be either to *in vivo* fluids or to an *in vitro* test medium. "Introduction" to a use environment includes either by ingestion or swallowing or use of implants or suppositories, where the use environment is *in vivo*, or being placed in a test medium where the use environment is *in vitro*.

DOSAGE FORM ARRANGEMENT

Four exemplary dosage form arrangements are schematically shown in FIGS. 1-4.

FIG. 1 depicts a "tri-layer" tablet 10 comprising a core 12 that has two drug-containing compositions 14a and 14b on either side of a water-swellable composition 16 and, surrounding the core 12, a coating 18 that has at least one delivery port 20 through the coating connecting each drug layer 14a and 14b with the exterior of the dosage form. The tri-layer dosage form provides several advantages. First, the dosage form may be used to deliver two different drugs. Thus, the drug-containing composition 14a may contain a drug that is different than the drug in drug-containing composition 14b. Second, even when the drug-containing compositions 14a and 14b contain the same drug, the two drug-containing compositions may be formulated differently so as to provide different release rates for the drug. Thus, for example, drug-containing composition 14a could provide a fast release rate for a drug, while drug-containing composition 14b could provide a slow release rate, thus allowing a wide range of drug profiles to be achieved.

Another advantage of the tri-layer design is that the delivery port is located on both sides of the core, rather than on a single side as in the bi-layer arrangement. It is desired that the bi-layer dosage form have at least one delivery

port in communication with the drug-containing composition. A problem when manufacturing bi-layer dosage forms is that for some compositions, providing a delivery port in communication with the water-swellable composition diminishes performance. Thus, care and added expense are required during manufacturing to locate the side of the dosage form facing the drug-containing composition and then provide a delivery port only on that side of the dosage form. In contrast, for the tri-layer design, it is desired to have a delivery port on both sides of the dosage form. Therefore, it is no longer necessary to locate the correct side for providing the delivery port, since a delivery port is provided on both sides of the dosage form.

FIG. 2 depicts a "concentric core" tablet 10' comprising a core 12 that has a drug-containing composition 14 that surrounds a water-swellable composition 16 and surrounding the core, a coating 18 that has at least one delivery port 20 through the coating 18 connecting the drug layer 14 with the exterior of the dosage form. The concentric core dosage form provides at least one processing advantage relative to the bi-layer arrangement in that the location of the delivery port is not critical, since the water-swellable composition is surrounded by the drug-containing composition. Thus any delivery port will be in communication with the drug-containing composition regardless of location. Also, water must pass through the drug-containing composition prior to entering the water-swellable composition ensuring that the drug-containing composition is fluid enough to be delivered prior to pressure being exerted by the water-swellable composition.

FIG. 3 depicts a "granular core" tablet 10" comprising a core 12, a coating 18 and at least one delivery port 20. The core comprises a drug-containing composition 14, and multiple granules of a water-swellable composition 16 mixed throughout the drug-containing composition 14. Like the concentric core embodiment, the location of the delivery port for the granular core is not important, and therefore provides a manufacturing advantage relative to the bi-layer arrangement.

Yet another advantage of the granular core tablet is that it may be formed using conventional single-layer tablet-manufacturing equipment. This avoids the expense of a multi-layer tablet press.

FIG. 4 depicts a "homogeneous core" tablet 100, comprising a core 12, a coating 18 and at least one delivery port 20. The core comprises a homogenous drug-containing composition 15 that contains both the drug and the swelling materials. The homogeneous core provides at least three manufacturing advantages. First, the location of the delivery port is not important, since any delivery port will be in communication with the drug-containing composition. Second, only a single drug-containing composition needs to be prepared, rather than

separate drug-containing compositions and water-swellable compositions. Third, standard single-layer tablet-making equipment can be used to form the core. Accordingly, the cost associated with preparing additional compositions is eliminated.

RELEASE CHARACTERISTICS

An important attribute of the dosage forms of the present invention is the delivery of drug to a use environment in a controlled manner. For some aspects of the present invention, the dosage forms start releasing drug soon after introduction to the use environment. When a rapid onset of delivery is desired, preferably the dosage forms release at least 5 wt% of the drug, and more preferably at least 10 wt% of the drug within 2 hours after introduction to the use environment, where these percentages correspond to the mass of drug released from the core relative to the total mass of drug originally present in the core. By quickly beginning the release of the drug, the dosage form shortens the time required to achieve an effective drug concentration in a use environment such as the upper GI tract. Rapid release can also reduce the time required to achieve an effective drug level in the blood.

It is also desired that the dosage forms release the drug in a controlled manner, preferably at a substantially constant rate. For many drugs, it is preferred that the dosage forms release no more than about 60 wt% of the drug, and more preferably no more than about 50 wt% of the drug, into the use environment within 2 hours after introduction to the use environment. The rate of release of drug from the dosage form should also be sufficiently high to allow release of the drug within a time frame that allows a substantial fraction of the drug delivered to be absorbed into the blood stream. For many drugs the dosage forms preferably release at least 60 wt% of the drug, and more preferably at least 70 wt% of the drug to the use environment within 16 hours after introduction to the use environment. The inclusion of a fluidizing agent in the drug-containing composition is particularly useful when more rapid delivery of drug to the use environment is desired. In particular, when it is desirable to deliver at least 70 wt% of the drug to the use environment within 12 hours after introduction thereto, the invention allows rapid drug release without rupture or otherwise failure of the dosage form coating during operation.

It is also desired that the dosage forms release a substantial amount of the drug contained within the dosage form, leaving a relatively small residual amount of drug after 24 hours. Obtaining low residual amounts of drug is particularly difficult when it is desired to deliver high doses of low-solubility drug. Preferably, the dosage forms of the present invention release at least 80 wt% of drug, more

preferably at least 90 wt%, and even more preferably at least 95 wt% of drug to the use environment within 24 hours after introduction of the dosage form to the use environment.

An *in vitro* test may be used to determine the release profile(s) of the dosage forms of the present invention. *In vitro* tests are well known in the art. An example is a "residual test," which is described below for sertraline HCl. One or more dosage forms is first placed into a stirred USP type 2 dissoette flask containing 900 mL of a buffer solution simulating gastric environment (10 mM HCl, 120 mM NaCl, pH 2.0, 261 mOsm/kg) at 37□C for 2 hours, then removed, rinsed with deionized water, and transferred to a stirred USP type 2 dissoette flask containing 900 mL of a buffer solution simulating the contents of the small intestine (6 mM KH_2PO_4, 64 mM KCl, 35 mM NaCl, pH 7.2, 210 mOsm/kg). In both flasks, the dosage forms are placed in a wire support to keep the dosage forms off of the bottom of the flask, so that all surfaces are exposed to the moving release solution and the solutions are stirred using paddles that rotate at a rate of 50 rpm. At each time interval, a single dosage form is removed from the solution, released material is removed from the surface, and the dosage form cut in half and placed in 100 mL of a recovery solution (1:1 wt/wt ethanol:water, pH adjusted to 3 with 0.1 N HCl), and vigorously stirred overnight at ambient temperature to dissolve the drug remaining in the dosage form. Samples of the recovery solution containing the dissolved drug are filtered using a Gelman Nylon® Acrodisc® 13, 0.45 μm pore size filter, and placed in a vial and capped. Residual drug is analyzed by HPLC. Drug concentration is calculated by comparing UV absorbance of samples to the absorbance of drug standards. The amount remaining in the tablets is subtracted from the total drug present prior to release to obtain the amount released at each time interval.

An alternative *in vitro* test is a direct test, in which samples of the dosage form are placed into a stirred USP type 2 dissoette flask containing 900 mL of a receptor solution such as USP sodium acetate buffer (27 mM acetic acid and 36 mM sodium acetate, pH 4.5) or 88 mM NaCl. Samples are taken at periodic intervals using a VanKel VK8000 autosampling dissoette with automatic receptor solution replacement. Tablets are placed in a wire support as above, paddle height is adjusted, and the dissoette flasks stirred at 50 rpm at 37□C. The autosampler dissoette device is programmed to periodically remove a sample of the receptor solution, and the drug concentration is analyzed by HPLC using the procedure outlined above. Since the drug is usually extruded from the dosage form as a suspension in an entraining polymer, there is often a time lag between when the drug is released and when it is dissolved in the test medium, and thus, measured in the direct test. This time lag depends on the solubility of the drug, the test medium,

and the ingredients of the drug-containing composition, but typically is on the order of 30 to 90 minutes.

While particular buffers or test media in which to conduct *in vitro* tests have been described above, any conventional test media may be used as is well known in the art.

Alternatively, an *in vivo* test may be used. However, due to the inherent difficulties and complexity of the *in vivo* procedure, it is preferred that *in vitro* procedures be used to evaluate dosage forms even though the ultimate use environment is often the human GI tract. Drug dosage forms are dosed orally to a group of mammals, such as humans or dogs and drug release and drug absorption is monitored either by (1) periodically withdrawing blood and measuring the serum or plasma concentration of drug or (2) measuring the amount of drug remaining in the dosage form following its exit from the anus (residual drug) or (3) both (1) and (2). In the second method, residual drug is measured by recovering the tablet upon exit from the anus of the test subject and measuring the amount of drug remaining in the dosage form using the same procedure described above for the *in vitro* residual test. The difference between the amount of drug in the original dosage form and the amount of residual drug is a measure of the amount of drug released during the mouth-to-anus transit time. This test has limited utility since it provides only a single drug release time point but is useful in demonstrating the correlation between *in vitro* and *in vivo* release.

In one *in vivo* method of monitoring drug release and absorption, the serum or plasma drug concentration is plotted along the ordinate (y-axis) against the blood sample time along the abscissa (x-axis). The data may then be analyzed to determine drug release rates using any conventional analysis, such as the Wagner-Nelson or Loo-Riegelman analysis. See also Welling, "Pharmacokinetics: Processes and Mathematics" (ACS Monograph 185, *Amer. Chem. Soc.*, Washington, D.C., 1986). Treatment of the data in this manner yields an apparent *in vivo* drug release profile.

DRUG-CONTAINING COMPOSITION

For the tri-layer, concentric core, and granular core embodiments of the present invention, the drug-containing composition 14 includes at least one drug and preferably additional excipients (the homogeneous core embodiment is discussed below). The drug-containing composition occupies a separate, substantially distinct region from the water-swellable composition. For the granular core embodiment, a substantially distinct region means that the water-swellable composition is present in a plurality of separate granules distributed throughout the drug-containing composition. When it is desired to deliver a relatively large dose of drug (about 100 mg or more) in a single dosage form, the drug-containing composition preferably comprises greater than about 50 wt% of the core. When it is desirable to deliver even greater amounts of drug (*e.g.*, 150 mg or more), the drug-containing composition comprises preferably greater than about 60 wt% of the core, and more preferably greater than about 70 wt% of the core. Preferably, the drug-containing composition 14 is in contact with or in close proximity to the coating 18 which surrounds the dosage form.

The drug-containing composition(s) may contain one or more drugs, and in the case of the tri-layer dosage form, the first drug-containing composition 14a may contain a different drug than the second drug-containing composition 14b. The drug may be virtually any beneficial therapeutic agent and may comprise from 0.1 to 65 wt% of the drug-containing composition 14. In cases where the dose to be delivered is high (*e.g.*, greater than about 100 mg), it is preferred that the drug comprise at least 35 wt% of the drug-containing composition 14. The drug may be in any form, either crystalline or amorphous. The drug may also be in the form of a solid dispersion.

The invention finds particular utility when the drug is a "low-solubility drug," meaning that the drug is either "substantially water-insoluble" (which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL), or "sparingly water soluble," that is, has a minimum aqueous solubility at physiologically relevant pH up to about 1 to 2 mg/mL, or has even low to moderate aqueous solubility, having a minimum aqueous solubility at physiologically relevant pH as high as about 10 to 20 mg/mL. In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than 10 mL, and more typically greater than 100 mL, where the drug solubility is the minimum value in mg/mL observed in any physiologically relevant aqueous solution (e.g., those with pH values between 1 and 8) including USP simulated gastric and intestinal buffers and the dose is in mg. The drug may be employed in its neutral

(e.g., free acid, free base, or zwitterion) form, or in the form of its pharmaceutically acceptable salts as well as in anhydrous, hydrated, or solvated forms, and pro drugs.

Preferred classes of drugs include, but are not limited to, antihypertensives, antidepressants, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, antibiotics, antiviral agents, anti-neoplastics, barbituates, sedatives, nutritional agents, beta blockers, emetics, anti-emetics, diuretics, anticoagulants, cardiotonics, androgens, corticoids, anabolic agents, growth hormone secretagogues, anti-infective agents, coronary vasodilators, carbonic anhydrase inhibitors, antiprotozoals, gastrointestinal agents, serotonin antagonists, anesthetics, hypoglycemic agents, dopaminergic agents, anti-Alzheimer's Disease agents, anti-ulcer agents, platelet inhibitors and glycogen phosphorylase inhibitors.

Specific examples of the above and other classes of drugs and therapeutic agents deliverable by the invention are set forth below, by way of example only. Specific examples of antihypertensives include prazosin, nifedipine, trimazosin, amlodipine, and doxazosin mesylate; a specific example of an antianxiety agent is hydroxyzine; a specific example of a blood glucose lowering agent is glipizide; a specific example of an anti-impotence agent is sildenafil citrate; specific examples of anti-neoplastics include chlorambucil, lomustine and echinomycin; specific examples of anti-inflammatory agents include betamethasone, prednisolone, piroxicam, aspirin, flurbiprofen and (+)-N-{4-[3-(4-fluorophenoxy)phenoxy]-2-cyclopenten-1-yl}-N-hyroxyurea; a specific example of a barbituate is phenobarbital; specific examples of antivirals include acyclovir, nelfinavir, and virazole; specific examples of vitamins/nutritional agents include retinol and vitamin E; specific examples of a -blocker include timolol and nadolol; a specific example of an emetic is apomorphine; specific examples of a diuretic include chlorthalidone and spironolactone; a specific example of an anticoagulant is dicumarol; specific examples of cardiotonics include digoxin and digitoxin; specific examples of an androgen include 17-methyltestosterone and testosterone; a specific example of a mineral corticoid is desoxycorticosterone; a specific example of a steroidal hypnotic/anesthetic is alfaxalone; specific examples of an anabolic agent include fluoxymesterone and methanstenolone; specific examples of antidepression agents include fluoxetine, pyroxidine, venlafaxine, sertraline, paroxetine, sulpiride, [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(lethylpropyl)-amine and

3,5-dimethyl-4-(3'-pentoxy)-2-(2',4',6'-trimethylphenoxy)pyridine; specific examples of an antibiotic include ampicillin and penicillin G; specific examples of an anti-infective include benzalkonium chloride and chlorhexidine; specific examples of a coronary vasodilator include nitroglycerin and mioflazine; a specific example of a hypnotic is etomidate; specific examples of a carbonic anhydrase inhibitor include acetazolamide and chlorzolamide; specific examples of an antifungal include econazole, terconazole, fluconazole, voriconazole and griseofulvin; a specific example of an antiprotozoal is metronidazole; a specific example of an imidazole-type anti-neoplastic is tubulazole; specific examples of an anthelmintic agent include thiabendazole and oxfendazole; specific examples of an antihistamine include astemizole, levocabastine, cetirizine, and cinnarizine; a specific example of a decongestant is pseudoephedrine; specific examples of antipsychotics include fluspirilene, penfluridole, risperidone and ziprasidone; specific examples of a gastrointestinal agent include loperamide and cisapride; specific examples of a serotonin antagonist include ketanserin and mianserin; a specific example of an anesthetic is lidocaine; a specific example of a hypoglycemic agent is acetohexamide; a specific example of an anti-emetic is dimenhydrinate; a specific example of an antibacterial is cotrimoxazole; a specific example of a dopaminergic agent is L-DOPA; specific examples of anti-Alzheimer agents are THA and donepezil; a specific example of an anti-ulcer agent/H2 antagonist is famotidine; specific examples of a sedative/hypnotic include chlordiazepoxide and triazolam; a specific example of a vasodilator is alprostadil; a specific example of a platelet inhibitor is prostacyclin; specific examples of an ACE inhibitor/antihypertensive include enalaprilic acid and lisinopril; specific examples of a tetracycline antibiotic include oxytetracycline and minocycline; specific examples of a macrolide antibiotic include azithromycin, clarithromycin, erythromycin and spiramycin; specific examples of glycogen phosphorylase inhibitors include [R-(R*S*)]-5-chloro-N-[2-hydroxy-3{methoxymethylamino}-3-oxo-l-(phenylmethyl)-propyl]-IH-indole-2-carboxamide and 5-chloro-1-Hindole-2-carboxylic acid [(IS)-benzyl(2R)-hydroxy-3-((3R,4S)dihydroxy-pyrrolidin-1-yl-)-oxypropyl]amide.

Further examples of drugs deliverable by the invention are the glucose-lowering drug chlorpropamide, the anti-fungal fluconazole, the anti-hypercholesterolemic atorvastatin calcium, the antipsychotic thiothixene hydrochloride, the anxiolytics hydroxyzine hydrochloride and doxepin hydrochloride, the anti-hypertensive amlodipine besylate, the antiinflammatories piroxicam and celicoxib and valdicoxib, and the antibiotics

carbenicillin indanyl sodium, bacampicillin hydrochloride, troleandomycin, and doxycycline hyclate.

In an alternative embodiment, the drug is present in the form of a solid, amorphous dispersion. By solid, amorphous dispersion is meant that the drug is dispersed in a polymer so that a major portion of the drug is in a substantially amorphous or non-crystalline state, and its non-crystalline nature is demonstrable by x-ray diffraction analysis or by differential scanning calorimetry. The dispersion may contain from about 5 to 90 wt% drug. The polymer is aqueous-soluble and inert, and, when enhancement of bioavailability is desirable, is preferably concentration-enhancing. Suitable polymers and methods for making solid amorphous dispersions are disclosed in commonly assigned provisional patent applications Serial Nos. 60/119,406 and 60/119,400, the relevant disclosures of which are incorporated by reference. Suitable dispersion polymers include ionizable and non-ionizable cellulosic polymers, such as cellulose esters, cellulose ethers, and cellulose esters/ethers; and vinyl polymers and copolymers having substituents selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido, such as polyvinyl pyrrolidone, polyvinyl alcohol, copolymers of polyvinyl pyrrolidone and polyvinyl acetate. Particularly preferred polymers include hydroxypropylmethyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), and polyvinyl pyrrolidone (PVP). Most preferred are HPMCAS, HPMCP, CAP and CAT.

When the drug has a low solubility (less than about 20 mg/ml) it is preferable that the drug-containing composition also comprise an entraining agent. The use of an entraining agent is necessitated by the low-solubility drug, which due to its low-solubility does not dissolve sufficiently within the core 12 to be extruded in the absence of an entraining agent. The entraining agent suspends or entrains the drug so as to aid in the delivery of the drug through the delivery port(s) 20 to the environment of use. While not wishing to be bound by any particular theory, it is believed that upon imbibing water into the dosage form, the entraining agent imparts sufficient viscosity to the drug-containing composition to allow it to suspend or entrain the drug, while at the same time remaining sufficiently fluid to allow the entraining agent to pass through the delivery port(s) 20 along with the drug. It has been found that there is a good correlation between the usefulness of a material as an entraining agent and the viscosity of an aqueous solution of the material. The entraining agent generally is a material that has high water solubility and in operation forms aqueous solutions with viscosities of at least 50 centipoise (cp) and preferably aqueous solutions with viscosities of 200 cp or greater.

The amount of the entraining agent present in the drug-containing composition may range from about 5 wt% to about 98 wt% of the drug-containing composition, preferably 10 wt% to 50 wt% more preferably 10 wt% to 40 wt%. The entraining agent may be a single material or a mixture of materials. Examples of such materials include polyols, and oligomers of polyethers, such as ethylene glycol oligomers or propylene glycol oligomers. In addition, mixtures of polyfunctional organic acids and cationic materials such as amino acids or multivalent salts, such as calcium salts may be used. Of particular utility are polymers such as polyethylene oxide (PEO), polyvinyl alcohol, PVP, cellulosics such as hydroxyethyl cellulose (HEC), hydroxypropylcellulose (HPC), HPMC, methyl cellulose (MC), carboxy methyl cellulose (CMC), carboxyethylcellulose (CEC), gelatin, xanthan gum or any other water-soluble polymer that forms an aqueous solution with a viscosity similar to that of the polymers listed above. An especially preferred entraining agent is non-crosslinked PEO or mixtures of PEO with the other materials listed above.

When the drug and a polymeric entraining agent make up about 80 wt% or more of the drug-containing composition, then the entraining agent should have a sufficiently low molecular weight that it becomes sufficiently fluid so that both the drug and entraining agent can be rapidly extruded from the dosage form, instead of swelling and rupturing the water-permeable coating that surrounds the dosage form. Thus, for example, when PEO is the drug-entraining agent, it is generally preferred that it have a molecular weight of from about 100,000 to about 300,000 daltons. (References to molecular weights of polymers herein and in the claims are to average molecular weights.)

When the drug and the entraining agent make up less than about 80 wt% of the drug-containing composition, a smaller portion of a more viscous entraining agent is preferred. For example, when the entraining agent is PEO, a lower fraction of a higher molecular weight of PEO from about 500,000 to 800,000 daltons may be used. Thus, there is an inverse relationship between the preferred PEO molecular weight and the weight fraction of the drug-containing composition that is drug and entraining agent. Thus, as the weight fraction decreases from about 0.9 to about 0.8, to about 0.7, to about 0.6, the preferred PEO molecular weight increases from about 200,000 daltons to about 400,000 daltons, to about 600,000 daltons, to about 800,000 daltons, respectively, and the weight fraction of entraining agent correspondingly decreases (the weight fraction of drug being relatively constant). It should be noted that for a particular formulation, the optimum PEO molecular weight for the entraining agent may vary higher or lower than those values by 20% to 50%. Likewise, when selecting an appropriate molecular weight of other polymeric entraining agents such as HEC, HPC, HPMC, or MC, as the weight

fraction of entraining agent in the drug-containing composition is reduced, a higher molecular weight for the entraining agent is generally preferred.

In one embodiment of the invention, the drug-containing composition further comprises a swelling agent. The swelling agent is generally a water-swellable polymer that substantially expands in the presence of water. Inclusion of even a small amount of such a swellable polymer can significantly enhance the onset, rate, and completeness of drug delivery. The degree of swelling of a swelling agent can be assessed by compressing particles of the swelling agent in a press to form a compact of the material having a "strength" ranging from 3 to 16 Kp/cm^2, where strength is the hardness of the compact in Kp as measured with a Schleuniger Tablet Hardness Tester, model 6D, divided by its maximum cross-sectional area normal to the direction of force in cm^2. For example, about 500 mg of a swelling agent can be compressed in a 13/32-inch die using an "f press." The swelling of a compact is measured by placing it between two porous glass frits in a glass cylinder and contacting it with a physiologically relevant test medium, such as simulated gastric or intestinal buffer, or water. The volume of the water-swollen compact after 16 to 24 hours contact with the test medium divided by its initial volume is termed the "swelling ratio" of the swelling agent. Generally, swelling agents suitable for inclusion in the drug layer are those water-swellable polymers that have swelling ratios, when water is the test medium, of at least 3.5, preferably greater than 5.

A preferred class of swelling agents comprises ionic polymers. Ionic polymers are generally polymers that have a significant number of functional groups that are substantially ionized in an aqueous solution over at least a portion of the physiologically relevant pH range 1 to 8. Such ionizable functional groups include carboxylic acids and their salts, sulfonic acids and their salts, amines and their salts, and pyridine salts. To be considered an ionic polymer, the polymer should have at least 0.5 milli-equivalents of ionizable functional groups per gram of polymer. Such ionic polymer swelling agents include sodium starch glycolate, sold under the trade name EXPLOTAB, and croscarmellose sodium, sold under the trade name AC-DI-SOL.

In one embodiment of the invention in which the drug-containing composition comprises a drug, a drug-entraining agent, and a swelling agent, the swelling agent is present in an amount ranging from about 2 to about 20 wt% of the drug-containing composition 14. In other embodiments of the invention, the swelling agent is optionally present in an amount ranging from 0 to about 20 wt%.

In another embodiment of the present invention, the drug-containing composition further comprises a fluidizing agent. As used herein, a "fluidizing agent" is a water-soluble compound that allows the drug-containing composition to rapidly

become fluid upon imbibing water when the dosage form is introduced into a use environment. Rapid fluidization of the drug-containing composition allows the composition to be extruded from the dosage form without a build-up of excessive pressure. This results in a relatively short time lag. That is, the time between introduction of the dosage form into the environment of use and the onset of drug delivery is relatively short. In addition, the inclusion of a fluidizing agent reduces the pressure within the core and thus reduces the risk of failure of the coating that surrounds the core of the dosage form. This is particularly important when a relatively rapid rate of drug release is desired, necessitating the use of a highly water-permeable coating that conventionally is relatively thin and weak. (By a rapid rate of release is generally meant that greater than 70 wt% of the drug originally present in the dosage form is released within 12 hours of the time the dosage form is introduced into the use environment.)

The fluidizing agent can be essentially any water-soluble compound that rapidly increases the fluidity of the drug-containing composition when water is imbibed into the core. Such compounds generally have aqueous solubilities of at least 30 mg/mL and generally have a relatively low molecular weight (less than about 10,000 daltons) such that upon imbibing a given quantity of water, the drug-containing composition rapidly becomes more fluid relative to a similar drug-containing composition that does not include the fluidizing agent. By more fluid is meant that the pressure required to extrude the drug through the delivery port(s) is lower than a similar composition without the fluidizing agent. This increased fluidity can be temporary, meaning that the increased fluidity occurs for only a short time after introduction of the dosage form to a use environment (*e.g.*, 2 hours), or the increased fluidity can occur over the entire time the dosage form is in the use environment. Exemplary fluidizing agents are sugars, organic acids, amino acids, polyols, salts, and low-molecular weight oligomers of water-soluble polymers. Exemplary sugars are glucose, sucrose, xylitol, fructose, lactose, mannitol, sorbitol, maltitol, and the like. Exemplary organic acids are citric acid, lactic acid, ascorbic acid, tartaric acid, malic acid, fumaric, and succinic acid. Exemplary amino acids are alanine and glycine. Exemplary polyols are propylene glycol and sorbitol. Exemplary oligomers of low-molecular weight polymers are polyethylene glycols with molecular weights of 10,000 daltons or less. Particularly preferred fluidizing agents are sugars and organic acids. Such fluidizing agents are preferred as they often improve tableting and compression properties of the drug-containing composition relative to other fluidizing agents such as inorganic salts or low-molecular weight polymers.

In order for the fluidizing agent to rapidly increase the fluidity of the drug-containing composition at low water levels in the core 12 of the dosage form, the fluidizing agent must generally be present in an amount such that it makes up at least about 10 wt% of the drug-containing composition 14. To ensure that the drug-containing composition 14 does not become so fluid such that the drug-entraining agent cannot properly entrain or suspend the drug, particularly long after (12 hours or longer) introduction of the dosage form into the use environment, the amount of fluidizing agent generally should not exceed about 60 wt% of the drug-containing composition. In addition, as mentioned above, when a fluidizing agent is included, a drug-entraining agent with a higher molecular weight and correspondingly higher viscosity is generally included in the drug-containing composition, but at a lower level. Thus, for example, when the drug-containing composition comprises about 20 to 30 wt% of the low-solubility drug and about 30 wt% of a fluidizing agent such as a sugar, about 20 to 50 wt% of a high molecular weight polymer such as PEO with a molecular weight of about 500,000 to 800,000 daltons is preferable to a lower molecular weight PEO.

The drug-containing composition 14 may further include solubilizing agents that promote the aqueous solubility of the drug, present in an amount ranging from about 0 to about 30 wt% of the drug-containing composition 14. Examples of suitable solubilizing agents include surfactants; pH control agents such as buffers, organic acids and organic acid salts and organic and inorganic bases; glycerides; partial glycerides; glyceride derivatives; polyhydric alcohol esters; PEG and PPG esters; polyoxyethylene and polyoxypropylene ethers and their copolymers; sorbitan esters; polyoxyethylene sorbitan esters; carbonate salts; and cyclodextrins.

There are a variety of factors to consider when choosing an appropriate solubilizing agent for a drug. The solubilizing agent should not interact adversely with the drug. In addition, the solubilizing agent should be highly efficient, requiring minimal amounts to effect the improved solubility. It is also desired that the solubilizing agent have a high solubility in the use environment. For acidic, basic, and zwitterionic drugs, organic acids, organic acid salts, and organic and inorganic bases and base salts are known to be useful solubilizing agents. It is desired that these compounds have a high number of equivalents of acid or base per gram. The selection of solubilizing agent will therefore be highly dependent on the properties of the drug.

A preferred class of solubilizing agents for basic drugs is organic acids. Since basic drugs are solubilized by protonation, and since the solubility of basic drugs in an aqueous environment of pH 5 or higher is reduced and often may reach an extremely low value by pH 7.5 (as in the colon), it is believed that addition

of an organic acid to the dosage form for delivery to the use environment with such drugs assists in solubilization and hence absorption of the drug. An exemplary basic drug is sertraline, which has moderate solubility at low pH, low solubility at pH values above 5 and extremely low solubility at pH of about 7.5. Even a slight decrease in the pH of the aqueous solution at high pH may result in dramatic increases in the solubility of basic drugs. In addition to simply lowering the pH, the presence of organic acids and their conjugate bases also raises the solubility at a given pH if the conjugate base salt of the basic drug has a higher solubility than the neutral form or the chloride salt of the drug.

It has been found that a preferred subset of organic acids meeting such criteria consists of citric, succinic, fumaric, adipic, malic and tartaric acids. The table below gives properties of these organic acids. Of these, fumaric and succinic are especially preferred when a high ratio of equivalents of acid per gram is desired. In addition, citric, malic, and tartaric acid have the advantage of extremely high water solubility. Succinic acid offers a combination of both moderate solubility and a high acid equivalent per gram value. Thus, the use of a highly soluble organic acid serves multiple purposes: it improves the solubility of the basic drug, particularly when the use environment is at a pH above about 5 to 6; it makes the drug-containing composition more hydrophilic so that it readily wets; and it dissolves, lowering the viscosity of the layer rapidly, thus acting as a fluidizing agent. Thus, by accomplishing multiple functions with a single ingredient, additional space is available for the low-solubility drug within the drug-containing composition.

Properties of Organic Acid Solubilizing Agents

Organic Acid	Equivalents Value (mEq/g)	Water Solubility (mg/mL)
Fumaric	17.2	11
Succinic	16.9	110
Citric	15.6	>2000
Malic	14.9	1750
Adipic	13.7	45
Tartaric	13.3	1560

For acidic drugs, solubility is increased as pH increases. Exemplary classes of solubilizing agents for acidic drugs include alkalinizing or buffering agents and organic bases. It is believed that addition of an alkylating agent or organic base

to the dosage form assists in solubilization and hence absorption of the drug. Examples of alkylating or buffering agents include potassium citrate, sodium bicarbonate, sodium citrate, dibasic sodium phosphate, and monobasic sodium phosphate. Examples of organic bases include meglumine, eglumine, monoethanol amine, diethanol amine, and triethanol amine.

The drug-containing composition 14 may optionally include a concentration-enhancing polymer that enhances the concentration of the drug in a use environment relative to control compositions that are free from the concentration-enhancing polymer. The concentration-enhancing polymer should be inert, in the sense that it does not chemically react with the drug in an adverse manner, and should have at least some solubility in aqueous solution at physiologically relevant pHs (e.g. 1-8). Almost any neutral or ionizable polymer that has an aqueous solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8 may be suitable. Especially useful polymers are those discussed above for forming solid-amorphous dispersions of the drug with a polymer. Preferred polymers include HPMCAS, HPMC, HPMCP, CAP, CAT, and PVP. More preferred polymers included HPMCAS, HPMCP, CAP and CAT. Without being bound by any particular theory or mechanism of action, it is believed that the concentration–enhancing polymer prevents or retards the rate at which a drug, delivered from the dosage form and present in the use environment at a concentration greater than its equilibrium value, approaches its equilibrium concentration. Thus, when the dosage form is compared to a control dosage form that is identical except for the absence of the concentration-enhancing polymer, the concentration-enhancing polymer-containing dosage form provides, at least for a short time period, a greater concentration of dissolved drug in the use environment. Appropriate drug forms and concentration-enhancing polymers are discussed in commonly assigned pending patent application "Pharmaceutical Compositions Providing Enhanced Drug Concentrations" filed December 23, 1999, U.S. provisional patent application No. 60/171,841, the relevant portions of which are herein incorporated by reference.

The drug-containing composition 14 may optionally include excipients that promote drug stability. Examples of such stability agents include pH control agents such as buffers, organic acids and organic acid salts and organic and inorganic bases and base salts. These excipients can be the same materials listed above for use as solubility-enhancing agents or fluidizing agents. Another class of stability agents is antioxidants, such as butylated hydroxy toluene (BHT), butylated hydroxyanisole (BHA), vitamin E, and ascorbyl palmitate. The amount of stability agent used in the drug-containing composition should be sufficient to stabilize the low-solubility drug. For pH control agents such as organic acids, the stability agent,

when present, may range from 0.1 to 20 wt% of the drug-containing composition. Note that in some formulations, antioxidants such as BHT can lead to discoloration of the dosage form. In these cases, the amount of antioxidant used should be minimized so as to prevent discoloration. The amount of antioxidant used in the drug-containing composition generally ranges from 0 to 1 wt% of the drug-containing composition.

Finally, the drug-containing composition 14 may also include other conventional excipients, such as those that promote performance, tableting or processing of the dosage form. Such excipients include tableting aids, surfactants, water-soluble polymers, pH modifiers, fillers, binders, pigments, osmagents, disintegrants and lubricants. Exemplary excipients include microcrystalline cellulose; metallic salts of acids such as aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, and zinc stearate; fatty acids, hydrocarbons and fatty alcohols such as stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol; fatty acid esters such as glyceryl (mono- and di-) stearates, triglycerides, glyceryl (palmitic stearic) ester, sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, and sodium stearyl fumarate; alkyl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; polymers such as polyethylene glycols, polyoxyethylene glycols, and polytetrafluoroethylene; and inorganic materials such as talc and dicalcium phosphate. In a preferred embodiment, the drug-containing composition 14 contains a lubricant such as magnesium stearate.

WATER-SWELLABLE COMPOSITION

Referring again to FIGS. 1-3, the tri-layer, concentric core, and granular core dosage forms further comprise a water-swellable composition 16. The water-swellable composition greatly expands as it imbibes water through the coating 18 from the use environment. As it expands, the water-swellable composition increases the pressure within the core 12, causing extrusion of the fluidized drug-containing composition through the port(s) 20 into the environment of use. To maximize the amount of drug present in the dosage form and to ensure that the maximum amount of drug is released from the dosage form so as to minimize residual drug, the water-swellable composition should have a swelling ratio of at least about 2, preferably 3.5, and more preferably 5.

The water-swellable composition 16 comprises a swelling agent in an amount ranging from about 30 to 100 wt% of the water-swellable composition 16. The swelling agent is generally a water-swellable polymer that greatly expands in the presence of water. As discussed above in connection with the swelling agent of the

drug-containing composition, the degree of swelling of a swelling agent, or the water-swellable composition itself, can be assessed by measuring its swelling ratio.

Suitable swelling agents for the water-swellable composition are generally hydrophilic polymers that have swelling ratios of about 2.0 or greater. Exemplary hydrophilic polymers include polyoxomers such as PEO, cellulosics such as HPMC and HEC, and ionic polymers. In general, the molecular weight of water swellable polymers chosen for the swelling agent is higher than that of similar polymers used as entraining agents such that, at a given time during drug release, the water-swellable composition 16 after imbibing water tends to be more viscous, less fluid, and more elastic relative to the drug-containing composition 14. In some cases the swelling agent may be even substantially or almost entirely water insoluble such that when partially water swollen during operation, it may constitute a mass of water-swollen elastic particles. Generally, the swelling agent is chosen such that, during operation, the water-swellable composition 16 generally does not substantially intermix with the drug-containing composition 14, at least prior to extruding a majority of the drug-containing composition 14. Thus, for example, when PEO is the swelling agent used in the water-swellable composition 16, a molecular weight of about 800,000 daltons or more is preferred and more preferably a molecular weight of 3,000,000 to 8,000,000 daltons.

A preferred class of swelling agents is ionic polymers, described above for use in various embodiments of the drug-containing composition 14. Exemplary ionic polymer swelling agents include sodium starch glycolate, sold under the trade name EXPLOTAB, croscarmellose sodium, sold under the trade name AC-DI-SOL, polyacrylic acid, sold under the trade name CARBOBOL, and sodium alginate sold under the trade name KELTONE.

The water-swellable composition may optionally further comprise osmotically effective agents, often referred to as "osmogens" or "osmagents." The amount of osmagent present in the water-swellable composition may range from about 0 to about 40 wt% of the water-swellable composition. Typical classes of suitable osmagents are water-soluble salts and sugars that are capable of imbibing water to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. The osmotic pressure of a material can be calculated using the van't Hoff equation. (See, e.g., *Thermodynamics*, by Lewis and Randall). By "osmotically effective agent" is meant the inclusion of a material with low enough molecular weight, high enough solubility, and sufficient mass in the water-swellable composition that upon imbibing water from the use environment it forms an aqueous solution within the interior of the tablet such that its osmotic pressure exceeds that of the use environment, thereby providing an osmotic pressure driving force for

permeation of water from the use environment into the tablet core. Typical useful osmagents include magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, d-mannitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, fructose, lactose, and mixtures thereof.

In one embodiment of the invention, the water-swellable composition 16 is substantially free from an osmotically effective agent, meaning that there is either a sufficiently small amount of osmagent or that any osmagent present has sufficiently low solubility so as not to increase the osmotic pressure of the water-swellable composition 16 substantially beyond that of the use environment. In order for the dosage form to provide satisfactory release of drug in the absence of an osmagent in the water-swellable composition 16, and when the water-swellable polymer is not an ionic polymer, the dosage form should have a coating that is highly permeable to water. Such high-permeability coatings are described below. When the water-swellable composition 16 is substantially free of an osmotically effective agent, the water swellable composition preferably contains a substantial quantity, typically at least 10 wt% and preferably at least 50 wt%, of a highly swelling polymer such as sodium starch glycolate or sodium croscarmellose. As described earlier, highly swelling materials can be identified by measuring the "swelling ratio" of the material formed into a compact using the method described previously. When the water-soluble composition is substantially free of an osmotically effective solute, it is preferred that the swelling polymer have a swelling ratio of at least 3.5, preferably at least 5. The dosage form should also have a high strength coating to prevent rupture when highly swelling materials are used. Such coatings are described below.

The release of a drug relatively quickly without the inclusion of an osmagent in the water-swellable composition is a surprising result, since conventional wisdom in the art has held that osmagents should be included in the water-swellable composition to achieve good performance. Circumventing the need for inclusion of an osmagent provides several advantages. One advantage is that the space and weight which would otherwise be occupied by osmagent may be devoted to drug, thus permitting an increase in the amount of drug within the dosage form. Alternatively, the overall size of the dosage form may be decreased. In addition, eliminating the osmagent simplifies the process for manufacture of the dosage form, since the water-swellable composition 16 may omit the step of including an osmagent.

In one embodiment of the invention, the water swellable composition 16 comprises a swelling agent and a tableting aid. The preferred swelling agents

(e.g., those that are highly swelling) are difficult to compress to a hardness suitable for use in the dosage form. However, it has been found that adding a tableting aid to the water-swellable composition in the amount of 5 to 50 wt% of the water-swellable composition 16 results in a material that compresses to a hardness suitable for use in the dosage form. At the same time inclusion of a tableting aid can adversely affect the swelling ratio of the water-swellable composition 16. Thus, the quantity and type of tableting aid used must be carefully selected. In general, hydrophilic materials with good compression properties should be used. Exemplary tableting aids include sugars such as lactose, in particular spray-dried versions sold under the trade name FASTFLOW LACTOSE, or xylitol, polymers such as microcrystalline cellulose, HPC, MC or HPMC. Preferred tableting aids are microcrystalline cellulose, both standard grades sold under the trade name AVICEL and silicified versions sold under the trade name PROSOLV and HPC. The amount of tableting aid is chosen to be sufficiently high so that the core 12 compresses well yet sufficiently low so that the water-swellable composition 16 still has a swelling ratio of at least 2, preferably 3.5, more preferably greater than 5. Typically, the amount is at least 20 but less than 60 wt%.

It is further desired that the mixture of swelling agent and tableting aid result in a material that has a "strength" of at least 3 Kiloponds (Kp)/cm^2, and preferably at least 5 Kp/cm^2. Here, "strength" is the fracture force, also known as the core "hardness," required to fracture a core 12 formed from the material, divided by the maximum cross-sectional area of the core 12 normal to that force. In this test, the fracture force is measured using a Schleuniger Tablet Hardness Tester, model 6D. Both the compressed water-swellable composition 16 and resulting core 12 should have a strength of at least 3 Kp/cm^2, and preferably at least 5 Kp/cm^2.

In a preferred embodiment, the water-swellable composition 16 comprises a mixture of swelling agents in addition to a tableting aid. For example, the swelling agent croscarmellose sodium can be compressed into a compact with higher strength than the swelling agent sodium starch glycolate. However, the swelling ratio of croscarmellose sodium is lower than that of sodium starch glycolate.

The water-swellable composition 16 may also include solubility-enhancing agents or excipients that promote stability, tableting or processing of the dosage form of the same types mentioned above in connection with the drug-containing composition. However, it is generally preferred that such excipients comprise a minor portion of the water-swellable composition 16. In one preferred embodiment, the water-swellable composition 16 contains a lubricant such as magnesium stearate.

THE HOMOGENEOUS CORE

The preceding discussion of drug-containing composition 14 and water-swellable composition 16 applies to the tri-layer, concentric core, and granular core embodiments. However, for the homogeneous core, the drug-containing composition 15 contains both the drug and swelling materials. In general, the drug-containing composition will simply be a mixture of materials suitable for use in the drug-containing composition 14 and the water-swellable composition 16 of the other embodiment described above. Thus, at a minimum, the drug-containing composition 15 comprises at least a drug, an entraining agent, and a swelling agent. The drug-containing composition 15 may optionally include a fluidizing agent, a solubility-enhancing agent, a concentration-enhancing polymer, a stability promoting agent, and/or conventional excipients discussed above in connection with the drug-containing composition. Likewise, the drug-containing composition may optionally also include osmogens, and/or tableting aids as discussed above in connection with the water-swellable composition.

The amounts of the respective materials will in general fall within the ranges described above in the discussion of the drug-containing composition and the water-swellable composition. In particular, preferred compositions for the homogeneous core embodiment are those that contain from 2 to about 30% of a swelling agent that has a swelling ratio of at least about 2 and preferably at least about 3.5, and more preferably at least about 5. Preferred swelling agents are ionic polymers such as carboxymethyl cellulose, sodium starch glycolate, crosscarmelose sodium, polyacrylic acid and sodium alginate. In addition, preferred homogeneous core compositions will also contain an entraining agent such as HEC, HPC, HPMC, or PEO in an amount from about 5 to about 80% of the core contents. Preferably, in addition to the drug, swelling agent, and entraining agent, the core also contains a fluidizing agent.

The various novel combinations of these agents in the core of the homogeneous core embodiment yield numerous advantages, including more rapid onset and more complete release of drug, relative to homogeneous core dosage forms previously known.

THE CORE

The core 12 may be any known tablet that can be formed by an extrusion or compression process and be subsequently coated and utilized for delivery of drug to a mammal. The tablet can generally range in size from about 1 mm to about 10 cm for its longest dimension. The maximum size of the tablet will be different for different mammalian species. It can have essentially any shape such that its aspect ratio, defined as the tablet's longest dimension divided by the tablet's shortest dimension, ranges from about 1 to about 5. In addition, the dosage form may comprise two or more relatively small tablets contained in a relatively large container such as a capsule.

Exemplary core 12 shapes are spheres, ellipsoids, cylinders, capsule or caplet shapes and any other known shape. The core 12, following coating, can comprise the entire or a portion of the dosage form. The final dosage form can be for oral, rectal, vaginal, subcutaneous, or other known method of delivery into the environment of use. When the dosage form 10 is intended for oral administration to a human, the core 12 generally has an aspect ratio of about 3 or less, a longest dimension of about 2 cm or less and a total weight of about 1.5 g or less and preferably a total weight of about 1.0 g or less.

To form the dosage form, the ingredients comprising the drug-containing composition 14 and the water-swellable composition 16 are first mixed or blended using processes known in the art. See for example, Lachman, et al., "The Theory and Practice of Industrial Pharmacy" (Lea & Febiger, 1986). For example, a portion of the ingredients of the drug-containing composition 14 can first be blended, then wet granulated, dried, milled, and then blended with additional excipients prior to tableting. Similar processes can be used to form the water-swellable composition.

Once the materials are properly mixed, the core 12 is formed using procedures known in the art, such as compression or extrusion.

For tri-layer dosage forms, the method used to make the core depends on whether the two drug-containing compositions 14a and 14b are the same. Where they are the same, a single drug-containing composition is prepared. A portion of the drug-containing composition mixture is placed in a tablet press and leveled by lightly tamping with the press. The desired amount of water-swellable composition 16 is then added. A second portion of the drug-containing composition is then added on top of the water-swellable composition. The tablet is then compressed.

Where the two drug-containing compositions 14a and 14b differ, then each drug-containing composition 14a and 14b are separately prepared. The tablet is prepared by placing first the drug-containing composition 14a in a tablet press and

leveling by lightly tamping with the press. The desired amount of water-swellable composition 16 is then added. The desired amount of the drug-containing composition 14b is then added on top of the water-swellable composition 16. The tablet is then compressed.

For the concentric core dosage form, the core 12 is first prepared by placing the desired amount of the water-swellable composition 16 in a press and compressing to form a small initial core. A first portion of the drug-containing composition is placed in a larger press, gently leveled and lightly compressed. The small initial core of water-swellable composition 16 is then placed on top of the first portion of the drug-containing composition and centered. The remaining amount of the drug-containing composition 14 is then added to the press. The tablet is compressed to the desired hardness.

For the granular dosage form, the water-swellable composition 16 is prepared and formed into granules using any conventional method, such as wet or dry granulation. The granules may vary in size from very small particulates less than 0.1 mm in diameter to large particles (up to 2 mm) that are each a significant fraction of the total volume of the dosage form. A preferred size range is an average diameter of between 0.1 mm and 2 mm, and more preferred is an average diameter of between 0.5 and 1.5 mm. In use, the size of the granules should be chosen so that upon swelling the granules are larger than the delivery ports in the coating. The granules will therefore be retained within the coating and displace the drug-containing composition, which is extruded through the delivery ports. The tablet core is prepared by adding the prepared granules of water-swellable composition 16 to the drug-containing composition 14, so that the granules are distributed throughout the drug-containing composition. The resulting composition is then placed into a tablet press, and then compressed.

Finally, for the homogeneous core dosage form, the drug-containing composition 15 is formed by mixing all of the ingredients using any conventional method to form a relatively homogeneous mixture. The mixture is then added to a tablet press, and then compressed. In contrast to the granular core embodiment, the swelling agent is present in particles having a small enough size (*e.g.*, less than 0.1 mm) so that even when swollen the swelling agent particles are extruded through the delivery port along with the other ingredients in the core.

The amount of force used to compress the tablet core will depend on the size of the dosage form, as well as the compressibility and flow characteristics of the compositions. Typically, a pressure is used that results in a tablet with a strength of 3 to 20 Kp/cm^2.

THE COATING:

Following formation of the core 12, coating 18 is applied. Coating 18 should have both a sufficiently high water permeability that the drug can be delivered within the desired time frame, and high strength, while at the same time be easily manufactured. A water permeability is chosen to control the rate at which water enters the core, thus controlling the rate at which drug is delivered to the use environment. Where a high dose of a low-solubility drug is required, the low solubility and high dose combine to make it necessary to use a high permeability coating to achieve the desired drug release profile while keeping the tablet acceptably small. High strength is required to ensure the coating does not burst when the core swells as it imbibes water, leading to an uncontrolled delivery of the core contents to the use environment. The coating must be easily applied to the dosage form with high reproducibility and yield. Furthermore, the coating must be non-dissolving and non-eroding during release of the drug-containing composition, generally meaning that it be sufficiently water-insoluble that drug is substantially entirely delivered through the delivery port(s) 20, in contrast to delivery via permeation through coating 18.

As described above, the coating 18 is highly water-permeable to allow rapid imbibition of water into core 12 and as a result a rapid release of the drug-containing composition 14. A relative measure of the water permeability of the coating can be made by conducting the following experiment. Finished dosage forms are placed in an open container which is in turn placed in an environmental chamber held at a constant temperature of 40□C and a constant relative humidity of 75%. The initial rate of weight gain of the dry dosage forms, determined by plotting the weight of the dosage form versus time, divided by the surface area of the dosage form yields a value termed "water flux (40/75)." The water flux (40/75) for a dosage form has been found to be a useful relative measure of the water permeabilities of coatings. When a rapid release of the drug is desired, the coating should have a water flux (40/75) value of at least 1.0×10^{-3} gm/hr·cm², and preferably at least 1.3×10^{-3} gm/hr·cm².

As mentioned, the coating should also have a high strength to ensure the coating 18 does not burst when the core swells due to imbibition of water from the use environment. A relative measure of coating strength can be made by conducting the following experiment that measures the "durability" of the coating. Finished tablets are placed into an aqueous medium for 10 to 24 hours, allowing the core to imbibe water, swell, and release drug to the media. The swollen dosage form can then be tested in a hardness tester, such as a Model 6D Tablet Tester manufactured by Schleuniger Pharmatron, Inc. When the delivery port(s) located on

the face(s) of the dosage form, the dosage form is placed into the tester so that its delivery port(s) (20) faces one side of the compression plates such that the delivery port(s) is blocked by the compression plate. The force, in Kp, required to rupture the coating is then measured. The durability of the coating is then calculated by dividing the measured rupture force by the maximum cross-sectional area of the dosage form normal to the applied force. Preferably, the coating has a durability of at least 1 Kp/cm^2, more preferably at least 2 Kp/cm^2, and even more preferably at least 3 Kp/cm^2. Coatings with this or greater durability ensure virtually no burst tablets when the dosage forms are tested *in vivo*.

Coatings with these characteristics can be obtained using hydrophilic polymers such as plasticized and unplasticized cellulose esters, ethers, and ester-ethers. Particularly suitable polymers include cellulose acetate ("CA"), cellulose acetate butyrate, and ethyl cellulose. A particularly preferred set of polymers are cellulose acetates having acetyl contents of 25 to 42%. A preferred polymer is CA having an acetyl content of 39.8%, and specifically, CA 398-10 manufactured by Eastman of Kingsport, Tennessee, having an average molecular weight of about 40,000 daltons. Another preferred CA having an acetyl content of 39.8% is high molecular weight CA having an average molecular weight greater than about 45,000, and specifically, CA 398-30 (Eastman) reported to have an average molecular weight of 50,000 daltons. The high molecular weight CA provides superior coating strength, which allows thinner coatings and thus higher permeability.

Coating is conducted in conventional fashion by first forming a coating solution and then coating by dipping, fluidized bed coating, or preferably by pan coating. To accomplish this, a coating solution is formed comprising the coating polymer and a solvent. Typical solvents useful with the cellulosic polymers noted above include acetone, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, 1,4-dioxane, tetrahydrofuran, diglyme, and mixtures thereof. A particularly preferred solvent is acetone. The coating solution typically will contain 3 to 15 wt% of the polymer, preferably 5 to 10 wt%, most preferably 7 to 10 wt%.

The coating solution may also comprise pore-formers, non-solvents, or plasticizers in any amount so long as the polymer remains substantially soluble at the conditions used to form the coating and so long as the coating remains water-permeable and has sufficient strength. Pore-formers and their use in fabricating coatings are described in U.S. Patent Nos. 5,612,059 and 5,698,220, the pertinent disclosures of which are incorporated herein. The term "pore former," as used

herein, refers to a material added to the coating solution that has low or no volatility relative to the solvent such that it remains as part of the coating following the coating process but that is sufficiently water swellable or water soluble such that, in the aqueous use environment it provides a water-filled or water-swollen channel or "pore" to allow the passage of water thereby enhancing the water permeability of the coating. Suitable pore-formers include polyethylene glycol (PEG), PVP, PEO, HEC, HPMC and other aqueous-soluble cellulosics, water-soluble acrylate or methacrylate esters, polyacrylic acid and various copolymers and mixtures of these water soluble or water swellable polymers. Enteric polymers such as cellulose acetate phthalate (CAP) and HPMCAS are included in this class of polymers. The pore former can also be a water soluble, pharmaceutically acceptable material, such as a sugar, organic acid, or salt. Examples of suitable sugars include sucrose and lactose; examples of organic acids include citric acid and succinic acid; examples of salts include sodium chloride and sodium acetate. Mixtures of such compounds may also be used. The pore former may be soluble in the solvent used in the coating solution, or it may be insoluble, such that the coating solution is a slurry or suspension. A particularly preferred pore former is PEG having an average molecular weight from 1000 to 8000 daltons. A particularly preferred PEG is one having a molecular weight of 3350 daltons. The inventors have found that to obtain a combination of high water permeability and high strength when PEG is used as a pore former, the weight ratio of CA:PEG should range from about 6.5:3.5 to about 9:1.

The addition of a non-solvent to the coating solution results in exceptional performance. By "non-solvent" is meant any material added to the coating solution that substantially dissolves in the coating solution and reduces the solubility of the coating polymer or polymers in the solvent. In general, the function of the non-solvent is to impart porosity to the resulting coating. As described below, porous coatings have higher water permeability than an equivalent weight of a coating of the same composition that is not porous and this porosity, when the pores are gas filled, as is typical when the non-solvent is volatile, is indicated by a reduction in the density of the coating (mass/volume). Although not wishing to be bound by any particular mechanism of pore formation, it is generally believed that addition of a non-solvent imparts porosity to the coating during evaporation of solvent by causing the coating solution to undergo liquid-liquid phase separation prior to solidification. As described below for the case of using water as the non-solvent in an acetone solution of cellulose acetate, the suitability and amount of a particular candidate material can be evaluated for use as a non-solvent by progressively adding the candidate non-solvent to the coating solution until it becomes cloudy. If this does not occur at any addition level up to about 50 wt% of

the coating solution, it generally is not appropriate for use as a non-solvent. When clouding is observed, termed the "cloud point," an appropriate level of non-solvent for maximum porosity is the amount just below the cloud point. When lower porosities are desired, the amount of non-solvent can be reduced as low as desired. It has been found that suitable coatings can be obtained when the concentration of non-solvent in the coating solution is greater than about 20% of the non-solvent concentration that results in the cloud point.

Suitable non-solvents are any materials that have appreciable solubility in the solvent and that lower the coating polymer solubility in the solvent. The preferred non-solvent depends on the solvent and the coating polymer chosen. In the case of using a volatile polar coating solvent such as acetone or methyl ethyl ketone, suitable non-solvents include water, glycerol, ethylene glycol and its low molecular-weight oligomers (e.g., less than about 1,000 daltons), propylene glycol and its low molecular weight oligomers (e.g., less than about 1,000 daltons), C_1 to C_4 alcohols such as methanol or ethanol, ethylacetate, acetonitrile and the like.

In general, to maximize its effect, (*e.g.*, formation of pores), the non-solvent should have similar or less volatility than the coating solution solvent such that, during initial evaporation of the solvent during the coating process, sufficient non-solvent remains to cause phase separation to occur. In many cases, where a coating solution solvent such as acetone is used, water is a suitable non-solvent. For acetone solutions comprising 7 wt% CA and 3 wt% PEG, the cloud point at room temperature is at about 23 wt% water. Thus the porosity and in turn the water permeability (which increases with increasing porosity) can be controlled by varying the water concentration up to near the cloud point. For acetone solutions comprising CA and PEG with a total concentration of about 10 wt%, it is desired that the coating solution contain at least 4 wt% water to obtain a suitable coating. When a higher porosity, and thus a higher water permeability is desired (to obtain a faster release rate), the coating solution should contain at least about 15 wt% water.

In one embodiment of the invention, the coating solution is homogeneous, in that when the polymer, solvent, and any pore formers or non-solvents are mixed, the solution comprises a single phase. Typically, a homogenous solution will be clear, and not be cloudy as discussed above.

When using CA 398-10, exemplary coating solution weight ratios of CA:PEG 3350:water are 7:3:5, 8:2:5, and 9:1:5, with the remainder of the solution comprising a solvent such as acetone. Thus, for example, in a solution having a weight ratio of CA:PEG 3350:water of 7:3:5, CA comprises 7 wt% of the solution, PEG 3350 comprises 3 wt% of the solution, water comprises 5 wt% of the solution, and acetone comprises the remaining 85 wt%. Preferred coatings are

generally porous even in the dry state (prior to delivery to the aqueous use environment). By "porous" is meant that the coating has a dry-state density less than the density of the nonporous coating material. By "nonporous coating material" is meant a coating material formed by using a coating solution containing no non-solvent, or the minimum amount of non-solvent required to produce a homogeneous coating solution. The coating in the dry state has a density that is less than 0.9 times, and more preferably less than 0.75 times that of the nonporous coating material. The dry-state density of the coating can be calculated by dividing the coating weight (determined from the weight gain of the tablets before and after coating) by the coating volume (calculated by multiplying the coating thickness, as determined by optical or scanning electron microscopy, by the tablet surface area). The porous nature of the coating is one of the factors that leads to the combination of high water permeability and high strength of the coating.

The coatings may also be asymmetric, meaning that there is a gradient of density throughout the coating thickness. Generally, the outside surface of the coating will have a higher density than the coating nearest the core.

The coating can optionally include a plasticizer. A plasticizer generally swells the coating polymer such that the polymer's glass transition temperature is lowered, its flexibility and toughness increased and its permeability altered. When the plasticizer is hydrophilic, such as polyethylene glycol, the water permeability of the coating is generally increased. When the plasticizer is hydrophobic, such as diethyl phthalate or dibutyl sebacate, the water permeability of the coating is generally decreased.

It should be noted that additives can function in more than one way when added to the coating solution. For example, PEG can function as a plasticizer at low levels while at higher levels it can form a separate phase and act as a pore former. In addition, when a non-solvent is added, PEG can also facilitate pore formation by partitioning into the non-solvent-rich phase once liquid-liquid phase separation occurs.

The weight of the coating around the core depends on the composition and porosity of the coating, the surface to volume ratio of the dosage form, and the desired drug release rate, but generally should be present in an amount ranging from about 3 to 30 wt%, preferably from 8 to 25 wt%, based on the weight of the uncoated core. However, a coating weight of at least about 8 wt% is generally preferred so as to assure sufficient strength for reliable performance, and more preferably a coating greater than about 13 wt%.

While porous coatings based on CA, PEG, and water yield excellent results, other pharmaceutically acceptable materials may be used so long as the

coating has the requisite combination of high water permeability, high strength, and ease of manufacture. Further, such coatings may be dense, or asymmetric, having one or more dense layers and one or more porous layers, as described in U.S. Patent Nos. 5,612,059 and 5,698,220.

The coating 18 must also contain at least one delivery port 20 in communication with the interior and exterior of the coating to allow for release of the drug-containing composition to the exterior of the dosage form. The delivery port can range in size from about the size of the drug particles, and thus could be as small as 1 to 100 microns in diameter and may be termed pores, up to about 5000 microns in diameter. The shape of the port may be substantially circular, in the form of a slit, or other convenient shape to ease manufacturing and processing. The port(s) may be formed by post-coating mechanical or thermal means or with a beam of light (*e.g.*, a laser), a beam of particles, or other high-energy source, may be formed by drilling completely through the dosage form, or may be formed *in situ* by rupture of a small portion of the coating. Such rupture may be controlled by intentionally incorporating a relatively small weak portion into the coating. Delivery ports may also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the coating over an indentation in the core. Delivery ports may be formed by coating the core such that one or more small regions remains uncoated. In addition, the delivery port can be a large number of holes or pores that may be formed during coating, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Patent Nos. 5,612,059 and 5,698,220, the disclosures of which are incorporated by reference. When the delivery pathways are pores there can be a multitude of such pores that range in size from about 1 □m to greater than about 100 □m. During operation, one or more of such pores may enlarge under the influence of the hydrostatic pressure generated during operation. The number of delivery ports 20 may vary from 1 to 10 or more. In aggregate, the total surface area of core exposed by delivery ports is less than about 5%, and more typically less than about 1%.

At least one delivery port is formed through the coating so that the drug-containing composition will be extruded out of the delivery port by the swelling action of the water-swellable composition. For the tri-layer embodiment, it is desired to have at least one delivery port located on each of the respective faces of the tablet opposite each of the drug-containing compositions 14a and 14b. For the remaining embodiments, the location of the delivery ports is not critical, since any location will provide a delivery port in communication with either the drug-containing composition 14, in the case of the concentric core and granular core embodiments, or the drug-containing composition 15 in the case of the homogeneous core embodiment. Thus,

for these embodiments the delivery port may be located at any location on the coating.

Other features and embodiments of the invention will become apparent from the following examples which are given for illustration of the invention rather than for limiting its intended scope.

Example 1

Exemplary dosage forms of the present invention were made with a tri-layer geometry of the type depicted in Fig. 1. The tri-layer core consisted of a drug containing composition distributed evenly between the top and bottom tablet layers and a water-swellable composition comprising the middle layer.

To form the drug-containing composition the following materials were wet granulated (see Table A): 35 wt% of the citrate salt of 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphony]-4-methylpiperazine, also known as sildenafil citrate (hereinafter referred to as Drug 1) having a solubility of about 20 □g/mL at pH 6, 30 wt% xylitol (trade name XYLITAB 200), 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% sodium starch glycolate (trade name EXPLOTAB), and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined with 26% of the total PEO, and without the magnesium stearate, in a twinshell mixer and blended for 10 minutes. Next, the ingredients were milled using a hammer mill and passed through a 0.065-inch screen. This material was blended again for 10 minutes in a twinshell mixer. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch screen. The drug-containing composition ingredients were again placed in a twinshell mixer and the remaining 74% of the total PEO was added to the mixer. The drug-containing composition ingredients were blended for 10 minutes, the magnesium stearate was added, and the mixture was blended again for 4 minutes.

To form the water-swellable composition (see Table B), the following materials were blended: 74.5 wt% EXPLOTAB, 24.5 wt% of the tableting aid silicified microcrystalline cellulose (trade name PROSOLV 90), and 1.0 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate in a twinshell mixer and blended for 20 minutes. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch

screen. The water-swellable composition ingredients were again placed in a twinshell mixer, the magnesium stearate was added, and the mixture was blended for 4 minutes.

Tablet cores were formed by placing 200 mg of drug-containing composition in a standard 13/32 inch die and gently leveling with the press. Then, 100 mg water-swellable composition was placed in the die on top of the drug-containing composition and leveled. The second half of the drug-containing composition (200 mg) was added and the tablet core compressed to a hardness of about 11 Kp. The resulting tri-layer tablet core had a total weight of 500 mg and contained a total of 28.3 wt% Drug 1 (141.5 mg), 24.3 wt% XYLITAB 200, 22.3 wt% PEO 600,000 daltons, 19.0 wt% EXPLOTAB, 4.9 wt% PROSOLV 90, and 1.2 wt% magnesium stearate.

Coatings were applied by a Vector LDCS-20 pan coater. The coating solution contained cellulose acetate (CA 398-10 from Eastman Fine Chemical, Kingsport, Tennessee), polyethylene glycol having a molecular weight of 3350 daltons (PEG 3350, Union Carbide), water, and acetone in a weight ratio of 7/3/5/85 (wt%). The flow rate of the inlet heated drying air of the pan coater was set at 40 ft^3/min with the outlet temperature set at 25□C. Nitrogen at 20 psi was used to atomize the coating solution from the spray nozzle, with a nozzle-to-bed distance of 2 inches. The pan rotation was set to 20 rpm. The so-coated tablets were dried at 50□C in a convection oven. The final dry coating weight amounted to 47.5 mg or 9.5 wt% of the tablet core. Five 900 μm diameter holes were then laser-drilled in the coating on each drug-containing composition side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

To simulate *in vivo* drug dissolution, tablets were placed in 900 mL of a simulated gastric solution (10 mM HCl, 100 mM NaCl, pH 2.0, 261 mOsm/kg) in a USP type 2 dissoette flask. Samples were taken at periodic intervals using a VanKel VK8000 autosampling dissoette with automatic receptor solution replacement. Tablets were placed in a wire support, the paddle height was adjusted, and the dissoette flasks were stirred at 100 rpm at 37□C. The autosampler dissoette device was programmed to periodically remove a sample of the receptor solution, and the drug concentration was analyzed by HPLC using a Waters Symmetry C_{18} column. The mobile phase consisted of 0.05 M triethanolamine (pH 3)/ methanol/ acetonitrile in a volume ratio of 58/25/17. Drug concentration was calculated by comparing UV absorbance at 290 nm to the absorbance of Drug 1 standards. Results are shown in Table 1 and summarized in Table F.

Table 1

Time (hours)	Drug (wt% released)
0	0
1	5
2	19
3	32
6	63
9	83
12	94
15	95
18	96
21	99
24	100

The data show that 19 wt% of the drug was released within 2 hours, 83 wt% within 9 hours, and 100 wt% of the drug was released within 24 hours. Thus, the present invention provided a rapid release of over 80 wt% within 9 hours and no residual value at 24 hours, of a relatively high dose (97 mgA) of a low-solubility drug in a relatively low mass (547.5 mg) dosage form.

Examples 2A–2D

These examples demonstrate the inventive delivery of various drugs from tri-layer tablets. For the tablets of Example 2A, the drug-containing composition consisted of 28 wt% sertraline HCl (Drug 2) having a solubility of 0.2 mg/mL at pH 7, 37 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

To form the water-swellable composition, the following materials were blended: 72.5 wt% EXPLOTAB, 25 wt% microcrystalline cellulose (AVICEL PH 102), and 2.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablet cores were formed by placing 200 mg of drug-containing composition in a standard 13/32 inch die and gently leveling with the press. Then, 100 mg water-swellable composition was placed in the die on top of the drug-containing composition and leveled. The second half of the drug-containing composition (200 mg) was added and the tablet core compressed to a hardness of about 11 Kp. The resulting tri-layer tablet core had a total weight of 500 mg and contained a total of 22.5 wt% Drug 2 (112.5 mg), 29.5 wt% XYLITAB 200, 23 wt% PEO 600,000 daltons, 18.5 wt% EXPLOTAB, 5 wt% AVICEL, and 1.5 wt% magnesium stearate.

Coatings were applied as described in Example 1. The final dry coating weight amounted to 50.5 mg or 10.1 wt% of the tablet core. Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

Dissolution tests were performed by placing the tablets in 900 mL of a simulated gastric solution (10 mM HCl, 100 mM NaCl, pH 2.0, 261 mOsm/kg) for 2 hours, then transferring the tablets to 900 mL of a simulated intestinal environment solution (6 mM KH_2PO_4, 64 mM KCl, 35 mM NaCl, pH 7.2, 210 mOsm/kg), both solutions being stirred at 100 rpm. A residual dissolution test was performed as described in the Detailed Description section. Residual drug was analyzed by HPLC using a Phenomenex Ultracarb 5 ODS 20 column. The mobile phase consisted of 35 vol% TEA-acetate buffer (3.48 mL triethanolamine and 2.86 mL glacial acetic acid in 1L HPLC H_2O) in acetonitrile. Drug concentration was calculated by comparing UV absorbance at 230 nm to the absorbance of sertraline standards. The amount of drug remaining in the tablets was subtracted from the total initial amount of drug in the tablet to obtain the amount released at each time interval. The results are presented in Table 2 and summarized in Table F.

For the tablets of Example 2B, the drug-containing composition consisted of 33 wt% of the mesylate salt of the drug 4-[3-[4-(2-methylimidazol-1-yl) phenylthio] phenyl]-3,4,5,6-tetrahydro-2H-pyran-4-carboxamide hemifumarate (Drug 3) having a solubility of 3.7 mgA/mL at pH 4, 31 wt% XYLITAB 200, 30 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate (see Table A). The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 24.5 wt% PROSOLV 90, and 1 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate in a twinshell mixer and blended for 20 minutes. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch screen. The water-swellable composition ingredients were again placed in a twinshell mixer, the magnesium stearate was added, and the mixture was blended for 4 minutes.

Tablets for Example 2B were compressed and coated as described in Example 1. The resulting tri-layer tablet cores had a total weight of 500 mg and contained a total of 25.9 wt% Drug 3 (129.5 mg), 25.0 wt% XYLITAB 200, 23.9 wt% PEO 600,000 daltons, 19.1 wt% EXPLOTAB, 4.9 wt% PROSOLV 90, and 1.2 wt% magnesium stearate. The final dry coating weight amounted to 46.5 mg or 9.3 wt% of the tablet core. Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A above, with the following exceptions: dissoette stir speed was 50 rpm, and residual drug was analyzed by dissolving tablets in 0.1 N HCl and measuring UV absorbance at 258 nm. Results are shown in Table 2 and summarized in Table F.

For the tablets of Example 2C, the drug-containing composition consisted of 35 wt% of nifedipine (Drug 4) having a solubility of 26 μg/mL in phosphate-buffered saline at pH 6.5, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate (see Table A). The drug-containing composition was processed as described in Examples 2A and 2B above.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% AVICEL PH200, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablets for Example 2C were compressed and coated as described in Example 1, with all weighing and tabletting procedures performed under low-light conditions (nifedipine is light-sensitive). The resulting tri-layer tablet cores had a total weight of 500 mg and contained a total of 28 wt% Drug 4 (140 mg), 24 wt% XYLITAB 200, 23 wt% PEO 600,000, 18.9 wt% EXPLOTAB, 5 wt% AVICEL, and 1.1

wt% magnesium stearate. The final dry coating weight amounted to 45.5 mg or 9.1 wt% of the tablet core. Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A above, with the following exceptions: residual drug was analyzed by HPLC using a C_{18} column with a mobile phase of 50% water/ 25% methanol/ 25% acetonitrile (vol. %) and UV detection at 235 nm. Results are shown in Table 2 and summarized in Table F.

For the tablets of Example 2D, the drug-containing composition consisted of 40 wt% of the drug 4-amino-5-(4-fluorophenyl)-6,7-dimethoxy-2-[4-(morpholinocarbonyl) perhydro-1,4-diazepin-1-yl]quinoline, (Drug 5) having a solubility of 0.4 mg/mL at pH 7.6, 28 wt% XYLITAB 200, 26 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate (see Table A). The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

The water-swellable composition consisted of 74.2 wt% EXPLOTAB, 25.0 wt% PROSOLV 90, 0.3 wt% Red Lake #40, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate in a twinshell mixer and blended for 20 minutes. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch screen. The water-swellable composition ingredients were again placed in a twinshell mixer, the magnesium stearate was added, and the mixture was blended for 4 minutes.

Tablets for Example 2D were compressed and coated as described in Example 1. The resulting tri-layer tablet cores had a total weight of 534 mg and contained a total of 32.58 wt% Drug 6 (174 mg), 22.49 wt% XYLITAB 200, 21.49 wt% PEO 600,000, 17.69 wt% EXPLOTAB, 4.70 wt% PROSOLV 90, 0.06 wt% Red Lake #40, and 0.99 wt% magnesium stearate. The final dry coating weight amounted to 61 mg or 11.4 wt% of the tablet core. Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A above, with the following exceptions:

dissoette stir speed was 50 rpm, and residual drug was analyzed by HPLC using a Phenomenex Luna C_{18} column with a mobile phase of 60% water/ 40% acetonitrile/ 0.1% diethylamine (vol. %) and UV detection at 255 nm. Results are shown in Table 2 and summarized in Table F.

Table 2

Example	Time (hours)	Drug (% released)
2A	0	0
	2	23
	4	46
	8	85
	14	92
	20	90
2B	0	0
	2	27
	4	48
	8	72
	12	81
	18	86
	24	83
2C	0	0
	2	33
	4	50
	8	69
	14	83
	20	85
2D	0	0
	2	17
	4	41
	8	67
	14	86
	20	90

Examples 2A through 2D show greater than 80% drug delivered after 20 hours with virtually no lag time. Along with Example 1, these examples show that different low-solubility drugs can be successfully delivered from dosage forms of this invention.

Example 3

This example demonstrates that the ionic swelling agent can be blended with a high percentage of tableting aid to form a tri-layer dosage form with the desired release profile.

For the tablets of Example 3, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer. The drug-containing composition was then wet-granulated using deionized water and dried overnight in a 40□ C oven.

The water-swellable composition consisted of 25 wt% EXPLOTAB, 74.5 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablets were compressed and coated as described in Example 1. The final dry coating weight was 48.5 mg (9.7 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A, except residual drug was analyzed using the HPLC method described in Example 1. The results are presented in Table 3 and summarized in Table F.

Table 3

Example	Time (hours)	Drug (wt% released)
3 EXPLOTAB/ PROSOLV 90 = 25/75*	0	0
	2	27
	4	43
	8	65
	12	77
	19	82
	24	93

* approximate

The data show that the weight ratio of swelling agent to tableting aid of about 75/25 can be used to achieve a desired drug release profile.

Example 4

This example demonstrates delivery of Drug 1 with the desired release profile from a tri-layer dosage form containing sodium croscarmellose as the ionic swelling agent in the water-swellable composition.

For the tablets of Example 4, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

For tablets of Example 4, the water-swellable composition consisted of 74.5 wt% sodium croscarmellose (AC-DI-SOL), 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablets for Example 4 were compressed and coated as described in Example 1. The final dry coating weight was 52 mg (10.4 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3 (using the gastric-to-intestinal transfer test of Example 2A with the HPLC method of Example 1). The results are presented in Table 4 and summarized in Table F.

Table 4

Time (hours)	Drug (wt% released)
0	0
2	21
4	48
8	81
14	90
20	89

The data show that 21 wt% of the drug was released within 2 hours, 81 wt% within 8 hours, and 89 wt% of the drug was released within 20 hours. Thus,

the present invention provided delivery of low-solubility Drug 1 using sodium croscarmellose as the ionic swelling agent.

Example 5

This example demonstrates that high drug loadings may be delivered from tri-layer dosage forms of the invention.

For the tablets of Example 5, the drug-containing composition consisted of 56 wt% Drug 1, 20 wt% XYLITAB 200, 19 wt% PEO with an average molecular weight of 600,000 daltons, 4 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablet cores were formed by placing 250 mg of drug-containing composition in a standard 13/32 inch die and gently leveling with the press. Then, 200 mg water-swellable composition was placed in the die on top of the drug-containing composition and leveled. The second half of the drug-containing composition (250 mg) was added and the tablet core compressed to a hardness of about 11 Kp. The resulting tri-layer tablet core had a total weight of 700 mg and contained a total of 40.0 wt% Drug 1 (280 mg), 14.3 wt% XYLITAB 200, 13.6 wt% PEO 600,000 daltons, 24.0 wt% EXPLOTAB, 7.1 wt% PROSOLV 90, and 1.0 wt% magnesium stearate.

Tablets for Example 5 were coated as described in Example 1. The final dry coating weight was 77 mg (11.0 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3. The results are presented in Table 5 and summarized in Table F.

Table 5

Time (hours)	Drug (wt% released)
0	0
2	13
4	34
8	63
14	85
20	85

The data show that 13 wt% of the drug was released within 2 hours, 63 wt% within 8 hours, and 85 wt% of the drug was released within 20 hours. Thus, the present invention provided delivery of a high dose of low-solubility Drug 1.

Examples 6A–6D

These examples demonstrate the relationship between the drug release profile and the water permeability of the coating. For the tri-layer tablets of Examples 6A, 6B, 6C, and 6D, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

The water-swellable compositions consisted of 74.5 wt% EXPLOTAB, 25 wt% AVICEL PH102, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablets for Examples 6A–6D were compressed and coated as described in Example 1. For the tablets of Example 6A, the coating had a final dry weight of 26 mg (5.2 wt%). For the tablets of Example 6B, the coating had a final dry weight of 49.5 mg (9.9 wt%). For the tablets of Example 6C, the coating had a final dry weight of 78 mg (15.6 wt%). For the tablets of Example 6D, the coating had a final dry weight of 107 mg (21.4 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage forms.

Generally, the thicker the coating, the lower the expected water permeability. Dissolution tests were performed on these tablets as described in Example 3. Results are shown in Table 6 and are summarized in Table F.

Table 6

Example	Time (hours)	Drug (wt% released)
6A	0	0
	2	32
	4	58
	8	90
	14	95
	20	94
6B	0	0
	2	25
	4	40
	8	73
	14	92
	20	92
6C	0	0
	2	11
	4	36
	8	66
	14	85
	20	92
6D	0	0
	2	4
	4	27
	8	54
	14	86
	20	90

Examples 6A–6D show that as the water permeability decreased, i.e., as the coating weight increased, the rate of drug release decreased. The data show that as the coating thickness increased, the fraction of drug delivered between 0 and 8 hours decreased, while the fraction of drug delivered from 8 to 20 hours increased.

Example 7

Exemplary dosage forms of the present invention were made with a tri-layer core geometry of the type depicted in FIG. 1. This example illustrates dosage forms of this invention which release drug over a short duration, utilizing a durable, high permeability coating.

For the tablets of Example 7, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablets were compressed and coated as described in Example 1, except that the coating solution contained CA, PEG 3350, water, and acetone in a weight ratio of 7/3/23/67 (wt%). The amount of water in the coating solution was increased to increase the porosity. The coating had a final dry weight of 56.5 mg (11.3 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3, except that the flasks were stirred at 50 rpm. The results are presented in Table 7 and summarized in Table F.

Table 7

Time (hours)	Drug (wt% released)
0	0
2	31
4	66
8	90
14	94
20	94

The data show that 31 wt% of Drug 1 was released within 2 hours, 90 wt% within 8 hours, and 94 wt% of the drug was released within 20 hours. Thus, for coatings with increased water permeability, the rate of drug release increased.

Example 8

This example illustrates the delivery of 5-(2-(4-(3-benzisothiazolyl)-piperazinyl)ethyl-6-chlorooxindole (Drug 6) having a solubility of 3 □g/mL in model fasted duodenal solution, from a tri-layer dosage form of the invention. The drug was in the form of a solid amorphous dispersion comprising 10 wt% of Drug 6 and 90 wt% hydroxy propylmethyl cellulose acetate succinate, HF grade (HPMCAS -HF), a concentration-enhancing polymer.

Amorphous solid dispersions of Drug 6 in HPMCAS were prepared by spray-drying a solution containing 0.30 wt% Drug 6, 2.7 wt% HPMCAS -HF, and 97 wt% methanol. The solution was spray-dried using a two-fluid external mix spray nozzle at 1.8 bar at a feed rate of 140 g/min into the stainless steel chamber of a Niro spray-dryer, maintained at a temperature of 264□C at the inlet and 62□C at the outlet.

To form the drug-containing composition, the following materials were blended: 35 wt% Drug 6 dispersion (1:9 Drug 1:HPMCAS), 29 wt% PEO having an average molecular weight of 600,000 daltons, 30 wt% XYLITAB 200, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, half of the magnesium stearate was added and the drug-containing composition was blended again for 4 minutes. The second half of the magnesium stearate was added and the mixture was blended for 5 minutes.

To form the water-swellable composition, the following materials were blended: 74.8 wt% EXPLOTAB, 24.8 wt% PROSOLV 90, and 0.4 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablets for Example 8 were compressed and coated as described in Example 1. Assays of these tablets confirmed 15 mg of active Drug 6 (mgA). The coating had a final dry weight of 43 mg (8.6 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

Release of the Drug 6 dispersion from the tri-layer tablets into simulated intestinal buffer was measured. The dissoette flasks were stirred at 50 rpm at 37□C. For each sampling interval, a tablet was removed from the test solution, placed in 200 mL of recovery solution consisting of 75% methanol/ 25% water, and stirred overnight to dissolve the remaining drug in the tablet. Residual drug was analyzed by HPLC using a Phenomenex ODS 20 column. The mobile phase consisted of 60% 0.02 M KH_2PO_4, pH 3/ 40% acetonitrile. Drug concentration was calculated by comparing UV absorbance at 254 nm to the absorbance of Drug 6 standards. The amount of drug remaining in the tablets was subtracted from the total initial amount of drug in the tablet to obtain the amount released at each time interval. The results are presented in Table 8 and summarized in Table F.

Table 8

Time (hours)	Drug (wt% released)
0	0
1	10
2	23
4	48
8	77
12	88
18	85
24	89

The data demonstrate satisfactory delivery of a dispersion of Drug 6 from tri-layer dosage forms of this invention.

Example 9 This example describes the results of tests to determine the swelling volume of swelling agents that may be used in the formulation of the water-swellable composition.

The following experiment was used to determine the swelling ratio of materials. The materials were first blended and then 500 mg of the material was compressed into a tablet using a 13/32-inch die, the tablet having a strength ranging from 3 to 16 Kp/cm^2. This compressed material was then placed into a glass cylinder of approximately the same inside diameter as the tablet. The height of the tablet was then measured. Using this height and the diameter of the tablet, the volume of the dry material was determined. Next, the glass cylinder was filled with test media of either deionized water, simulated intestinal buffer, or simulated gastric buffer. The glass cylinder and test media were all equilibrated at a constant temperature of 37□C. As the materials in the tablet absorbed water, the height of the tablet increased. At each time interval, the height of the tablet was measured, from which the volume of the swollen tablet was determined. The ratio of the volume of the tablet after reaching a constant height to that of the volume of the dry tablet is the swelling ratio of the material. The results of these tests are shown in Table 9.

Table 9

Water-Swellable Composition			Swelling Ratio (v/v)		
Swelling Agent	Tableting Aid/ Additive	Swelling Agent/ Tableting Aid (w/w)	Gastric Buffer	Intestinal Buffer	Water
PEO 5,000,000	NONE	100/0	2.4	2.4	2.4
PEO 5,000,000	Microcrystal-line cellulose[1]	85/15	2.2	2.1	2.4
PEO 5,000,000	Microcrystal-line cellulose	70/30	2.0	2.1	2.4
PEO 5,000,000	Microcrystal-line cellulose	50/50	2.0	1.9	1.9
PEO 5,000,000	NaCl	70/30	2.6	2.6	2.8
PEO 2,000,000	Microcrystal-line cellulose	85/15	2.8	2.8	3.0
Polyacrylic acid[2]	Silicified microcrystal-line cellulose[3]	70/30	1.9	1.5	-
Polyacrylic acid	Microcrystal-line cellulose	50/50	1.8	1.7	-
Sodium cros-carmelose[4]	None	100/0	7.0	5.4	7.1
Sodium cros-carmellose	Microcrystal-line cellulose	85/15	7.1	5.9	7.2
Sodium cros-carmellose	Microcrystal-line cellulose	70/30	5.5	6.3	5.5
Sodium cros-carmellose	Microcrystal-line cellulose	50/50	4.6	5.3	5.7
Sodium starch glycolate[5]	Microcrystal-line cellulose	50/50	7.1	7.7	25.2
Sodium starch glycolate	Microcrystal-line cellulose	70/30	9.0	9.6	26.8
Sodium starch glycolate	Microcrystal-line cellulose	85/15	10.9	11.9	34.7
Sodium starch glycolate	Silicified Microcrystal-line cellulose	50/50	7.9	8.7	-
Sodium starch glycolate	Silicified Microcrystal-line cellulose	75/25	7.4	9.1	14.4
Sodium starch glycolate	Silicified Microcrystal-line cellulose	70/30	10.6	11.2	-
Sodium starch glycolate	Hydroxypropyl cellulose[6]	98/2	-	17.2	-
Sodium starch glycolate	Hydroxypropyl cellulose	95/5	5.6	8.4	-

Sodium starch glycolate	Hydroxypropyl cellulose	90/10	7.2	6.9	-
Sodium starch glycolate	Hydroxypropyl cellulose	85/15	-	3.8	3.8
Sodium starch glycolate	Hydroxypropyl cellulose	70/30	3.7	3.9	3.3
Sodium starch glycolate	Hydroxypropyl cellulose	50/50	2.4	2.5	2.4
Sodium alginate[7]	Silicified microcrystal-line cellulose	50/50	2.7	2.9	-
Hydroxyethyl cellulose[8]	NONE	100/0	2.8	2.8	2.7
Hydroxyethyl cellulose	Microcrystal-line cellulose	50/50	2.4	2.1	2.5
1 = AVICEL 2 = CARBOPOL 974PNF 3 = PROSOLV 90 4 = AC-DI-SOL 5 = EXPLOTAB 6 = Klucel 7 = Keltone LVCR 8 = Natrosol					

Examples 10A–10C These examples demonstrate that various osmogens can be used in the drug-containing composition to form tri-layer dosage forms with the desired release profile. For the tablets of Example 10A, the drug-containing composition consisted of 35 wt% Drug 1, 29 wt% PEO having an average molecular weight of 600,000 daltons, 30 wt% sorbitol, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. For the tablets of Example 10B, the drug-containing composition consisted of 35 wt% Drug 1, 29 wt% PEO having an average molecular weight of 600,000 daltons, 30 wt% FAST FLO Lactose, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. For the tablets of Example 10C, the drug-containing composition consisted of 35 wt% Drug 1, 19 wt% PEO having an average molecular weight of 600,000 daltons, 40 wt% XYLITAB 200, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

For the tablets of Examples 10A-10C, the water-swellable compositions consisted of 74.5 wt% EXPLOTAB, 25.0 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. For the tablets of Example 10C, the water-swellable composition ingredients were processed as described in Example 4. For the tablets of Examples 10A and 10B, the water-swellable composition ingredients were processed as described in Example 1.

Tablets for Examples 10A–10B were compressed and coated as described in Example 1. The final dry coating weights for each example were 58 mg (11.6 wt%) for 10A, 35 mg (7.0 wt%) for 10B, and 48.5 mg (9.7 wt%) for 10C respectively. For all of these examples, five 900 μm diameter holes were then laser-

drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage forms.

Dissolution tests were performed as described in Example 3, except that the flasks for Examples 10A–10C were stirred at 50 rpm. The results are presented in Table 13 and summarized in Table F.

Table 10

Example	Time (hours)	Drug (wt% released)
10A	0	0
	1	4
30% Sorbitol	2	20
	4	40
	6	53
	8	68
	14	86
	20	90
10B	0	0
	2	11
30% Lactose	4	35
	8	60
	12	90
	18	89
	20	90
	24	90
10C	0	0
	1	12
40% XYLITAB	2	30
	4	48
	6	77
	8	81
	14	89
	20	89

The data show that a variety of materials may be used as the osmogen in the drug-containing composition without any adverse effect on the desired drug release profile.

Example 11

This example illustrates delivery of two different drugs from a tri-layer dosage form of the invention. Tri-layer tablets for Example 11 were made with two different drug layers.

For the tablets of Example 11, the top drug-containing composition consisted of 17 wt% cetirizine dihydrochloride (Drug 7), 25 wt% PROSOLV 90,

40 wt% XYLITAB 200, 17 wt% EXPLOTAB, and 1 wt% magnesium stearate. The top layer did not contain a drug entraining agent (e.g., PEO), which reduced the viscosity of the solvated layer and allowed faster release of Drug 7. The bottom drug-containing composition consisted of 60 wt% pseudoephedrine hydrochloride (Drug 8), 34 wt% PEO having an average molecular weight of 600,000, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. Each mixture of drug-containing composition ingredients was processed as described in Example 4. The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 1.

Tablets for Example 11 were compressed as described in Example 1, except that 400 mg of the bottom layer containing pseudoephedrine was placed in the f-press and leveled, 100 mg of the sweller layer was added and leveled, and 60 mg of the top layer containing cetirizine was added and the tablet compressed. Tablets were coated as described in Example 1. The final dry coating weight for Example 11 was 125.5 mg (22.4 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on the pseudoephedrine side of the tablet, and five 2000 μm diameter holes were laser-drilled in the coating on the cetirizine side of the tablet, to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3, except that the flasks for Example 11 were stirred at 50 rpm, and the recovery solution for dissolution of residual drug was 50% acetonitrile/ 50% water for Example 11. The HPLC method for analysis of pseudoephedrine and cetirizine uses a Zorbax Stablebond® CN column with a mobile phase of 50% 0.1M KH_2PO_4, pH 6.5/ 50% methanol containing 1 g/L sodium octanesulfonate, and UV detection at 214 nm. The results are presented in Table 11 and summarized in Table F.

Table 11

Example	Time (hours)	Drug (wt% released)
11 Drug 7	0	0
	0.5	23
	1	47
	2	52
	4	56
	8	97
	12	97
	18	97
	24	97
11 Drug 8	0	0
	0.5	0
	1	5
	2	17
	4	32
	8	64
	12	74
	18	97
	24	98

The data show that two different drugs can be successfully delivered from tri-layer dosage forms of the invention, and that the rate of delivery for each drug can be independently modified.

Examples 12A–12C

Examples 12A–12C illustrate the delivery of a low solubility drug (Drug 1) using three different dosage form geometries, each comprising a drug-containing composition and a water-swellable composition.

Tablets for Example 12A were tri-layer dosage forms, with the drug-containing composition consisting of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4. The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% AVICEL PH200, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4. Tablets were compressed and coated as described in Example 1. The coating had a final dry weight of 52.5 mg (10.5 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Tablets for Example 12B were concentric core dosage forms, with the same drug-containing composition and water-swellable composition as Example 12A, blended using the same processes. To form the tablets, 100 mg of the water-swellable composition was compressed with 1/4-inch tooling to a hardness of 6 Kp. Next, 200 mg of the drug-containing composition was placed in the f-press and gently leveled and compressed with a spatula. The sweller core was placed on top of this and centered. The remaining drug-containing composition (200 mg) was added and the tablet compressed with 9/16-inch tooling to a hardness of about 11 Kp. Tablets were coated as described in Example 1. The coating had a final dry weight of 55 mg (11.0 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Tablets for Example 12C were homogeneous core dosage forms (as in FIG. 4). The tablet cores contained 28 wt% Drug 1, 21 wt% XYLITAB 200, 20 wt% PEO with an average molecular weight of 600,000 daltons, 30 wt% EXPLOTAB, and 1 wt% magnesium stearate. The homogeneous core ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the composition was blended again for 4 minutes in the same mixer. Tablets contained 500 mg each. Tablets were coated as described in Example 1. The coating had a final dry weight of 47.5 mg (9.5 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests for Examples 12A–12C were performed as described in Example 3. The results are presented in Table 12 and summarized in Table F.

Table 12

Example	Time (hours)	Drug (wt% released)
12A	0	0
	2	25
	4	53
	8	75
	14	95
	20	95
12B	0	0
	2	27
	4	49
	8	69
	14	87
	20	88
12C	0	0
	2	11
	4	40
	8	65
	14	81
	20	85

The data show that drug can be delivered from dosage forms of the invention in various geometries, with no time lag and low residual drug.

Example 13

This example demonstrates delivery of Drug 1 with the desired release profile from a concentric core dosage form containing sodium croscarmellose as the ionic swelling agent.

For the tablets of Example 13, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

For tablets of Example 13, the water-swellable composition consisted of 74.5 wt% sodium croscarmellose, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

To form the tablets, 100 mg of the water-swellable composition was compressed with 1/4-inch tooling to a hardness of 5 Kp. Next, 200 mg of the drug-containing composition was placed in the f-press and gently leveled and compressed with a spatula. The sweller core was placed on top of this and centered. The

remaining drug-containing composition (200 mg) was added and the tablet compressed with 9/16-inch tooling to a hardness of about 11 Kp. Tablets were coated as described in Example 1. The coating had a final dry weight of 50 mg (10.0 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3. The results are presented in Table 13 and summarized in Table F.

Table 13

Time (hours)	Drug (wt% released)
0	0
2	21
4	54
8	75
14	85
20	84

The data show that 21 wt% of the drug was released within 2 hours, 75 wt% within 8 hours, and 84 wt% of the drug was released within 20 hours.

Example 14 This example demonstrates delivery of Drug 1 with the desired release profile from a granular core dosage form containing a granular swelling agent.

The tablets contained 28 wt% Drug 1, 24 wt% XYLITAB 200, 23 wt% PEO with an average molecular weight of 600,000 daltons, 24 wt% EXPLOTAB (granular, 0.85-1.18 mm), and 1 wt% magnesium stearate. The mixture was processed using the same procedures used to process the drug-containing composition of Example 4. Tablets contained 500 mg each. Tablets were coated as described in Example 1. The coating had a final dry weight of 47.5 mg (9.5 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3. The results are presented in Table 14 and summarized in Table F.

Table 14

Time (hours)	Drug (wt% released)
0	0
2	20
4	45
8	69
14	81
20	85

The data show that 20 wt% of the drug was released within 2 hours, 69 wt% within 8 hours, and 85 wt% of the drug was released within 20 hours. Thus, the present invention provided delivery of a low-solubility drug from a granular core dosage form using granular EXPLOTAB as the swelling agent.

Example 15

This example demonstrates the in vivo release of Drug 2 from a granular core dosage form. The tablets of Example 15 contained 22.5 wt% Drug 2, 30 wt% XYLITAB 200, 26.5 wt% PEO with an average molecular weight of 600,000 daltons, 20 wt% EXPLOTAB (granular, 0.85-1.18 mm), and 1 wt% magnesium stearate. The mixture was processed using the same procedures used to process the drug-containing composition of Example 4. Tablets contained 500 mg each. Tablets were coated as described in Example 1. The coating had a final dry weight of 55.5 mg (11.1 wt%). Eight 1000 µm diameter slits were then laser-drilled in the coating on the band of the tablet to provide delivery ports.

In vivo residual tests were performed in 5 dogs as follows: Each of five dogs were dosed with tablets (which were marked for later identification) over a six-hour period (i.e., one tablet every two hours) with oral gavage of 50 mL water. The bowel movement was screened for tablets and the recovery time noted. All tablets were recovered intact, i.e., there were no splits in the coatings. The amount of undelivered drug was determined by extracting the unreleased drug from the tablets and the drug released was determined by subtracting the unreleased amount from the known initial amount of drug present in the tablets. Results are shown in Table 15.

Table 15.1

Dog No.	Time (hours)	Drug (wt% released)
1	7.75	51
	5.75	27
	3.75	15
2	24	75
	22	66
	20	71
3	7.5	47
	5.5	30
	3.5	28
4	7.5	48
	5.5	33
	3.5	25
5	28	68
	26	74
	24	68

These tablets were also tested in vitro using a residual dissolution test. These tests were performed in a USP type 2 dissoette using the conditions described in Example 2A. Results are shown in Table 15.2.

Table 15.2

Time (hours)	Drug (wt% released)
0	0
2	22
4.5	52
8.3	61
14	65
20	71

The data show satisfactory in vivo drug delivery with dosage forms of the invention. Good correlation is observed between in vitro and in vivo data.

Example 16

This example demonstrates the in vivo delivery of Drug 2 from tri-layer tablets. For the tablets of Example 16, the drug-containing composition consisted of 28 wt% Drug 2, 37 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate; and the water-swellable composition consisted of 72.5 wt% EXPLOTAB, 25 wt% AVICEL PH102, and 2.5 wt% magnesium stearate. The drug-containing compositions and water-swellable composition were processed as described in Example 4. Tablets were compressed and coated as described in Example 1. The coating had a final dry weight of 50.5 mg (10.1 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

In vivo residual tests were performed in dogs as follows: Each of five dogs were dosed with tablets (which were marked for later identification) over a six-hour period (i.e., one tablet every two hours) with oral gavage of 50 mL water. The bowel movement was screened for tablets and the recovery time noted. All tablets were recovered intact, i.e., there were no splits in the coatings. The amount of undelivered drug was determined by extracting the unreleased drug from the tablets and the drug released was determined by subtracting the unreleased amount from the known initial amount of drug present in the tablets. Results are shown in Table 16.1.

Table 16.1

Dog No.	Time (hours)	Drug (wt% released)
1	24	86
	22	86
	20	84
2	26.5	87
	24.5	87
	22.5	86
3	26.5	86
	24.5	86
	22.5	85
4	33 - 48	87
	31 - 46	90
	29 - 44	87
5	26.5	88
	24.5	85
	22.5	82

These tablets were also tested in vitro using a residual dissolution test. These tests were performed in a USP type 2 dissoette using the conditions described in Example 2A. Results are shown in Table 16.2.

Table 16.2

Time (hours)	Drug (wt% released)
0	0
2	23
4	46
8	85
14	92
20	90

The data show satisfactory in vivo drug delivery with dosage forms of the invention. Good correlation is observed between in vitro and in vivo data.

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention, in the use of such terms and expressions, of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

Table A. Composition of the Drug-containing Layer for "Trilayer" and Concentric Core Examples

Example	Drug	Drug-containing Layer Composition								
		Drug Conc. (wt%)	PEO Type	PEO Conc. (wt%)	Explotab Conc. (wt%)	Xylitab 200 Conc. (wt%)	Mg Stearate Conc. (wt%)	Other Ingredients	Conc. (wt%)	Processing Method
1	1	35	600K	29	5	30	1	-	-	Wet Granulated
2A	2	28	600K	29	5	37	1	-	-	Dry Blended
2B	3	33	600K	30	5	31	1	-	-	Dry Blended
2C	4	35	600K	29	5	30	1	-	-	Dry Blended
2D	5	40	600K	26	5	28	1	-	-	Dry Blended
3	1	35	600K	29	5	30	1	-	-	Wet Granulated
4	1	35	600K	29	5	30	1	-	-	Dry Blended
5	1	56	600K	19	4	20	1	-	-	Dry Blended
6A	1	35	600K	29	5	30	1	-	-	Dry Blended
6B	1	35	600K	29	5	30	1	-	-	Dry Blended
6C	1	35	600K	29	5	30	1	-	-	Dry Blended
6D	1	35	600K	29	5	30	1	-	-	Dry Blended
7	1	35	600K	29	5	30	1	-	-	Dry Blended
8	6	3.5 Dispersion	600K	29	5	30	1	HPMCAS-HF	31.5	Dry Blended
10A	1	35	600K	29	5	30 sorbitol	1	-	-	Dry Blended
10B	1	35	600K	29	5	30 lactose	1	-	-	Dry Blended

10C	1	35	600K	19	5	40	1	-	Dry Blended
11(1)	7	17	-	0	17	40	1	PROSOLV	25	Dry Blended
11(2)	8	60	600K	34	5	0	1	-	-	Dry Blended
12A	1	35	600K	29	5	30	1	-	-	Dry Blended
12B	1	35	600K	29	5	30	1	-	-	Dry Blended
13	1	35	600K	29	5	30	1	-	-	Dry Blended
16	2	28	600K	29		37	1	-	-	Dry Blended

Table B. Composition of the Water-swellable Composition for Trilayer and Concentric Core Examples

Example	Sweller Type	Sweller Conc. (wt%)	Tabletting Aid Type	Tabletting Aid Conc. (wt%)	Mg Stearate Conc. (wt%)	Other Ingredients	Conc. (wt%)	Processing Method
1	Explotab	74.5	Prosolv 90	24.5	1.0	-	-	Wet Granulated
2A	Explotab	72.5	Avicel	25	2.5	-	-	Dry Blended
2B	Explotab	74.5	Prosolv 90	24.5	1.0	-	-	Wet Granulated
2C	Explotab	74.5	Avicel	25	0.5	-	-	Dry Blended
2D	Explotab	74.2	Prosolv 90	25	0.5	Red Lake #40	0.3	Wet Granulated
3	Explotab	25	Prosolv 90	74.5	0.5	-	-	Dry Blended
4	sodium croscar-mellose	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
5	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6A	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6B	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6C	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6D	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
7	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
8	Explotab	74.8	Prosolv 90	24.8	0.4	-	-	Dry Blended
10A	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
10B	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended

10C	Explotab	74.5	Prosolv 90	25	0.5	-	Dry Blended
11	Explotab	74.5	Prosolv 90	25	0.5	-	Dry Blended
12A	Explotab	74.5	Prosolv 90	25	0.5	-	Dry Blended
12B	Explotab	74.5	Avicel	25	0.5	-	Dry Blended
13	sodium croscar-mellose	74.5	Prosolv 90	25	0.5	-	Dry Blended
16	Explotab	72.5	Avicel	25	2.5	-	Dry Blended

Table C. Details of Tablet Formulations for Trilayer and Concentric Core Examples

Example	Core Weight (mg)	Ratio of Total Drug Layers to Sweller Layer (w/w)	CA Conc. (wt%)	PEG Cont. (wt%)	H_2O Conc. (wt%)	Coating Amount (wt% of uncoated tablet)	Number of Holes	Hole Size (µm)
1	500	4:1	7	3	5	9.5	10	900
2A	500	4:1	7	3	5	10.1	10	900
2B	500	4:1	7	3	5	9.3	10	900
2C	500	4:1	7	3	5	9.1	10	900
2D	534	4:1	7	3	5	11.4	10	900
3	500	4:1	7	3	5	9.7	10	900
4	500	4:1	7	3	5	10.4	10	900
5	500	2.5:1	7	3	5	11.0	10	900
6A	500	4:1	7	3	5	5.2	10	900
6B	500	4:1	7	3	5	9.9	10	900
6C	500	4:1	7	3	5	15.6	10	900
6D	500	4:1	7	3	5	21.4	10	900
7	500	4:1	7	3	23	11.3	10	900
8	500	4:1	7	3	5	8.6	10	900
10A	500	4:1	7	3	5	11.6	10	900
10B	500	4:1	7	3	5	7.0	10	900
10C	500	4:1	7	3	5	9.7	10	900

11	500	4.6:1	7	3	5	22.4	10	2000, 900
12A	500	4:1	7	3	5	10.5	10	900
12B	500	4:1	7	3	5	11.0	10	900
13	500	4:1	7	3	5	10.0	10	900
16	500	4:1	7	3	5	10.1	10	900

Table D. Composition of the Core for "Granular Core" and Homogeneous Core Examples

		Drug-containing Layer Composition						
Example	Drug	Drug Conc. (wt%)	PEO Type	PEO Conc. (wt%)	Explotab Conc. (wt%)	Xylitab 200 Conc. (wt%)	Mg Stearate Conc. (wt%)	Processing Method
12C	1	28	600K	29	20	22	1	Dry Blended
14	1	28	600K	23	24 granular	24	1	Dry Blended
15	2	22.5	600K	26.5	20 granular	30	1	Dry Blended

Table E. Details of Tablet Formulations for "Granular Core" and Homogeneous Core Examples

Example	Core Weight (mg)	Sweller (wt% of core)	CA Conc. (wt%)	PEG Cont. (wt%)	H2O Conc. (wt%)	Coating Amount (wt% of uncoated tablet)	Number of Holes	Hole Size (□m)
12C	500	20	7	3	5	9.5	10	900
14	500	24	7	3	5	9.5	10	900
15	500	20	7	3	5	11.1	8	1000 slits

Table F. Summary of Release Rates For All Examples

Example	2-hr Release (%)	8-hr Release (%)	12-hr Release (%)	16-hr Release (%)	20-hr Release (%)	Release Rate 2-12 hr (%/hr)
1	19	76*	94	95*	100 (24 hr)	7.5
2A	23	85	90*	91*	90	6.7
2B	27	72	81	84*	83 (24 hr)	5.4
2C	33	69	78*	84*	85	4.5
2D	17	67	80*	87*	90	6.3
3	27	65	77	80*	93 (24 hr)	5.0
4	21	81	87*	90*	89	6.6
5	13	63	78*	85*	85	6.5
6A	32	90	93*	95*	94	6.1
6B	25	73	86*	92*	92	6.1
6C	11	66	79*	87*	92	6.8
6D	4	54	75*	87*	90	7.1
7	31	90	93*	94*	94	6.2
8	23	77	88	88*	89 (24 hr)	6.5
10A	20	68	80*	87*	90	6.0
10B	11	60	90	89*	90 (24 hr)	7.9
10C	30	81	86*	89*	89	5.6
11 Drug 7	23	97	97	97*	97 (24 hr)	7.4

11 Drug 8	17	64	74	89*	98 (24 hr)	5.7
12A	25	75	88*	95*	95	6.3
12B	27	69	81*	87*	88	5.4
12C	11	65	76*	82*	85	6.5
13	21	75	88*	85*	84	6.7
14	20	69	77*	82*	85	5.7
15	22	61	64*	67*	71	4.2
16	23	85	90*	92*	90	6.7

* Interpolated from data.

CLAIMS

1. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core comprises a drug-containing composition, another drug-containing composition, and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition being located between said drug-containing composition and said another drug-containing composition; and

(b) said coating is water-permeable, water-insoluble, and has at least one delivery port for communication with said drug-containing composition and another delivery port for communication with said another drug-containing composition.

2. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said drug-containing composition surrounding said water-swellable composition;

(b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent;

(c) said water-swellable composition comprises a swelling agent; and

(d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

3. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition comprising a plurality of granules;

(b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent;

(c) said water-swellable composition comprises a swelling agent; and

(d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

4. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core is substantially homogeneous throughout and comprises a mixture of a low-solubility drug, a drug-entraining agent, and a swelling agent; and

(b) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

5. The dosage form of claim 1 wherein said drug-containing composition has a different formulation than said another drug-containing composition.

6. The dosage form of claim 1 wherein said drug-containing composition comprises a low-solubility drug, and said first drug-containing composition comprises a drug-entraining agent.

7. The dosage form of any one of claims 2-4 and 6 wherein said drug-entraining agent is selected from the group consisting of polyols, oligomers of polyethers, mixtures of polyfunctional organic acids, cationic materials, polyethylene oxide, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, carboxyethylcellulose, gelatin, and xanthan gum.

8. The dosage form of any one of claims 1-3 wherein said drug-containing composition further comprises a swelling agent.

9. The dosage form of any one of claims 1-4 wherein said core further comprises a solubilizing agent.

10. The dosage form of any one of claims 1-3 wherein said drug-containing composition further comprises a fluidizing agent having a solubility of at least 30 mg/mL and said fluidizing agent comprises at least 10 wt% of said drug-containing composition, and said fluidizing agent is selected from the group

consisting of an organic acid, a salt, a sugar, an amino acid, a polyol, and a low-molecular weight oligomer of a water-soluble polymer.

11. The dosage form of any one of claims 1-4 comprising an ionic swelling agent.

12. The dosage form of any one of claims 1-3 wherein said water-swellable composition has a swelling ratio of at least 2.

13. The dosage form of any one of claims 2-4 and 6 wherein said low-solubility drug is selected from the group consisting of sildenafil and pharmaceutically acceptable salts of sildenafil, sertraline and pharmaceutically acceptable salts of sertraline, the mesylate salt of the drug 4-[3-[4-(2-methylimidazol-1-yl) phenylthio] phenyl]-3,4,5,6-tetrahydro-2H-pyran-4-carboxamide hemifumarate, nifedipine, (+)-2-(3-benzyl-4hydroxy-chroman-7-yl)-4-trifluoromethyl-benzoic acid, 4-amino-5-(4-fluorophenyl)-6,7-dimethoxy-2-[4-(morpholinocarbonyl) perhydro-1,4-diazepin-1-yl]quinoline, and 5-(2-(4-(3-benzisothiazolyl)-piperazinyl)ethyl-6-chlorooxindole.

14. The dosage form of any one of claims 1-4 wherein said coating has a water flux (40/75) of at least 1.0×10^{-3} gm/cm^2-hr.

15. The dosage form of any one of claims 1-4 and 14 wherein said coating has a durability of at least 1 Kp/cm^2.

16. The dosage form of any one of claims 1-4 wherein said coating is formed from a solution having a weight ratio of cellulose acetate to polyethylene glycol of from 9:1 to 6.5:3.5.

17. The dosage form of any one of claims 1-4 wherein said coating comprises a polymeric asymmetric membrane comprising a thick, porous region and a dense thin region.

18. The dosage form of any one of claims 2-4 and 6 wherein, following introduction of said dosage form to a use environment, no more than 50 wt% of said low-solubility drug is released to said use environment within 2 hours and at least 60 wt% to said use environment is released within 12 hours.

19. The dosage form of any one of claims 2-4 and 6 wherein, following introduction of said dosage form to a use environment, at least about 80 wt% of said low-solubility drug is released to said use environment within about 24 hours.

20. The dosage form of any one of claims 1-4 wherein said core further comprises a concentration-enhancing polymer.

FIG. 1

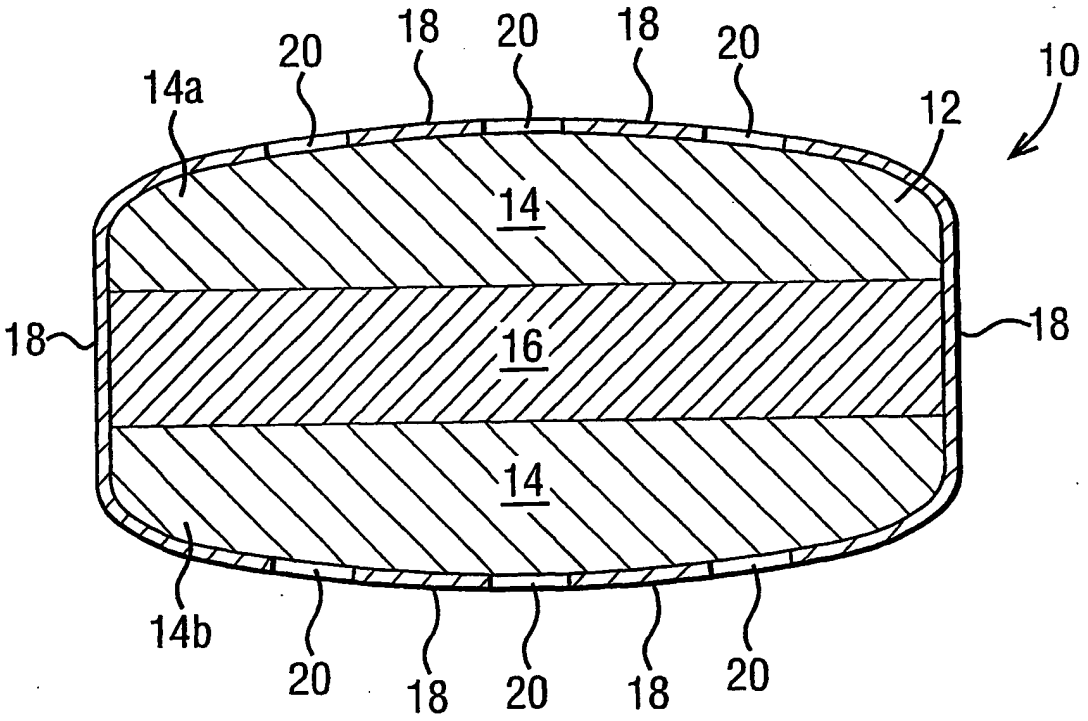

FIG. 2

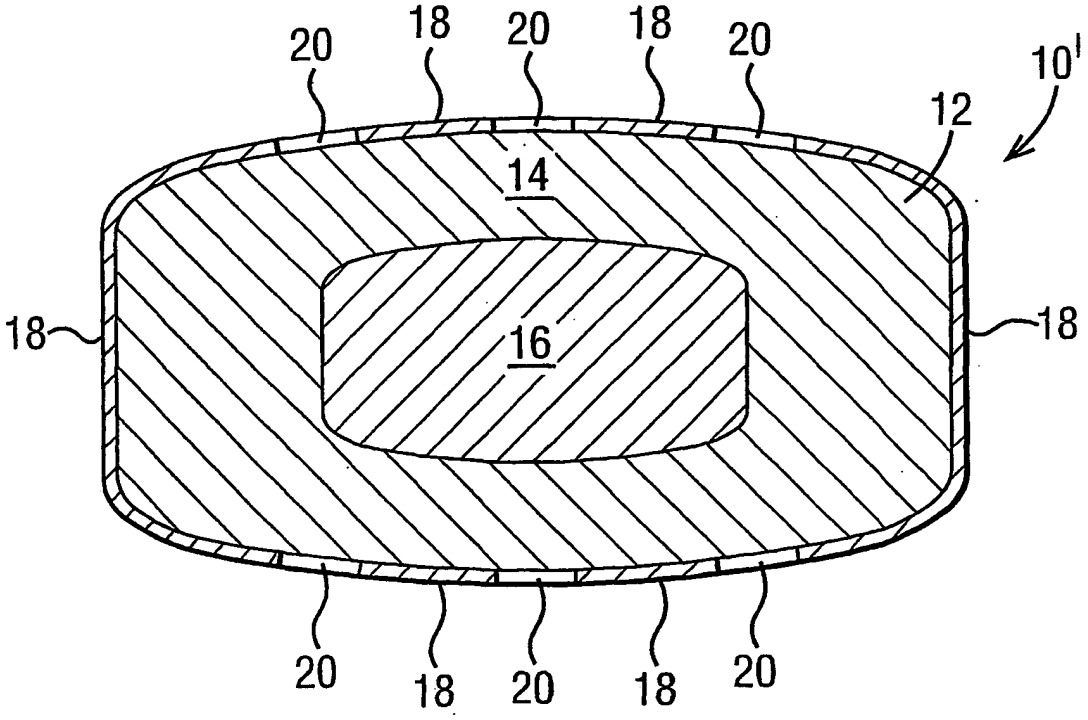

FIG. 3

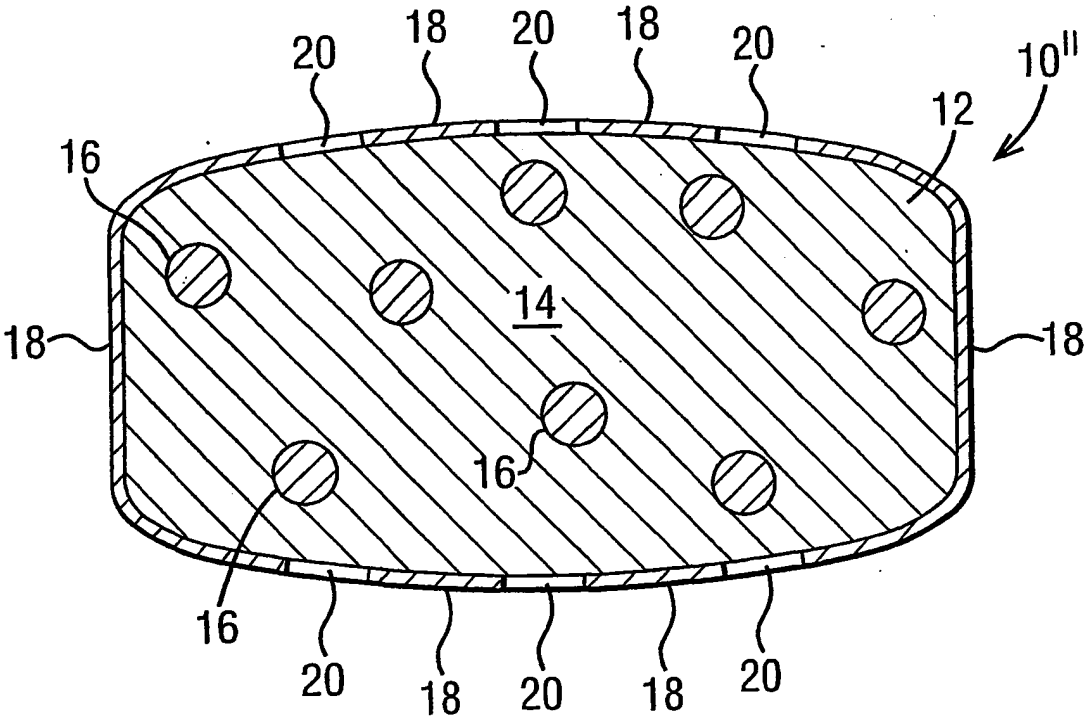
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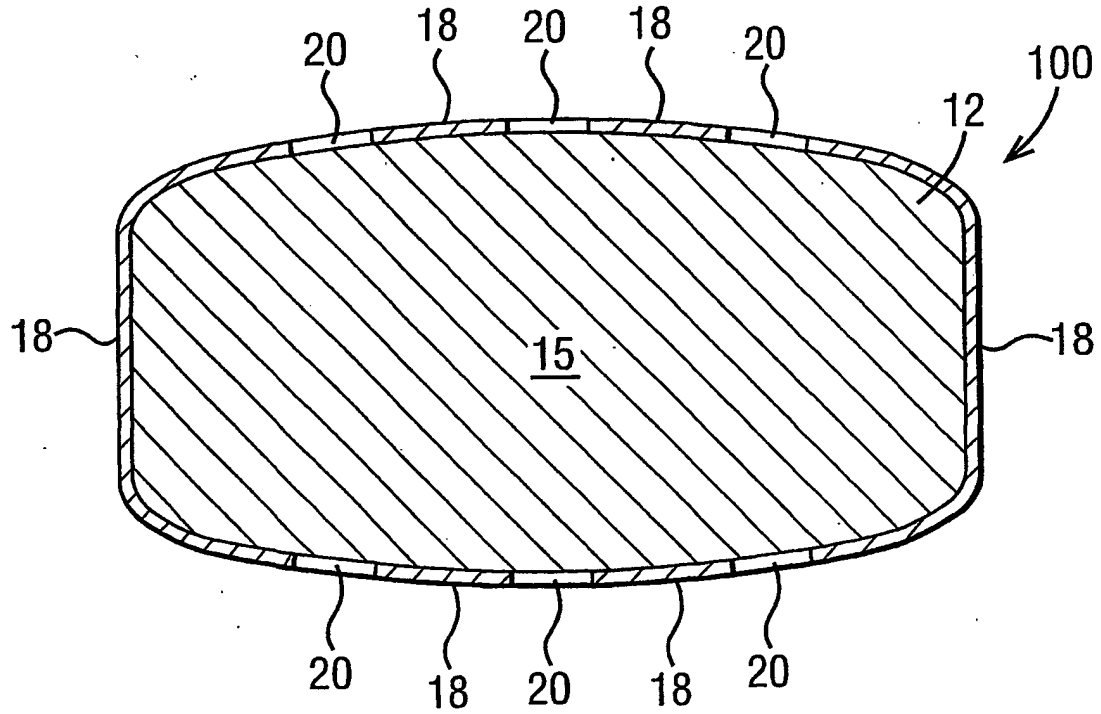
FIG. 4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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(25) Filing Language: English

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(30) Priority Data:
60/224,199 9 August 2000 (09.08.2000) US

(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

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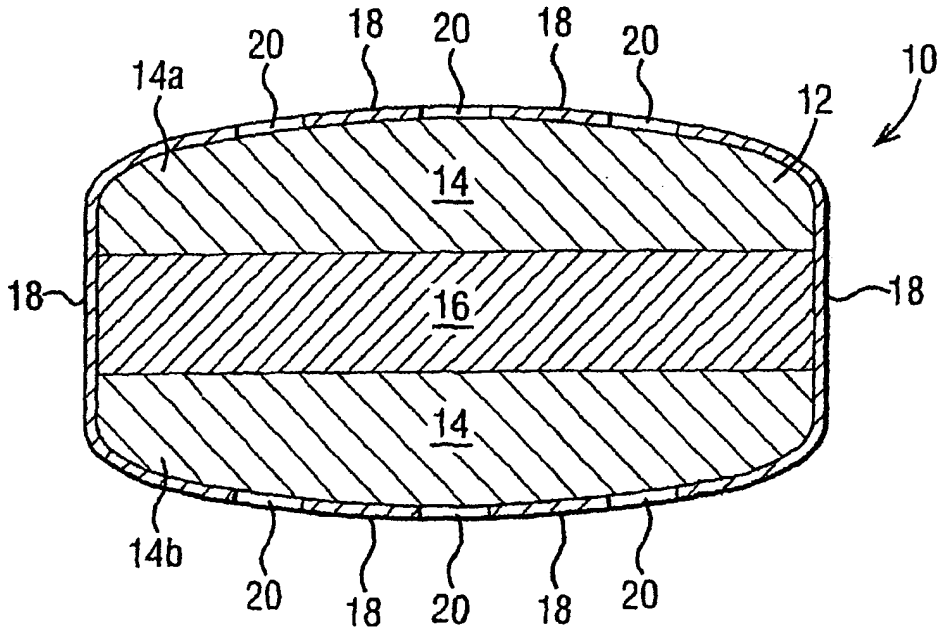
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: HYDROGEL-DRIVEN DRUG DOSAGE FORM



(57) Abstract: A controlled release dosage form has a coated core with the core comprising a drug-containing composition and a water-swellable composition, each occupying separate regions within the core. The coating around the core is water-permeable, water-insoluble and has at least one delivery port therethrough. A variety of geometric arrangements are disclosed.

WO 02/011702 A3

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
28 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01390

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 116 842 A (ALZA CORP) 5 October 1983 (1983-10-05) page 2, line 2 - line 18 page 2, line 43 -page 3, line 48; figures 1-3 page 5, line 58 -page 6, line 12 figures 7,8; examples 1-5 claims ---	1,5-12, 14,15, 18-20
P,X	EP 1 027 888 A (PFIZER PROD INC) 16 August 2000 (2000-08-16) cited in the application paragraph [0008] figure 4; examples 3,6 --- -/--	1,6-12, 14-16, 18-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2002	06. 09. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01390

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 197 47 261 A (BAYER AG) 29 April 1999 (1999-04-29) page 2, line 38 - line 47 page 2, line 54 - line 60 examples 1-4 ---	
A	WO 99 01120 A (PFIZER PROD INC) 14 January 1999 (1999-01-14) page 2, line 17 - line 24 page 14, line 25 - line 30 example 7 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/01390

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,5,6,7-20(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 5, 6, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core comprises a drug-containing composition, another drug-containing composition, and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition being located between said drug-containing composition and said another drug-containing composition; and (b) said coating is water-permeable, water-insoluble, and has at least one delivery port for communication with said drug-containing composition and another delivery port for communication with said another drug-containing composition.

2. Claims: 2, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said drug-containing composition surrounding said water-swellable composition; (b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent; (c) said water-swellable composition comprises a swelling agent; and (d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

3. Claims: 3, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition comprising a plurality of granules; (b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent; (c) said water-swellable composition comprises a swelling agent; and (d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

4. Claims: 4, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core is substantially homogeneous throughout and comprises a mixture of a low-solubility drug, a drug-entraining agent, and a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

swelling agent; and (b) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 01/01390

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		TR 9903297 T2	21-07-2000
		ZA 9805708 A	10-01-2000

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PCT

(10) International Publication Number
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(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US02/20257

(22) International Filing Date: 26 June 2002 (26.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/895,463 29 June 2001 (29.06.2001) US

(71) Applicant: **BRIDGE PHARMA, INC.** [US/US]; 902 Contento Street, Sarasota, FL 34242 (US).

(72) Inventor: **ABERG, A., K., Gunnar**; 902 Contento Street, Sarasota, FL 34242 (US).

(74) Agents: **LEMACK, Kevin, S.** et al.; Nields & Lemack, 176 E. Main Street, Westboro, MA 01581 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

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WO 03/002059 A2

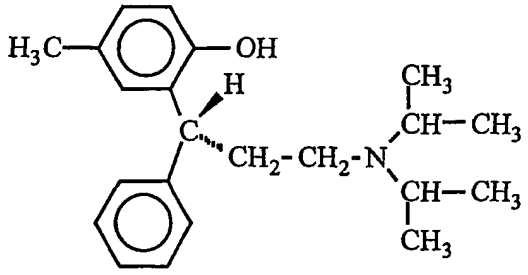
(54) Title: TOLTERODINE METABOLITES

(57) Abstract: Methods for treating smooth muscle hyperactivity, including urinary incontinence, while avoiding concomitant liability of adverse effects associated with tolterodine and the racemic version thereof are disclosed. The methods comprise administering a therapeutically effective amount of a mono-isopropyl metabolite or a parahydroxymethyl metabolite or a parahydroxymethyl mono-isopropyl metabolite of tolterodine or racemic versions thereof or a pharmaceutically acceptable salt of either metabolite. Pharmaceutical compositions in the form of tablets and transdermal devices comprising said compounds and acceptable carriers are also disclosed.

TOLTERODINE METABOLITES

FIELD OF THE INVENTION

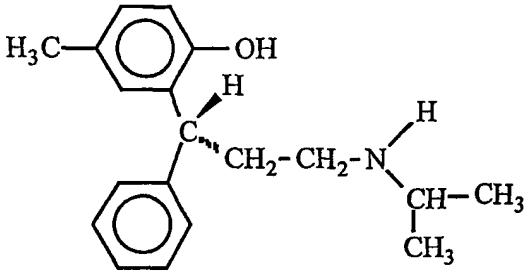
This invention relates to a compound named tolterodine and having the formula:



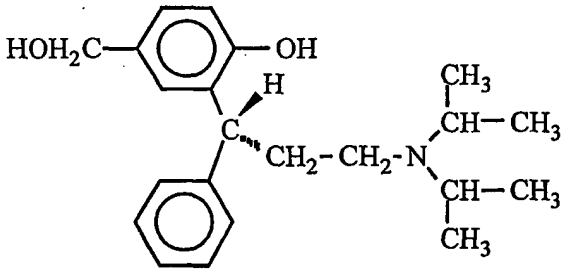
Tolterodine

The generic name TOLTERODINE (CAS-124937-51-5; INN) refers to the R-enantiomer of the drug. In this document, the racemate of this drug is referred to as RS-tolterodine (or RS-TOLT). The R-isomer (tolterodine) is here referred to as TOLT. The chemical name of tolterodine is R(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and the chemical name of RS-TOLT is RS-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine. Des-isopropyl-tolterodine is a metabolite of TOLT and is here referred to as DES-TOLT and the racemate thereof is referred to as RS-DES-TOLT. The chemical name for RS-DES-TOLT is RS-*N*-Isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and the chemical name of DES-TOLT is R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine. The compound 5-hydroxymethyl-tolterodine is a metabolite of TOLT and is here referred to as 5-HM and the racemate thereof is referred to as RS-5-HM. The chemical name for RS-5-HM and 5-HM are RS-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine and R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine, respectively. The compounds DES-TOLT can undergo hepatic oxidation of the paramethyl substituent, whereby the compound 5-HM-DES-TOLT is formed. The chemical name for 5-HM-DES-TOLT is R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine and this compound exists in the racemic form as well as. The 5-

hydroxylated compound 5-HM-DES-TOLT can undergo further oxidative metabolism and via the aldehyde, the 5-carboxylic acid metabolite is formed in the liver.



R(+)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine
DES-TOLT)



R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-
3-phenylpropylamine **5-HM)**

Specifically, the invention relates to processes for preparing certain metabolites of tolterodine and to methods for treating smooth muscle hyperactivity disorders using such metabolites. Smooth muscle hyperactivity disorders of the urinary bladder cause urinary disorders, including urinary incontinence and pollakiuria. Smooth muscle hyperactivity disorders of the gastrointestinal tract cause gastrointestinal disorders, including irritable bowel syndrome and diarrhea. Other smooth muscle hyperactivity disorders occur also in conjunction with asthma, urolithiasis, choledocholithiasis and cholelithiasis. The present invention describes the use of the anticholinergic compounds DES-TOLT, RS-DES-TOLT, 5-HM, RS-5-HM, 5-HM-DES-TOLT and RS-5-HM-DES-TOLT and pharmaceutical compositions containing at least one of said compounds, while avoiding side effects of the parent compounds, said parent compounds being TOLT and RS-TOLT.

BACKGROUND OF THE INVENTION.

TOLT has been shown to reduce urinary bladder hyperactivity in patients suffering from urinary incontinence and the drug exerts a spasmolytic effect on bladder smooth muscle by inhibiting the action of acetylcholine. TOLT has selectivity for muscarinic receptors over nicotinic receptors and as a result, no blocking effects are observed at skeletal neuromuscular junctions. Like TOLT and RS-TOLT, the active metabolites thereof exert antimuscarinic activities that account for their therapeutic activities.

The compounds DES-TOLT and 5-HM have been described as major metabolites of TOLT by several investigators, such as for example Nilvebrant et al. 1997 (Antimuscarinic potency and bladder selectivity of PNU-200577, a major metabolite of tolterodine. Pharmacol Toxicol 81:169-172), Brynne et al. 1997 (Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther 35: 287-295), Andersson et al. 1998 (Biotransformation of tolterodine, a new muscarinic antagonist, in mice, rats, and dogs. Drug Metab Dispos. 26:528-535) and Postlind et al 1998 (Tolterodine, a new muscarinic receptor antagonist, is metabolized by cytochromes P450 2D6 and 3A in human liver microsomes. Drug Metab Dispos 26: 289-293). It is not known to us if the compound 5-HM-DES-TOLT, or any of the further oxidized metabolites thereof have previously been synthesized. The medicinal use of the tolterodine metabolite 5-HM has been described by Johansson et al. in US Pat. 5,559,269 (1996) and US 5,686,464 (1997), both with foreign application priority date November 06, 1992 (SE 9203318). The medicinal use of RS- DES-TOLT or DES-TOLT or any of the paramethyl-oxidized metabolites thereof have to our knowledge not been described.

SUMMARY OF THE INVENTION

Methods for treating smooth muscle hyperactivity, including urinary incontinence, while avoiding concomitant liability of adverse effects associated with tolterodine and the racemic version thereof are disclosed. The methods comprise administering a therapeutically effective amount of a mono-isopropyl metabolite or a parahydroxymethyl metabolite or a parahydroxymethyl mono-isopropyl metabolite of tolterodine or racemic versions thereof or a pharmaceutically acceptable salt of either

metabolite. Pharmaceutical compositions in the form of tablets and transdermal devices comprising said compounds and acceptable carriers are also disclosed.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological studies of the metabolites of tolterodine and the corresponding racemates have now been performed in comparison with tolterodine. These studies demonstrate that DES-TOLT, as well as 5-HM-DES-TOLT and the further oxidized metabolites thereof have potent antimuscarinic activities.

It has been found that TOLT and RS-TOLT cause a prolongation of the QTc-interval of the EKG. Prolongation of the QTc interval is indicative of risk for a type of fatal cardiac arrhythmias that is called torsades des Pointes, as described for terfenadine by Woosley et al. 1993 (Mechanism of the cardiotoxic actions of terfenadine. JAMA 269: 1532-1536). The risk for cardiac arrhythmias with TOLT and RS-TOLT in patients may be particularly high when one of said compounds is combined with other drugs that utilize the same metabolic enzyme as said compounds or when said compound is given to patients who are "poor metabolizers" as described by Stahl et al., 1995. However, it was surprisingly found that DES-TOLT and 5-HM as well as RS-DES-TOLT and RS-5-HM did not cause a prolongation of the QTc interval of the EKG. It is therefore concluded that DES-TOLT, 5-HM, RS-DES-TOLT, RS-5-HM, 5-HM-DES-TOLT and RS-5-HM-DES-TOLT offer anticholinergic treatment for smooth muscle hyperactivity disorders, while being devoid of electrophysiological cardiac side effects that reside in the parent compounds, said parent compounds being TOLT and RS-TOLT.

Synthesis of DES-TOLT and RS-DES-TOLT.

Synthetic methods of making of DES-TOLT and RS-DES-TOLT were described by Jönsson et al. in European Patent Application 89850017.8 and are hereby incorporated by reference.

Synthesis of 5-HM and RS-5-HM.

Synthetic methods of making of 5-HM and RS-5-HM were described by Johansson et al. in US Pat 5,559,269 and are hereby incorporated by reference.

Synthesis of 5-HM-DES-TOLT.

The synthesis of 5-HM-DES-TOLT was performed by using a combination of the methods for making 5-HM and DES-TOLT as described in the above mentioned references by Jönsson et al. (European Patent Application 89850017.8) and Johansson et al. (US Pat 5,559,269), and as known to those skilled in the art of synthetic chemistry.

Therapeutic doses.

The magnitude of a prophylactic or therapeutic dose of a compound of the present invention in the acute or chronic management of disease will vary with the severity and nature of the condition to be treated and the route of administration. The dose and the frequency of the dosing will also vary according to the age, body weight and response of the individual patient. In general, the total daily oral dose range for DES-TOLT or 5-HM or 5-HM-DES-TOLT for the conditions described herein is from about 0.5 mg to about 100 mg in single or divided doses, preferably in divided doses or in single dose using a controlled release oral formulation. In managing the patient, the therapy should be initiated at a low dose, perhaps at 1 or 2 mg to about 10 mg orally, and may be increased up to about 50 mg depending on the patient's global response. It is further recommended that patients over 65 years and those with impaired renal or hepatic function initially receive low doses and that they be titrated based on individual response(s) and plasma drug level(s). It may be necessary to use dosages outside these ranges in some cases, particularly if the drug is administered by routes other than the oral route, as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "a therapeutically effective amount" and "an amount sufficient to treat the disorder but insufficient to cause adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the compounds of the present invention. For example, oral, sublingual, parental (i.e. subcutaneous, intramuscular, intravenous, etc.), transdermal, vaginal, aerosol and like forms of administration may be employed. Additionally, the drug may be administered directly into the bladder, as described for oxybutynin by Massad et al.

[J. Urol. 148, 595-597 (1992)] or rectally directly into the gastrointestinal canal as known in the art. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, suppositories, microencapsulated systems, slow-release and controlled release systems, transdermal delivery systems, and the like.

The pharmaceutical compositions of the present invention comprise of DES-TOLT, 5-HM, RS-DES-TOLT, RS-5-HM, 5-HM-DES-TOLT or RS-5-HM-DES-TOLT as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pathothenic, phosphoric, p-toluenesulfonic, succinic, sulfuric, tartaric, and the like. The hydrochloride is particularly preferred.

The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the more advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and by means of various delivery devices as known by those skilled in the art. Controlled release means transdermal delivery and delivery devices include patches, ionophoretic systems and the like, as well as slow release or controlled release oral formulations.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete unit dosage forms such as capsules,

cachets, suppositories, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation, just as is known for the racemic mixture. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. All of the foregoing techniques are well know to persons of skill in the pharmaceutical art. Each tablet may contain from about 0.5 mg to about 25 mg of the active ingredient.

Example 1

ORAL UNIT DOSAGE FORMULATION

Tablets:

Ingredients	per tablet	per batch of 10,000 tablets
DES-TOLT	5 mg	50 g
Microcrystalline cellulose	30 mg	300 g
Lactose	70 mg	700 g

Calcium stearate	2 mg	20 g
FD&C Blue #1 Lake	0.03 mg	300 mg

The DES-TOLT is blended with lactose and cellulose until a uniform blend is formed. The lake is added and further blended. Finally, the calcium stearate is blended in, and the resulting mixture is compressed into tablets using a 9/32 inch (7 mm) shallow concave punch. Tablets of other strengths may be prepared by altering the ration of active ingredient to the excipients or to the final weight of the tablet.

Pharmacological studies of tolterodine and metabolites thereof.

1. Ligand binding studies: Affinity for muscarinic receptors.

The experiments are carried out on membranes prepared from SF9 cells infected with baculovirus to express human recombinant muscarinic receptor subtypes. After incubation with the test article and the proper radioligand (^{3}H pirenzepine) and washing, bound radioactivity is determined with a liquid scintillation counter, using a commercial scintillation cocktail. The specific radioligand binding to a muscarinic receptor is defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabelled ligand. IC_{50} values (concentrations required to inhibit 50% of specific binding) are determined by non-linear regression analysis of the competition curves. These parameters are obtained by curve fitting using Sigmaplot™ software.

2. Functional Characterization of Antimuscarinic Activities on Smooth Muscle Strips.

Experiments are performed using methods similar to those described by Kachur et al, 1988 (R and S enantiomers of oxybutynin: Pharmacological effects in guinea pig bladder and intestine. J Pharmacol Exp Ther 247: 867-872) and Noronha-Blob and Kachur, 1991 (Enantiomers of Oxybutynin: In vitro pharmacological characterization at M1, M2 and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs. J Pharmacol Exp Ther 256: 562-567). Strips of tissue (approximately 10 mm long and 1.5 mm wide) are removed from the body of the urinary bladder of male guinea pigs weighing 400-600 g. Preparations of the longitudinal smooth muscle of the colon of guinea pigs are prepared as known from the prior art (Acta Physiol

Scand 64: 15-27, 1965). This method is also modified and used for the testing of the drugs on smooth muscle from the kidney, the gall bladder and the airways. The tissues are suspended in an oxygenated buffer of the following composition, in mM: NaCl 133; KCl 4.7; $CaCl_2$ 2.5; $MgSO_4$ 0.6; NaH_2PO_4 1.3; $NaHCO_3$ 16.3; and glucose 7.7, or of a similar composition. The smooth muscle strips are maintained at or about 37.5 C. In each experiment up to seven strips are removed from a single animal, suspended in tissue chambers and allowed to equilibrate with the bathing solution for one hour before proceeding with the experiment. Contractions are recorded with transducers on a polygraph.

The present series of experiments focuses on the anticholinergic actions of DES-TOLT, and RS-DES-TOLT and their metabolites. In these experiments, in order to assess the viability of each tissue and to serve as a frame of reference, contractions of each strip of tissue are recorded initially in response to exposure to tissue medium in which NaCl is replaced by KCl to yield a concentration of 137.7 mM KCl in the medium. This is followed by return to the standard medium, and then by exposures to progressively in creasing concentrations of carbachol, with separate exposures to each concentration only until the peak response has been recorded. Then, leaving one strip untreated and/or one strip exposed to the test solution to serve as control tissue(s), the remaining strips each are exposed for one hour to one concentration of an antagonist. Finally, the responses to increasing concentrations of carbachol are recorded a second time.

4. Cardiac side effects.

Male guinea pigs (450-600 g) are anesthetized with freshly prepared dialurethane sodium. The jugular vein is catheterized for iv administration of test drugs and the trachea is exposed and cannulated. Subdermal electrodes are positioned for Lead II electrocardiogram recording, monitored on a Grass Polygraph recorder, set at a paper speed of 50 mm/sec. The animals are allowed to stabilize for 30 minute after completion of surgery, and three baseline EKG recordings are then made at 10-minute intervals. The animals are then given a dose of the test compound or vehicle as an intravenous infusion over 30 min. EKG recordings are used to determine QT intervals and heart rates. To compensate for variations in heart rates, QTc intervals are calculated from QT- and RR-intervals as known to those skilled in the art. Prolongation of QTc is indicative of a prolonged action potential, caused by an inhibition of

the delayed rectifier potassium channel. Prolongation of QTc is the known cause of Torsades de Pointes ventricular fibrillation by drugs such as terfenadine, astemizole and terodiline (now withdrawn from the market).

Other methods for studying cardiac side effects are also used.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents include numerous pharmaceutically acceptable salt forms e.g. sulfate, fumarate, hydrobromide, hydrochloride, dihydrochloride, methanesulphonate, hydroxynaphthoate, or where appropriate one or other of the hydrate forms thereof, see Merck Index 11th edition (1989) items 9089, 209, 3927, 4628, 8223, 5053, 5836, 8142, 2347, 7765, 1840, 9720, 7461, 1317,4159, and 963 and references cited therein and Am. Rev. Resp. Dis. 1988, 137: (4;2/2) 32. Such equivalents also include the co-administration of at least one compound of the present invention with any other drug that is used to combat diseases in mammals, mentioned in this document. Such equivalents also include the co-administration of at least one compound of the present invention with any other compound or drug that may be used in combination with medication for urinary incontinence or other forms of smooth muscle hyperactivity. Those skilled in the art of pharmacology will realize that the pharmacologically active compounds of the present invention may also be combined with in different concentrations with cholinergically inert compounds, such as S-tolterodine or a metabolite thereof. Those skilled in the art of medicine will also realize that higher or lower doses than those indicated here may be preferred and the doses may be given more or less frequently than suggested here.

Those skilled in the art of drug metabolism will realize that 5-hydroxymethyl metabolites of TOLT or RS-TOLT can and will undergo further oxidative metabolism as described in this document. All such further oxidized metabolites, including aldehydes and the carboxylic acids are included in the present invention.

Those skilled in the art of drug metabolism will realize that DES-TOLT can and will undergo additional dealkylation, whereby a di-des-isopropyl metabolite is formed. This pharmacologically active antimuscarinic metabolite and the paramethyl-oxidized forms thereof are included in the present invention.

Those skilled in the art, will realize that smooth muscle hyperactivity disorders comprise such disorders of the urinary bladder, the gastrointestinal tract, the urinary ducts ("kidney stone pain") the gall fluid ducts ("gall stone pains") and the smooth muscles of the airways.

Those skilled in the art of pharmacology, will realize that the compounds of the invention, having certain pharmacological properties such as antihistaminic activity and anticholinergic activity may be useful for other indications than those listed here. Such indications include but are not limited to cardiovascular indications such as heart failure, myocardial infarction, stroke, and allergic disorders and are equivalents to the specific embodiments of the invention described herein.

Those skilled in the art know that transdermal delivery systems often contain one or more permeation enhancer(s) that dramatically may improve the transdermal absorption of a drug of this invention.

All equivalents are intended to be included in this present invention.

What is claimed is:

1. A method for treating cholinergically induced smooth muscle hyperactivity disorders, comprising the administration to a mammal in need of such treatment a therapeutically effective amount of a compound selected from the group consisting of R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine, RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein said compound is R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

3. The method of claim 1, wherein said compound is R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine, or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein said compound is RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

5. The method of claim 1, wherein said compound is R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

6. A method for treating cholinergically induced smooth muscle hyperactivity disorders, comprising the administration to a mammal in need of such treatment a therapeutically effective amount of a compound selected from the group consisting of R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine, R(+)-*N*-Isopropyl-3-

(2-hydroxy-5-(hydroxymethyl) phenyl)-3-phenylpropylamine, RS-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl) phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof, while reducing or eliminating concomitant liability of adverse side effects associated with the corresponding parent compounds, those parent compounds being RS-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and R(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine.

7. The method of claim 6, wherein said compound is R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

8. The method of claim 6, wherein said compound is R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

9. The method of claim 6, wherein said compound RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

10 The method of claim 6, wherein said compound is R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

11. The method of claim 6, wherein said compound is RS-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

12. The method of claim 6, wherein said compound is R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

13. The method of claim 6, wherein said disorders are selected from the group consisting of urinary incontinence and pollakiuria.

14. The method of claim 6, wherein said compound or a pharmaceutically acceptable salt thereof is administered in a dose from about 0.5 mg to about 100 mg per day.

15. The method of claim 6, wherein said compound or a pharmaceutically acceptable salt thereof is administered by inhalation or by parenteral, transdermal, rectal, sublingual or oral administration.

16. The method of claim 6, wherein said compound or a pharmaceutically acceptable salt thereof is administered orally in the pharmaceutical unit dosage form of a tablet or capsule.

17. The pharmaceutical unit dosage form of claim 16. wherein said tablet or capsule is formulated for controlled release upon administration.

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(54) Title: TOLTERODINE METABOLITES

(57) Abstract: Methods for treating smooth muscle hyperactivity, including urinary incontinence, while avoiding concomitant liability of adverse effects associated with tolterodine and the racemic version thereof are disclosed. The methods comprise administering a therapeutically effective amount of a mono-isopropyl metabolite or a parahydroxymethyl metabolite or a parahydroxymethyl mono-isopropyl metabolite of tolterodine or racemic versions thereof or a pharmaceutically acceptable salt of either metabolite. Pharmaceutical compositions in the form of tablets and transdermal devices comprising said compounds and acceptable carriers are also disclosed.

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B. FIELDS SEARCHED

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U.S. : 514/649, 648, 647

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,559,269 A (JOHANSSON et al.) 24 September 1996, see abstract, column 1, lines 12-59, column 2, lines 1-20, column 5, lines 55-65, and column 5, lines 50-54.	6, 11-16
X — Y	US 5,686,464 A (JOHANSSON et al.) 11 November 1977, see abstract and columns 1-2 and column 6, column 5, lines 55-65, column 1, lines 57-59.	6, 11-16 ——— 1,4-6, 9-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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INTERNATIONAL SEARCH REPORT

Continuation of B. FIELDS SEARCHED Item 3:
WEST search terms include: tolterod$7, des-tolt, 5-HM, cholinerg$10, (controlled or extended or timed) near release, urin$8 near4 (incontinence), pollakiuria

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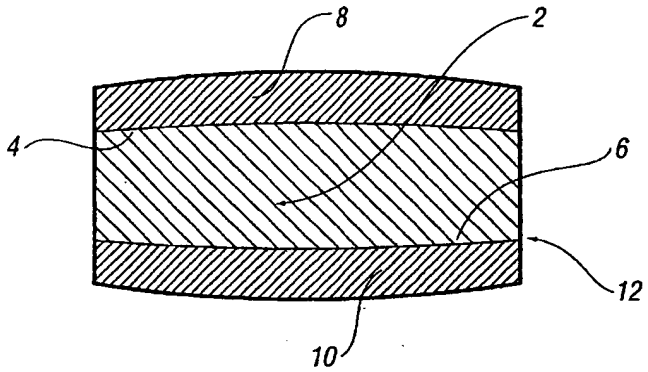
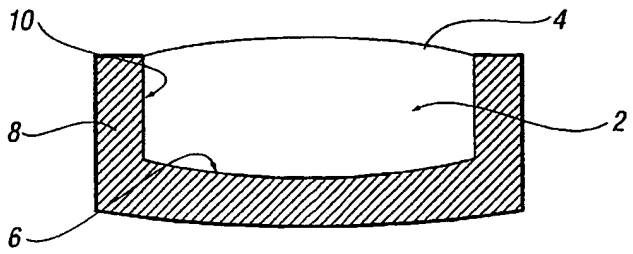
[Continued on next page]

(54) Title: ZERO ORDER CONTROLLED DRUG DELIVERY SYSTEM





(57) Abstract: A controlled release dosage form comprising: (i) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable matrix forming polymers, (ii) a substantially insoluble casing extended over the tablet core covering between 25 to 99% of the surface area of the tablet core, like for example covering only the major surfaces like in Figure 1 or on major surface and the sidewells like in Figure 2, the casing resulting from electrostatic deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film such that the said electrostatic coated tablet releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations $y = k*t^n$ in which y is the fraction of active ingredient released, k is the kinetic constant, t is time, n is the release exponent and n is the range 0.70 to 1.0 i.e. an approximately zero order release profile.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ZERO ORDER CONTROLLED DRUG DELIVERY SYSTEM

The present invention relates to a controlled drug delivery system that releases an active material at a constant rate (i.e. zero order) into a biological fluid, in particular, the fluid of the gastrointestinal tract.

Tablets are often the preferred means of administering medicine to patients. A conventional immediate release tablet releases the drug active in the body rapidly reaching a maximum concentration then decaying expeditiously until the next administration. This method often leads to peaks and troughs of drug concentration in the blood and requires frequent administration of tablets. Consequently, this could lead to either exacerbated harmful side effects at high concentrations or diminished therapeutic effects at low concentrations. These effects can become acute with actives of relatively short biological half life. To counter these, controlled release dosage forms which release actives at a constant rate over a defined period of time (zero order release) have been frequently employed.

Many controlled release tablets are prepared either using a matrix system through the formation of polymer networks, or using a membrane system such as film coating. The dissolution kinetics over the time when the majority of drug is released can be represented by the following mathematical equation:-

$$y = k^{*}t^{n}$$

Where y is the fraction released

k is the kinetic constant

t is time

n is the release exponent

The release exponent n is characteristic of release mode, if n = 0.5, Fickian diffusion dominates, i.e. the structural relaxation of polymer network is rapid and the rate limiting step is the self-diffusion of drug active. This is termed first order release. If n = 1, the release of active is at a constant rate, i.e. zero order release. The rate-limiting step is the rate of polymer relaxation.

There are numerous factors affecting the release rate of the actives, for example the molecular weight, glass transition temperature, the swelling volume, gelation potential of the network forming polymer etc. Hence, in practice, the release rate can only be controlled to a limited extent by polymer matrix alone with the release exponent n at a value close to 0.5.

US4792448 discloses a device for the controlled release of one or more active substances into a fluid medium at a substantially constant rate (i.e. zero oder) which comprises said substance homogenously dispersed in the shape of a cylindrical tablet or bolus by means of an all-covering, essentially impermeable wall or coating except for one or more strips of removed wall or coating from the side of said device.

EP0259113 claims a device for the controlled release of one or more active substances into a fluid medium which comprises said substance homogenously disposed, with or without one or more inert diluents, and

contained substantially in the shape of a truncated cone by means of an impermeable wall or coating on the base and side of said truncated cone.

US5004614 discloses controlled release devices having a core including an active agent and an outer coating which is substantially impermeable to the entrance of an environmental fluid and substantially impermeable to the release of the active agent during a dispensing period allow the controlled release of the active agent through an orifice in the outer coating. The coating thickness, the position, number and the sizes of the orifices are the key variables influencing the release profile.

US4839177 discloses a system for the controlled-rate release of active substances, consisting of: (a) a deposit core comprising the active substance and having defined geometric form; (b) a support-platform applied to said deposit core. Said deposit core contains, mixed with the active substance, a polymeric material having a high degree of swelling on contact with water or aqueous liquids, a gellable polymeric material, said polymeric materials being replaceable by a single polymeric material having both swelling and gelling properties. Said support-platform consists of a polymeric material insoluble in aqueous liquids and partially coating said deposit-core. However, these tablets have the drawback that the rigid support can result in cracking and sometimes flaking before the active substance has been completely released. This patent was superseded by US5422123, which discloses tablets with zero order controlled rate of release of the active substances, consisting of a core of defined geometrical form containing the active substance, polymer

substances which swell on contact with aqueous liquids and polymer substances with gelling properties, and a support applied to said core or partly cover its surface, the support consisting of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids, plasticizing substances, and possible substances with an adjuvant function.

US6033685 provides a tablet for controlled release of an active agent consisting of (a) a matrix layer comprising an active agent embedded in non-swelling, non-gelling hydrophobic matrix; (b) a first barrier layer laminated to a single face of the matrix layer; and (c) an optional second barrier layer laminated to the opposite face of the matrix layer and oppositely disposed to the first barrier layer.

US6083533 discloses a layered tablet for controlled release of active substances in a liquid medium comprising at least one active substance containing, layered matrix with contact surfaces to the liquid medium which are at least partially provided with a cover layer delaying or preventing the active substance release, is characterised by the fact that the cover layer is at least one additional layer lying with thickness gradients on contact surfaces of the layered, prefabricated matrix.

US6264985 discloses a compression-coated tablet with an erodible core and a substantially erosion resistant shell. The shell has at least one opening and one end of the core extends as far as the opening.

WO 921445 discloses that electrostatic deposition may be used to apply a coating of controlled thickness and may be employed for a medicinal product containing a drug that is to be instantaneously released when administered or that is to be the subject of controlled or modulated release, such control of modulation being achieved from the nature of the coating and/or from the nature of core. Where the desired form of release is to be achieved by characteristics of the coating, it may be preferred to leave one portion of the product uncoated or coated with different material. In the case of a tablet having faces at opposite ends connected by a cylinder side wall, the portion that is uncoated or coated with different material may be one of the faces of the tablet, a small portion of one of the faces or a side wall of the tablets. However, there is no disclosure as to whether or how a zero order release profile can be achieved.

There is a need for an effective pharmaceutical dosage form having controlled release of an active ingredient at substantially constant rate.

In accordance with the present invention there is provided a controlled release dosage form comprising:

(i) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable matrix forming polymers, the tablet core releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k^*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.30 to 0.65

(ii) a substantially insoluble casing extended over the tablet core covering between 25 to 99% of the surface area of the tablet core, the casing resulting from electrostatic deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film such that the said electrostatic coated tablet releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.7 to 1.0 i.e. an approximately zero order release profile.

It has been surprisingly found that a pharmaceutical dosage form having controlled release of an active ingredient at a substantially constant rate, i.e. zero order release rate, can be obtained by electrostatic application of a thin film on the selected surface of a tablet. The release profile does not require the application of a thick film nor rely on the controlled thickness so long as a

complete and uniform coating within the defined area is obtained. Furthermore, there are no needs for a special designed geometric shape, the mechanical removal of a portion of film coating at a defined position with a defined surface area or the presence of specific matrix forming polymers.

The invention provides a simple and effective means of producing a pharmaceutical dosage form having an approximately zero order release profile for a pharmaceutical active agent. A drug reservoir, in the form of a tablet core and having an approximately first order release profile, which may be made by conventional techniques, is provided with an insoluble casing covering 25 to 99% of the surface area of the tablet. In this manner, the area of the tablet exposed to the body fluids, e.g. gastric juices when the dosage form is administered, is reduced thereby decreasing the hydration rate of the tablet core and the drug release rate such that the resulting tablet has an approximately zero order release profile.

The electrostatic coated tablet preferably has the release profile in which n = 0.7 to 1.0 over 0 to at least 50% by weight release of active ingredient, more preferably from 0 to at least 60% by weight release of active ingredient, most preferably from 0 to greater than 70% release of active ingredient. In preferred embodiments the release profile requires at least four hours, more preferably at least five hours to achieve 70% by weight release of active ingredient.

The release profile of a pharmaceutical active is determined by standard US Pharmacopoeia method using a paddle stirring element (Apparatus II), Vankel™ 7000 dissolution apparatus (Apparatus II). The assembly consists of the following: a covered vessel made of glass or other inert, transparent material; a motor; a paddle formed from a blade and a shaft. The shaft is positioned so that its axis is not more than 2mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical centre line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The distance of 25± 2mm between the paddle and the inside bottom of the vessel is maintained during the test.

The vessel is partially immersed in a suitable waterbath which maintains the temperature inside the vessel at 37±0.5°C during the test and keeping the bath fluid in constant, smooth motion. The vessel is cylindrical, with a hemispherical bottom. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. Demineralised water is added to the vessel. The dosage unit (one single tablet) is allowed to sink to the bottom of the vessel before the rotation of the blade is started. The stirring rate is set at 50 rpm. The released active ingredient with time is measured by any suitable means e.g. u.v. analysis, HPLC etc. and expressed as percentage release (w/w) of the total weight of active ingredient.

The casing extending over the tablet core results from the electrostatic deposition of a powder comprising fusible particles. This technique allows the

formation of a thin, continuous casing over the tablet core. Although the release profile does not depend on the coating thickness, it is of importance that a continuous and complete coverage is applied in order to minimise pore formation. Typically this requires the deposition of several layers of powdered material (the powders have a mean diameter of 10 μm) to give a coating thickness of at least 20 μm after fusion. Generally the maximum coating thickness of the tablets is not more than 75μm. Coating thickness in the range 20 to 50μm is preferred. Generally the coating results in a weight gain of less than 5%, often less than 4% and frequently less than 3% by weight of the tablet core. In general, the casing will cover from 25 to 99% of the surface area of the tablet core, generally 50 to 99% , preferably 65 to 95% of the surface area of the tablet core, leaving the reminder exposed.

The shape of the tablet core is not critical since the electrostatic deposition of powder can readily be achieved over a variety of shaped bodies. The tablet core is conveniently formed by conventional tableting techniques e.g. compression of powder and/or granules, although other moulding techniques may be employed. A convenient tablet core has a circular cross-section and two major opposing surfaces which may be, for example, planar, planar with a bevelled edge, concave, convex etc. The insoluble casing may conveniently extend over one of the major surfaces and the side wall leaving the other major surface exposed.

The tablet core comprises at least one adjuvant and a pharmaceutically active ingredient. Generally the adjuvant will comprise a binder. Suitable binders are well known and include acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxypropylmethylcellulose,

maltodextrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

The tablet core preferably comprises a release rate controlling additive. For example, the drug may be held within a hydrophobic polymer matrix so that it is gradually leached out of the matrix upon contact with body fluids. Alternatively, the drug may be held within a hydrophilic matrix which gradually dissolves or swells in the presence of body fluid.

Suitable release rate controlling polymers include polymethacrylates, ethylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol, polyethylene oxide, carrageenan, cellulose acetate, glyceryl monostearate, zein etc.

The tablet core may comprise other conventional tableting ingredients, including diluents, disintegrants, lubricants, wetting agents, glidants, surfactants, release aids, colourants, gas producers, etc.

Suitable diluents include lactose, cellulose, dicalcium phosphate, sucrose, dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate, dextrates, dextrin, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose.

Suitable lubricants include magnesium stearate and sodium stearyl fumarate.

Suitable glidants include colloidal silica and talc.

Suitable wetting agents include sodium lauryl sulphate and docusate sodium.

Suitable gas producers include sodium bicarbonate and citric acid.

The pharmaceutically active ingredient may be selected from a wide range of substances which may be administered orally. Suitable ingredients include acid-peptic and motility influencing agents, laxatives antidiarrhoeials, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics, fibrinolytics, haemostatics, hypolipidaemic agents, anti-anaemia and neurotropenia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents, hyperglycaemic agents, diagnostic agents, antibiotics, anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytic, decongestants, anti-glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.

The electrostatic application of powder material to a substrate is known. Methods have already been developed in the fields of electrophotography and electrography and examples of suitable methods are described, for example, in Electrophotography and Development Physics, Revised Second Edition, by L.B. Schein, published by Laplacian Press, Morgan Hill California. The electrostatic application of powder material to a solid dosage form is known and techniques are disclosed, for example, in GB9929946.3, WO92/14451, WO96/35413, WO96/35516 and PCT/GB01/00425, and British Patent Application No. 9929946.3.

For example, WO92/14451 describes a process in which the cores of pharmaceutical tablets are conveyed on an earthed conveyor belt and electrostatically charged powder is deposited on the cores to form a powder coating on the surface of the cores.

A powder material for electrostatic application to a substrate should have certain properties. For example, the electrical properties of the powder material should be such as to make the powder material suitable for electrostatic application, and other properties of the powder material should be such that the material can be secured to the substrate once electrostatic application has taken place.

WO96/35413 describes a powder material which is especially suitable for electrostatic application to a poorly-conducting (non-metal) substrate such as a pharmaceutical tablet. Because it may be difficult to find a single component capable of providing the powder material with all the desired properties, the powder material comprises a number of different components which together are capable of providing the material with all or at least as many as possible of the desired properties, the components being co-processed to form "composite particles". For example, the powder material may comprise composite particles including one component which is fusible to form a continuous film on the surface of the substrate, and another component which has desirable electrical properties.

A potential disadvantage of the above mentioned powder materials, however, is that they are not readily adaptable to changes in formulation. The formulation of a powder material may be changed for a number of different reasons. For example, if the material is a coloured material, there may be a change in the colourant, or if the material is an active material, for example a physiologically active material there may be a change in the type of active

material, or in the concentration of that active material. Because all the components of the powder material are intimately mixed, any change in the components will alter the material's electrical properties and hence its performance in electrostatic application. Whenever there is a change in formulation, it may therefore be necessary, for optimum performance, to adjust the content of the component(s) that make the material suitable for electrostatic application, or perhaps even to use a different component.

PCT/GB01/00425 discloses a method of electrostatically applying a powder material to a substrate, wherein at least some of the particles of the material comprise a core and a shell surrounding the core, the core and the shell having different physical and/or chemical properties.

Where the particles of the powder material comprise a core and a shell surrounding the core, it is possible to place those components which are likely to be altered, for example colourant in the core, and to provide a more universal shell composition which is suitable for use with various core compositions, so that alterations may be made to the components that are in the core without substantially affecting the overall suitability of the powder material; thus, the shell ensures that the change in composition of the core does not affect the performance of the material in electrostatic application. Accordingly, alterations to one component of the powder material may be made with minimum alteration in the amounts of other components.

Generally, the powder material includes a component which is fusible, and that component may be present in the shell or in the core or in both the shell and the core. Advantageously, the fusible component is treatable to form a continuous film coating. Examples of suitable components are as follows: polyacrylates, for example polymethacrylates; polyesters; polyurethanes; polyamides, for example nylons; polyureas; polysulphones; polyethers;

polystyrene; polyvinylpyrrolidone; biodegradable polymers, for example polycaprolactones, polyanhydrides, polylactides, polyglycolides, polyhydroxybutyrates and polyhydroxyvalerates; sugars, for example lactitol, sorbitol xylitol, galactitol, maltitol, fructose, xylose and galactose; hydrophobic waxes and oils, for example vegetable oils and hydrogenated vegetable oils (saturated and unsaturated fatty acids) e.g. hydrogenated castor oil, carnauba wax, and beeswax; hydrophilic waxes; polyalkenes and polyalkene oxides; polyethylene glycol. Clearly there may be other suitable materials, and the above are given merely as examples. One or more fusible materials may be present. Preferred fusible materials generally function as a binder for other components in the powder.

In general the powder material should contain at least 30%, usually at least 35%, advantageously at least 80%, by weight of material that is fusible, and, for example, fusible material may constitute up to 95%, e.g. up to 85%, by weight of the powder. Wax, if present, is usually present in an amount of no more than 6%, especially no more than 3% by weight, and especially in an amount of at least 1% by weight, for example 1 to 6%, especially to 1 to 3%, by weight of the powder material.

Of the materials mentioned above, polymer binders (also referred to as resins) should especially be mentioned. Examples include polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate and methacrylate polymers, for example an ammonio-methacrylate copolymer, for example those sold under the name Eudragit.

Often resin will be present with a wax as an optional further fusible component in the core; the presence of a wax may, for example, be useful where fusing is to take place by a contact system for example using a heated roller, or where

it is desired to provide a glossy appearance in the fused film. The fusible component may comprise a polymer which is cured during the treatment, for example by irradiation with energy in the gamma, ultra violet or radio frequency bands. For example, the core may comprise thermosetting material which is liquid at room temperature and which is hardened after application to the substrate.

Preferably, the powder material includes a material having a charge-control function. That functionality may be incorporated into a polymer structure, as in the case of Eudragit resin mentioned above, and/or, for a faster rate of charging, may be provided by a separate charge-control additive. Material having a charge-control function may be present in the shell or in the core or in both shell and core. Examples of suitable charge-control agents are as follows: metal salicylates, for example zinc salicylate, magnesium salicylate and calcium salicylate; quaternary ammonium salts; benzalkonium chloride; benzethonium chloride; trimethyl tetradecyl ammonium bromide (cetrimide); and cyclodextrins and their adducts. One or more charge-control agents may be used. Charge-control agent may be present, for example, in an amount of up to 10% by weight, especially at least 1% by weight, for example from 1 to 2% by weight, based on the total weight of the powder material.

The powder material may also include a flow aid. The flow aid reduces the cohesive and/or other forces between the particles of the material to improve the flowability of the powder. Suitable flow aids (which are also known as "surface additives") are, for example, as follows: colloidal silica; metal oxides, e.g. fumed titanium dioxide, zinc oxide or alumina; metal stearates, e.g. zinc, magnesium or calcium stearate; talc; functional and non-functional waxes, and polymer beads, e.g. poly-methyl methacrylate beads, fluoropolymer beads and the like. Such materials may also enhance tribocharging. A mixture of flow aids, for example silica and titanium dioxide, should especially be mentioned. The powder material may contain, for example, 0 to 3% by

weight, advantageously at least 0.1%, e.g. 0.2 to 2.5%, of surface additive flow aid.

Often the powder material includes a colourant and/or an opacifier. When the powder comprises a core and shell such components are preferably present in the core. Examples of suitable colourants and opacifiers are as follows: metal oxides, e.g. titanium dioxide, iron oxides; aluminium lakes, for example, indigo carmine, sunset yellow and tartrazine; approved food dyes; natural pigments. A mixture of such materials may be used if desired. Opacifier preferably constitutes no more than 50%, especially no more than 40%, more especially no more than 30%, for example no more than 10% by weight of the powder material, and may be used, for example, in an amount of at least 5% by weight of the powder. Titanium dioxide is an especially useful opacifier, providing white colour and having good hiding power and tinctorial strength. Colourant present with opacifier may, for example, constitute no more than 10%, preferably from 1 to 5%, by weight of the powder. If there is no opacifier, the colourant may be, for example, 1 to 15%, e.g. 2 to 15%, especially 2 to 10%, by weight of the powder. To achieve optimum colour, amounts of up to 40% by weight of colourant may be needed in some cases, for example if inorganic pigments, e.g. iron oxides, are used. However, the powder material usually contains, for example, from 0 to 25% by weight in total of colourant and/or opacifier.

The powder material may also include a dispersing agent, for example a lecithin. The dispersing agent is preferably present with the colourant/opacifier (that is, preferably in the core), serving to improve the dispersion of the colourant and opacifier, more especially when titanium dioxide is used. The dispersing component is preferably a surfactant which may be anionic, cationic or non-ionic, but may be another compound which would not usually be referred to as a "surfactant" but has a similar effect. The dispersing component may be a co-solvent. The dispersing component may

be one or more of, for example, sodium lauryl sulphate, docusate sodium, Tweens (sorbitan fatty acid esters), polyoxamers and cetostearyl alcohol. Preferably, the powder material includes at least 0.5%, e.g. at least 1%, for example from 2% to 5%, by weight of dispersing component, based on the weight of the powder material. Most often it is about 10% by weight of the colourant and opacifier content.

The powder material may also include a plasticiser, if necessary, to provide appropriate rheological properties. A plasticiser may be present in the core and/or the shell, but usually, if present, a plasticiser is included with resin used for the core to provide appropriate rheological properties, for example for preparation of the core by extrusion in a melt extruder. Examples of suitable plasticisers include polyethylene glycols, triethyl citrate, acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

A plasticiser may be used with a resin in an amount, for example, of up to 50% by weight of the total of that resin and plasticiser, the amount depending inter alia on the particular plasticisers used. The powder may contain an amount of up to 50% by weight of plasticiser.

The powder coating material may further include one or more taste modifiers, for example aspartame, acesulfame K, cyclamates, saccharin, sugars and sugar alcohols or flavourings. Preferably there is no more than 5%, more preferably no more than 1%, of flavouring based on the weight of the powder material, but larger or smaller amounts may be appropriate, depending on the particular taste modifier used.

If desired the powder material may further include a filler or diluent. Suitable fillers and diluents are essentially inert and low cost materials with generally little effect on the colour or other properties of the powder. Examples are as follows: alginic acid; bentonite; calcium carbonate; kaolin; talc; magnesium aluminium silicate; and magnesium carbonate.

The particle size of the powder material has an important effect on the behaviour of the material in electrostatic application. Although materials having a small particle size are recognised as having disadvantages such as being more difficult to produce and to handle by virtue of the material's cohesiveness, such material has special benefits for electrostatic application and the benefits may more than counter the disadvantages. For example, the high surface to mass ratio provided by a small particle increase the electrostatic forces on the particle in comparison to the inertial forces. Increasing the force on a particle has the benefit of increasing the force that causes it to move into contact with the substrate, whilst a reduction in the inertia reduces the force needed to accelerate a particle and reduces the likelihood of a particle arriving at the substrate bouncing back off the substrate. However, very small particle sizes may not be achievable where the coating material comprises a high proportion of a particular ingredient, for example a high proportion of active material.

Preferably, at least 50% by volume of the particles of the material have a particle size no more than 100μm. Advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 5μm to 40μm. More advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 10 to 25μm.

Powder having a narrow range of particle size should especially be mentioned. Particle size distribution may be quoted, for example, in terms of

the Geometric Standard Deviation ("GSD") ratios d_{90}/d_{50} or d_{50}/d_{10} where d_{90} denotes the particle size at which 90% by volume of the particles are below this figure (and 10% are above), d_{10} represents the particle size at which 10% by volume of the particles are below this figure (and 90% are above) , and d_{50} represents the mean particle size. Advantageously, the mean (d_{50}) is in the range of from 5 to 40μm, for example, from 10 to 25μm. Preferably, d_{90}/d_{50} is no more than 1.5, especially no more than 1.35, more especially no more than 1.32, for example in the range of from 1.2 to 1.5, especially 1.25 to 1.35, more especially 1.27 to 1.32, the particle sizes being measured, for example, by Coulter Counter. Thus, for example, the powder may have d_{50} = 10μm, d_{90} = 13μm, d_{10} = 7μm, so that d_{90}/d_{50} = 1.3 and d_{50}/d_{10} = 1.4.

The powder material is fusible so that it is treatable to form a continuous film coating.

It is important that the powder can be fused or treated without degradation of any active material in the powder and without degradation of the tablet core. For some materials it may be possible for the treatment step to involve temperatures up to and above 250°C. Preferably, however, the powder material is fusible at a pressure of less than 100lb/sq. inch, preferably at atmospheric pressure, at a temperature of less than 200°C, and most commonly below 150°C, and often at least 80°C, for example in the range of from 100 to 140°C.

Fusing of the powder material may be carried out by any of a number of different fusing methods. If desired, rupture of the shell and fusing of the material may be carried out in a single step. The powder material is preferably fused by changing the temperature of the powder, for example by radiant fusing using electromagnetic radiation, for example infra red radiation or ultra-violet radiation, or conduction or induction, or by flash fusing. The

amount of heat required may be reduced by applying pressure to the powder material, for example by cold pressure fusing or hot roll fusing.

Preferably, the powder material has a glass transition temperature (Tg) in the range of 40°C to 120°C. Advantageously, the material has a Tg in the range of 50°C to 100°C. A preferred minimum Tg is 55°C, and a preferred maximum Tg is 70°C. Accordingly, more advantageously, the material has a Tg in the range of 55°C to 70°C. Generally, the powder material should be heated to a temperature above its softening point, and then allowed to cool to a temperature below its Tg.

The powder material once fused is substantially insoluble, preferably completely insoluble in aqueous media at temperatures up to the body temperature. Thus, the powder material will comprise a significant amount of an insoluble material. Preferred material comprises a polymer resin selected from polymethacrylates, polyvinyl alcohols and esters, cellulose and its derivatives, cellulose ethers and esters and cellulose acetate phthalate.

The electrostatic coating of the tablet core by the powder material may be conducted by any of the methods disclosed in the above referenced patents. The partial coating of the tablet core may be achieved by the use of a mask. However, preferably the partial coating is achieved by coating one face and the sides of a tablet core in accordance with the first stage of coating as described in the above mentioned patents. Thereafter the electrostatically deposited powder is fused to form a tablet core having a casing covering one face and the sides, leaving the other face exposed.

The invention will be illustrated by the following Examples and drawings in which:

Figures 1 and 2 represent diagrams of different solid dosage forms in accordance with the invention.

Figure 3a shows the release profile of a tablet core containing diltiazem and mixed hydrophobic/hydrophilic polymers as described in Example 1.

Figure 3b to 3g shows the release profile of a coated tablet containing diltiazem and mixed hydrophobic/hydrophilic polymers on the two major faces of the tablets, with 0.5%, 0.7%, 1.4%, 1.9%, 2.3% and 2.8% weight gains respectively as described in Example 1.

Figures 4a and 4b show the release profiles of a tablet core and the coated tablet containing salbutamol and hydrophobic matrix as described in Example 2.

Figures 5a and 5b show the release profiles of a hydrophilic tablet core and the coated tablet as described in Example 3.

Figures 6a and 6b show the release profiles of a mixed hydrophilic/hydrophobic tablet core and the coated tablet as described in Example 4.

Figures 7a and 7b show the release profiles of a hydrophilic tablet core and the coated tablet as described in Example 5.

Figures 8a and 8b show the release profiles of a hydrophobic tablet core and the coated tablet as described in Example 6.

Figures 9a and 9b show the release profiles of a hydrophilic tablet core and the coated tablet as described in Example 7.

Figure 1 shows a dosage form in accordance with the invention comprises a tablet core (2), which is circular in shape and has opposing major faces (4,6), which are convex. The faces (4,6) are coated with an insoluble coating (8, 10) leaving the sidewall (12) exposed.

Referring to Figure 2, which illustrates a cross-section through a dosage form with the invention, a tablet core (2) has a circular cross-section and opposing major convex surfaces (4, 6). The insoluble casing (8) extends over the major surface (6) and side (10) leaving major surface (4) exposed.

The following materials were used in the Examples:

Eudragit RS30D	a methacrylate polymer commercially available from Rhom
Methocel 66LV	hydroxy propyl methyl cellulose commercially available from Dow Chemicals
Methocel K4M	hydroxy propyl methyl cellulose commercially available from Dow Chemicals

Methocel K15M	hydroxy propyl methyl cellulose commercially available from Dow Chemicals
Methocel K100M	hydroxy propyl methyl cellulose commercially available from Dow Chemicals
Eudragit RSPO	a methacrylate copolymer commercially available from Rohm
Eudragit RLPO	a methacrylate copolymer commercially available from Rohm
Eudragit NE30D	a methacrylate copolymer commercially available from Rohm

In the Examples all parts and percentages are by weight unless otherwise stated.

Example 1

Effect of coating thickness: mixed polymer coated on both major faces with insoluble coat

The construction of the dosage form is shown in Figure 1.

Tablet cores were formulated by mixing:

Diltiazem HCl	17.14%
Eudragit RS30D	5.00% (added as 30% aqueous solution)
Methocel 66LV	2.00%
Microcrystalline cellulose	20.00%

DCPA (dihydrogen calcium phosphate anhydrous) 44.86%

Eudragit RSPO 10.00%

The mixture was oven dried to approximately 1% moisture. 1.00% magnesium stearate was added to the dried granules and mixture was compressed into 10mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of about 19 kp.

Two coating formulations for the casing were prepared. Coating Formulation I had the following composition:

Eudragit RSPO	89.8%
Polyethylene glycol 6000	2.7%
Titanium dioxide	5.0%
Indigo Carmine (blue)	2.5%

Coating Formulation II was blended with 0.2% Aerosil 200 before application and it has the following composition:

Eudragit RSPO	87.2%
Triethyl citrate	5.37%
Titanium dioxide	5.0%
Sunset yellow (orange)	2.5%

To prepare the coating powder, the above ingredients were weighed, blended, then extruded. The extrudates were pin-milled, micronised and classified in an air jet mill to give a median particle size of approximately 10 μm.

A blend containing 4.5% of Coating Formulation I and 95.5% of a silicone coated ferrite was prepared. The tablets were coated electrostatically using the coat/carrier blend in a conventional dual component delivery device adapted from the electrophotographic industry such that the Coating Formulation I (without ferrite carrier) was applied to both faces of the tablet leaving the sides uncoated. Details of the coating process are disclosed in British Patent Application No. 9929946.3. The coat was fused onto the tablets at approximately 100°C, to provide a range of coating thickness between 10 and 60μm . The tablets were then turned over and the second coating applied on the other sides of the tablets by the same technique using Coating Formulation II.

Six uncoated and six coated tablets of each coating thickness (as expressed by % weight gain) were assessed for release rate in 900 ml of demineralised water at 37°C using USP Apparatus II (paddles) at 50 rpm as described above and diltiazem analysed by UV.

The results are summarised in Table 1.

Table 1

Sample	Coat thickness I (centre μm)		Coat thickness II (edges μm)		Release exponent (n)
% Weight gain	Side 1	Side 2	Side 1	Side 2	
a 0 (core)	0	0	0	0	0.37
b 0.5%	10	14	12	13	0.50
c 0.7%	43	<10	14	<10	0.45
d 1.4%	33	33	23	30	0.78
e 1.9%	26	28	22	26	0.80
f 2.3%	33	30	26	23	0.79
g 2.8%	39	64	30	44	0.82

The release rate with time for each different tablet is shown in Figures 3a to 3g.

These results demonstrate that electrostatic application of a thin coat on the selected surface of a tablet core, which had a release profile close to first order release, i.e. release exponent n = 0.30 –0.65, resulted in a dosage form having a release profile substantially close to zero order, i.e. n = 0.7 –1.0.

It is known that conventional solvent coating results in a substantial thick coating with a weight gain of at least 5%, or frequently above 10% for modified release systems. The present results demonstrate that zero order release can be achieved with a very thin coat by electrostatic coating and the release profiles are insensitive to coating thickness provided a continuous and complete coverage of the coated area is achieved, i.e. the deposition of several layer coating powder to give a fused coat of approximately 20 μm thick.

Example 2

Hydrophobic tablet core coated on both major faces with insoluble coat

The construction of the dosage form is as illustrated in Figure 1.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

71.26% anhydrous DCPA

25% Eudragit RLPO

1% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of 10 kp. Coating Formulation III was used to coat both sides of the tablets as described in Example 1 to provide a casing of 20 to 50 μm. Coating Formulation III comprises:

84.0% Eudragit RSPO

8.5% polyethylene glycol 6000

5.0% titanium dioxide

2.5% sunset yellow lake

Three uncoated and three coated tablets were assessed for release rate in 500 ml of demineralised water at 37°C using USP Apparatus II (paddles) at 50 rpm and the release rate analysed by UV over 12 hours. The release rate with time is shown in Figures 4a and 4b. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 - 100% release range):

Core: $y = 22.3t^{0.59}$

Coated: $y = 10.8t^{0.90}$

It is evident that electrostatic application of a thin coat substantially modified the release profile of a tablet core comprising hydrophobic polymers.

Example 3

Hydrophobic tablet core comprising a different active coated on both major faces with insoluble coat

The construction of the dosage form is as shown in Figure 1.

Tablet cores were formulated by mixing:

17.14% ditiazem hydrochloride

20.00% microcrystalline cellulose

51.86% anhydrous DCPA

10.00% Eudragit RS30D added as 30% aqueous dispersion

The mixture was oven dried to approximately 1% moisture. 1% magnesium stearate was added to the dried granules and the mixture compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of 19 kp.

A blend containing 10% of Coat Formulation III as described in Example 2 and 90% of a silicone coated strontium ferrite carrier was prepared. The tablet cores were coated on both major faces using the materials and method as described in Example 2 with the exception that the coat was fused at 120°C. The coating thickness was in the range 20 to 50μm

Six cores and six coated tablets were assessed for release rate in 900 ml of demineralised water at 37°C using USP Apparatus II (paddles) at 50 rpm and the release rate analysed by HPLC.

The release of diltiazem over time is shown in Figures 5a and 5b respectively. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 90% release range):

Core: $y = 52t^{0.43}$

Coated: $y = 22t^{0.70}$

It is evident that electrostatic application of a thin coat on the major faces of the tablet substantially modified the release profile of a tablet core comprising hydrophobic polymers.

Example 4

Mixed hydrophobic/hydrophilic tablet core coated on both major faces with insoluble coat

The construction of the dosage form is as illustrated in Figure 1.

The tablet cores were formulated by mixing:

17.14% Diltiazem hydrochloride

20.00% microcrystalline cellulose

50.86% anhydrous DCPA

1% Methocell K15M

10% (as solid) Eudragit NE30D (30% aqueous dispersion)

The mixture was oven dried to approximately 1% moisture. 1% magnesium stearate was added to the dried granules and the mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of about 19 kp.

The tablet cores were coated using the materials and method as described in Example 3. The release rate was determined as described in Example 3 and the results are shown in Figures 6a and 6b. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 80% release):

Core: $y = 38.5t^{0.56}$

Coated: $y = 10.5t^{0.85}$

It is evident that electrostatic application of a thin coat on the major faces of tablets substantially modified the release profile of a tablet core comprising mixed hydrophilic/hydrophobic polymers.

Example 5

Hydrophilic tablet core coated on both faces of the tablet

The construction of the dosage form is shown in Figure 1.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

46.26% anhydrous lactose DC (directly compressible)

50.00% Methocel K4M

1.00% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of 350 mg and a hardness of about 19 kp. Coating Formulation III was applied on the major opposite faces of the tablet core as described in Example 2 to provide a coating having a thickness in the range of from 20 to 50µm.

The release rate with time was determined according to the method described in Example 2 and the results are shown in Figures 7a and 7b respectively. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 80%):

Core: $y = 22.1t^{0.56}$

Coated: $y = 11.0t^{0.80}$

It is evident that electrostatic application of a thin coat on the major faces of tablets substantially modified the release profile of a tablet core comprising hydrophilic polymers.

Example 6 Hydrophobic tablet core coated on one face and the sides of the tablet

The construction of the dosage form is shown in Figure 2.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

71.26% anhydrous DCPA

25.00% Eudragit RLPO

1.00% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of 350 mg and a hardness of about 11 kp. Coating Formulation III was applied on one major face and the sides of the tablet core and the method of coating was as described in Example 2 to provide a coating thickness in the range 20 to 50µm.

The release rate with time was determined according to the method described in Example 2 and the results are shown in Figures 8a and 8b respectively.

The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 95% for the core and 0 – 80% for the coated tablet):

Core: $y = 70\ t^{0.47}$

Coated: $y = 16.3\ t^{0.90}$

It is evident that electrostatic application of a thin coat on the major faces of tablets substantially modified the release profile of a tablet core comprising hydrophilic polymers.

Example 7:

Hydrophilic tablet core coated on one face and the sides of the tablet

The construction of the dosage form is shown in Figure 2.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

46.26% anhydrous lactose DC (directly compressible)

50.00% Methocel K100M

1.00% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of 350 mg and a hardness of about 15 kp. Coating formulation III was applied on one face and the sides of the tablet core and the method of coating was as described in Example 2 to provide a coating thickness in the range 20 to 50μm.

The release rate with time was determined according to the method described in Example 2 and the results are shown in Figures 9a and 9b respectively.

The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 70%):

Core: $y = 21.0\ t^{0.55}$

Coated: $y = 10.9\ t^{0.78}$

It is evident that electrostatic application of a thin coat on one face and the sides of tablets substantially modified the release profile of a tablet core comprising hydrophilic polymers.

CLAIMS

1. A controlled release dosage form comprising:

(i) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable matrix forming polymers, the tablet core releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.30 to 0.65

(ii) a substantially insoluble casing extended over the tablet core covering between 25 to 99% of the surface area of the tablet core, the casing resulting from electrostatic deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film such that the said electrostatic coated tablet releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.70 to 1.0.

2. A solid pharmaceutical dosage form as claimed in Claim 1 in which the insoluble casing covers from 65 to 95% of the surface area of the tablet core.

3. A solid pharmaceutical dosage form as claimed in Claim 1 or Claim 2 in which the tablet core comprises two major opposing surfaces separated by a sidewall(s) at least the major surfaces being covered by the casing.

4. A solid pharmaceutical dosage form as claimed in Claim 1 or Claim 2 in which the tablet core comprises two major opposing surfaces separated by a sidewall(s) one major surface and the sidewall(s) being covered by the casing .

5. A solid pharmaceutical dosage form as claimed in any preceding claim in which the controlled release dosage form has a release profile in which n = 0.7 to 1.0 over from 0 to at least 70% by weight release of the active ingredient.

6. A solid pharmaceutical dosage form as claimed in any preceding claim in which the release profile of the controlled release dosage form requires at least 4 hours to achieve 70% by weight release of active ingredient.

7. A solid pharmaceutical dosage form as claimed in any preceding claim in which the tablet core comprises a binder selected from acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydrogenated vegetable oil, hydroxypropylmethylcellulose, magnesium aluminium silicate, Maltodextrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

8. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core additionally comprises a release rate controlling polymer is selected from polymethacrylates, ethylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol,

polyethylene oxide, carrageenan, cellulose acetate, glyceryl monostearate and zein.

9. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core additionally comprises a diluent selected from lactose, cellulose, dicalcium phosphate, sucrose, dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate, dextrates, dextrin, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose.

10. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises a hydrophobic matrix containing an active ingredient, a hydrophilic matrix containing an active ingredient, or a mixture of hydrophilic and hydrophobic materials

11. A solid pharmaceutical dosage form as claimed in any preceding claim in which the active ingredient is selected from acid-peptic and motility influencing agents, laxatives, antidiarrheials, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics, fibrinolytics, haemostatics, hypolipidaemic agents, anti-anaemia and neurotropenia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents, hyperglycaemix agents, diagnostic agents, antibiotics, anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytes, decongestants, anti-glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.

12. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises a polymeric material which swells on contact with aqueous liquid, said swellable polymeric material being selected

from cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high molecular weight hydroxypropylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone and high molecular weight polyvinylalcohols.

13. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the casing comprises a polymer resin selected from polymethacrylates, cellulose and its derivatives, cellulose ethers and esters and cellulose acetate phthalate.

14. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the casing additionally comprises one or more adjuvants selected from opacifiers, colourants, plasticisers, flow aids and charge control materials.

15. A solid pharmaceutical dosage form as claimed in Claim 14 in which the casing comprises a plasticiser selected from polyethylene glycols, triethyl citrate, acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

16. A solid pharmaceutical dosage form as claimed in any preceding claim in which the casing has an average thickness of from 20 to 50μm.

17. A solid pharmaceutical dosage form as claimed in any preceding claim in which the casing results in a weight gain of less than 4% by weight of the tablet core.

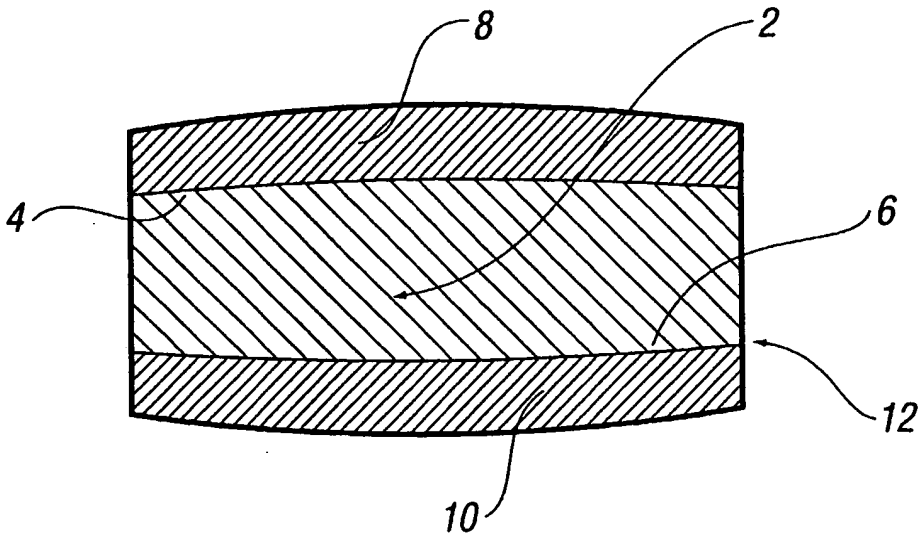

FIG. 1

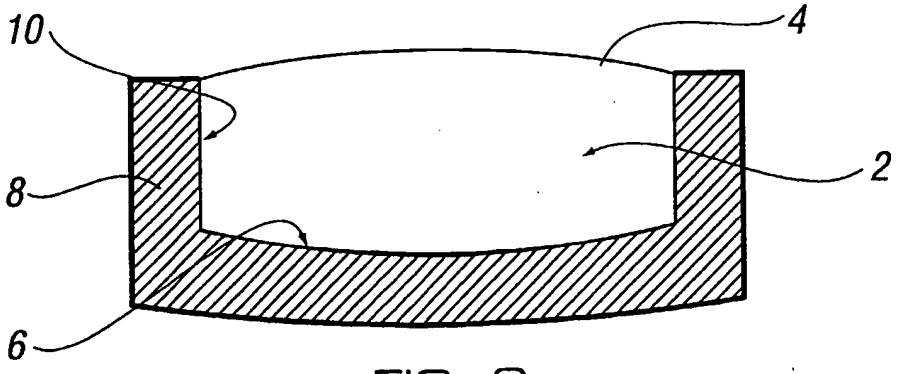

FIG. 2

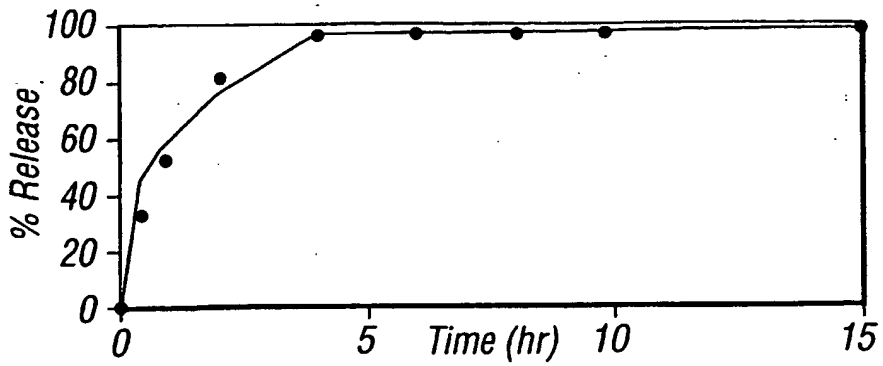

FIG. 3A

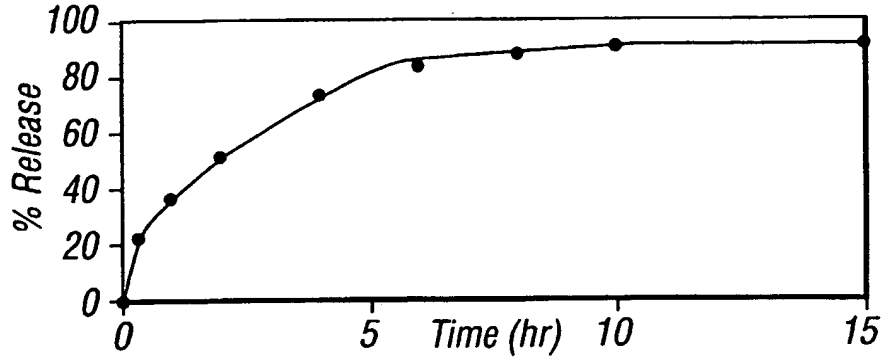

FIG. 3B

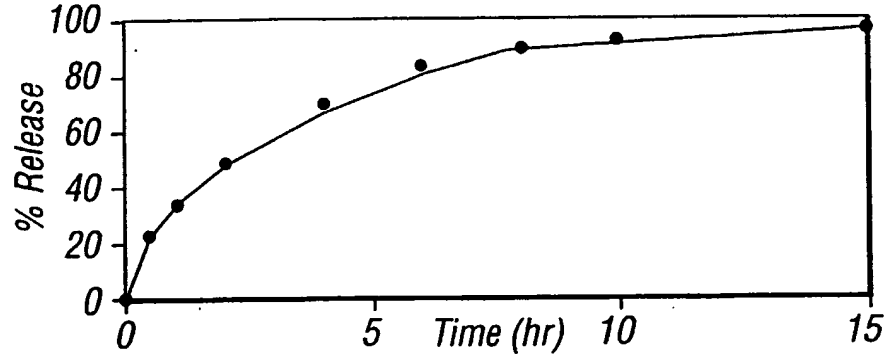

FIG. 3C

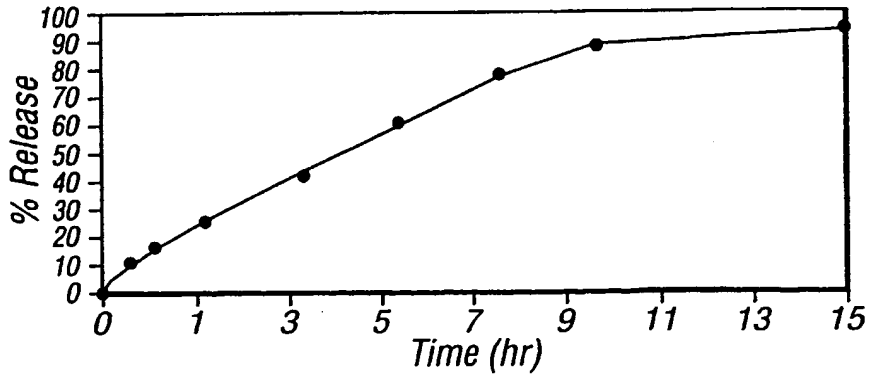

FIG. 3D

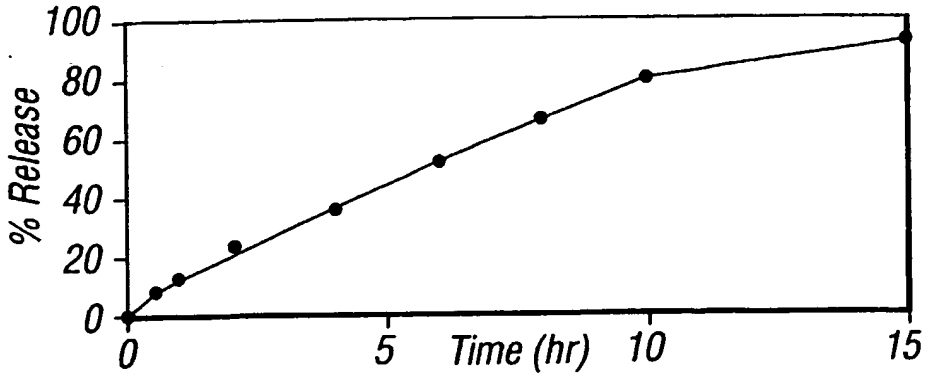

FIG. 3E

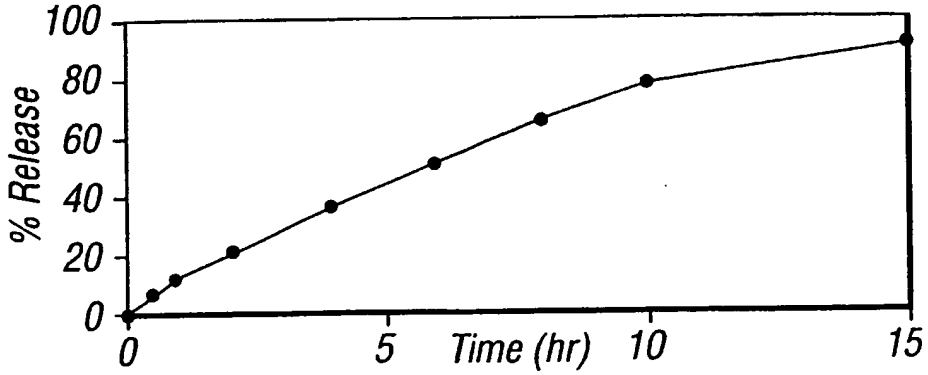

FIG. 3F

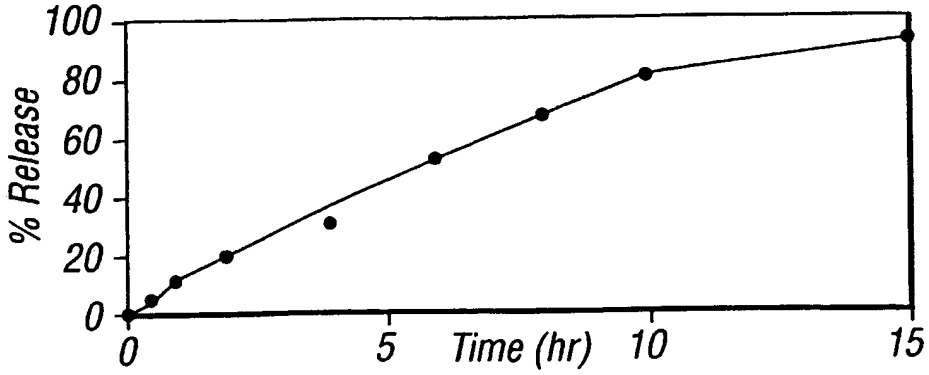

FIG. 3G

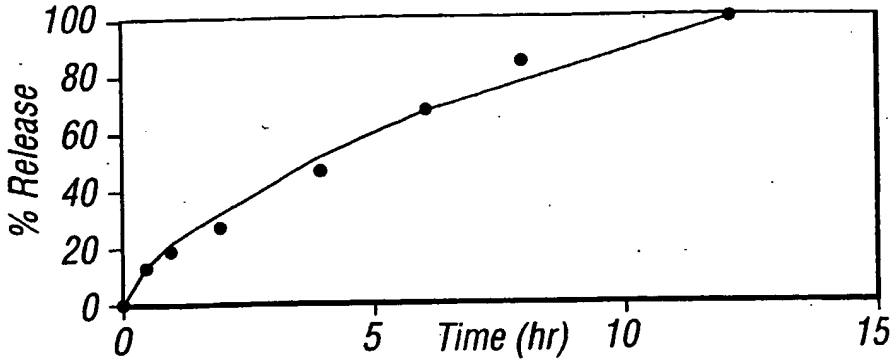

FIG. 4A

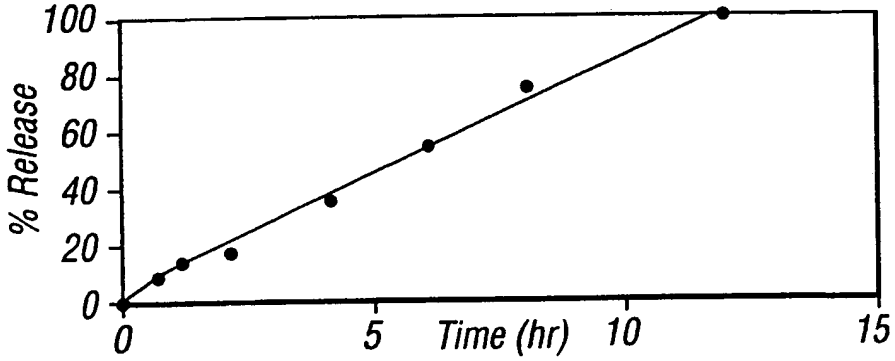

FIG. 4B

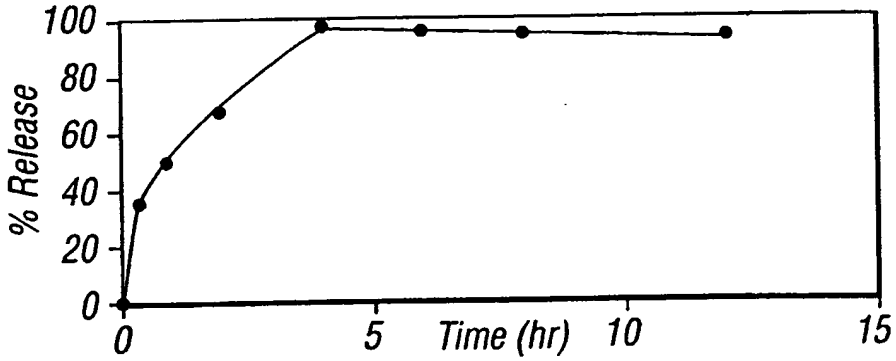

FIG. 5A

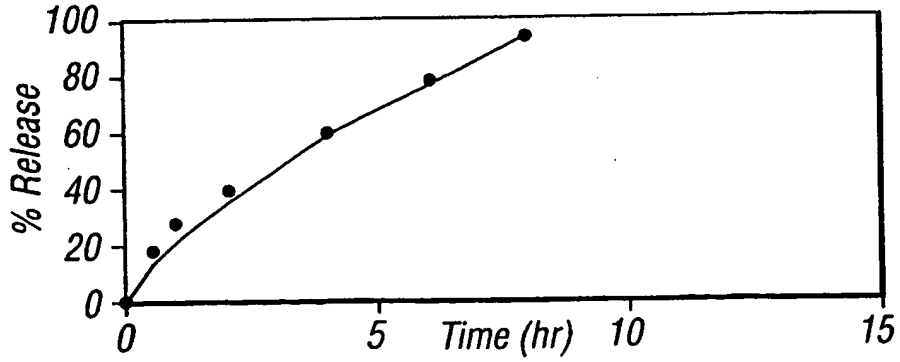

FIG. 5B

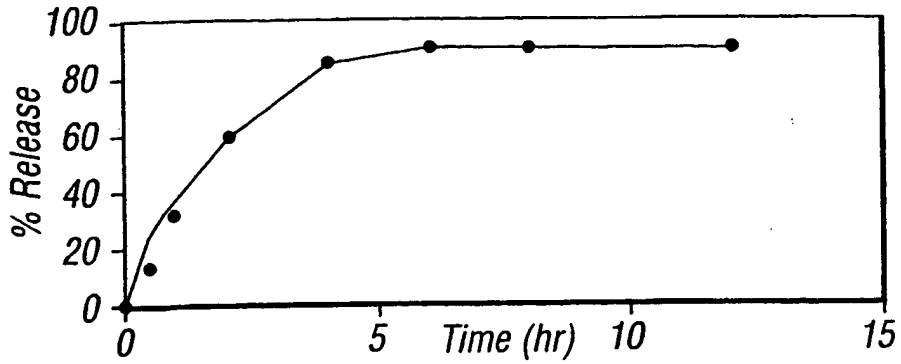

FIG. 6A

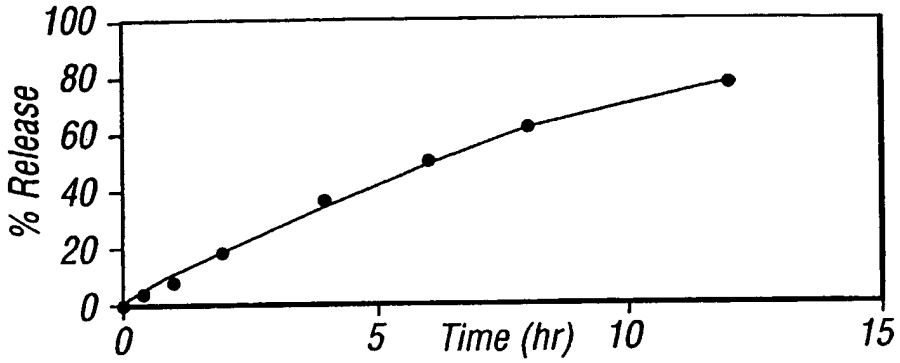

FIG. 6B

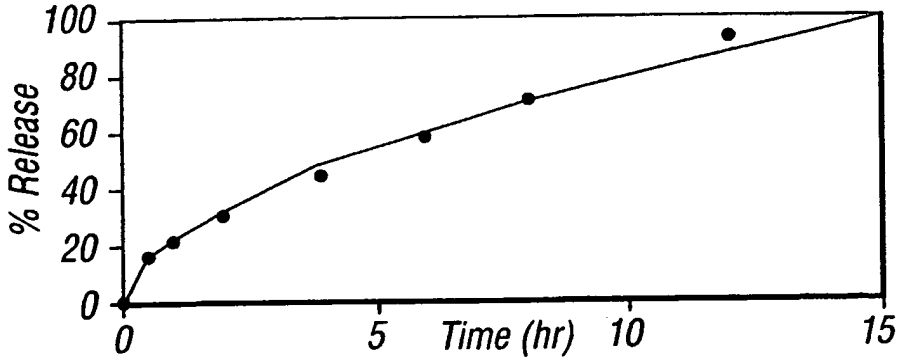

FIG. 7A

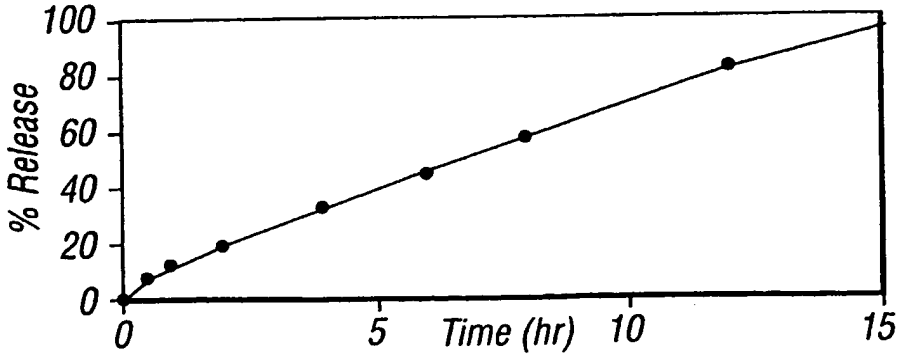

FIG. 7B

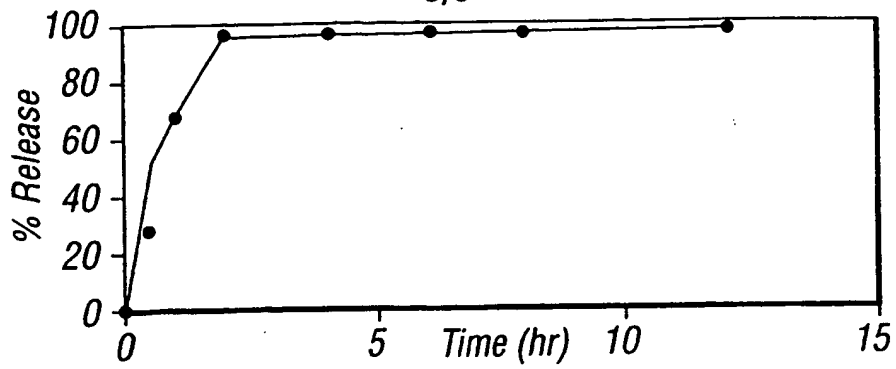

FIG. 8A

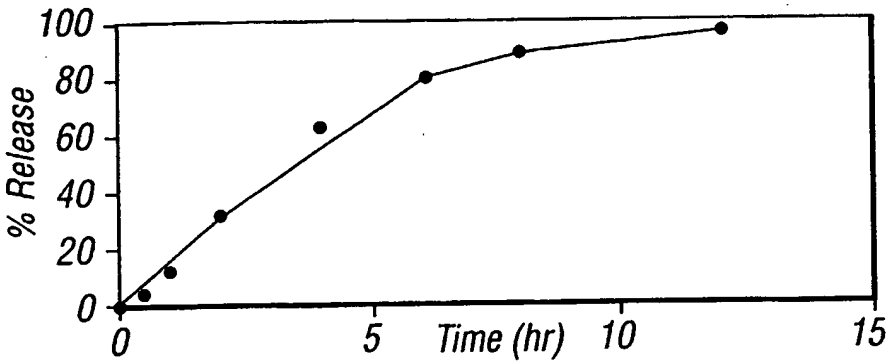

FIG. 8B

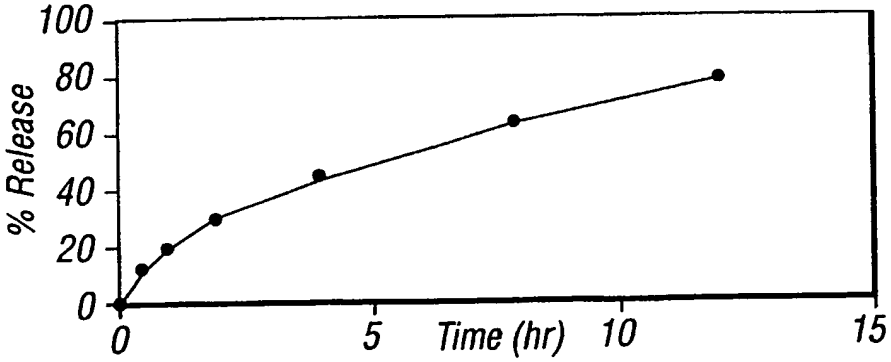

FIG. 9A

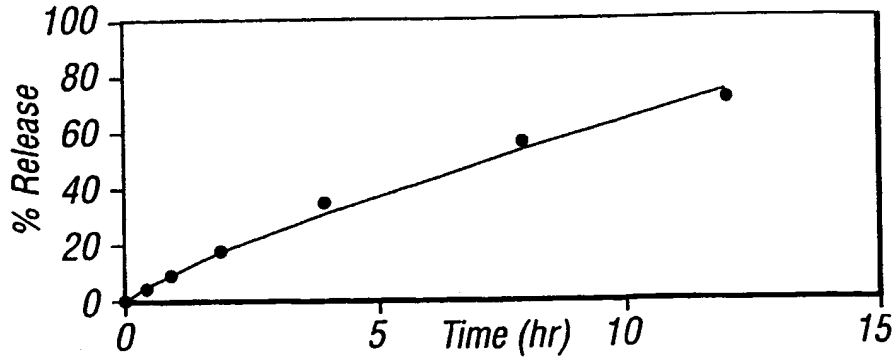

FIG. 9B

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03292

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 5 470 603 A (STANIFORTH JOHN N ET AL) 28 November 1995 (1995-11-28) column 2, line 1 - line 17 column 2, line 27 - line 28 column 5, line 3,4 column 5, line 6 - line 18 column 5, line 38 - line 52 ---	1-4,14 5-13,16, 17
X Y	US 6 117 479 A (PAGE TREVOR ET AL) 12 September 2000 (2000-09-12) column 3, line 1 column 6, line 25 - line 41 column 7, line 9 - line 13 claims 1-84 --- -/--	1,7, 13-15 2-6, 8-12,16, 17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2002	25/10/2002

Name and mailing address of the ISA	Authorized officer
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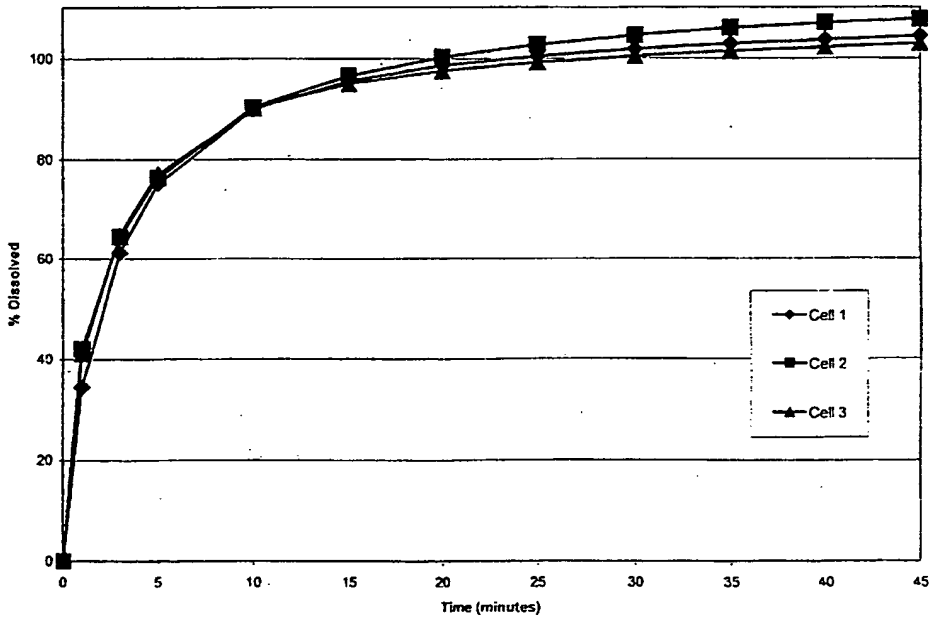
(54) Title: FUNCTIONAL POWDERS FOR ORAL DELIVERY



(57) Abstract: In certain embodiments the invention is directed to a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core overcoated with a functional coating, said drug particles having a mean diameter of greater than 10 μm to about 1 mm.

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FUNCTIONAL POWDERS FOR ORAL DELIVERY

This application claims the benefit of U.S. Provisional Serial No. 60/317,522, filed September 5, 2001, the entire disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0001] The present is directed to a functional powders for oral use. Preferably, the powders are used in a multiple dose delivery device which dispenses a unit dose of the powder upon actuation.

BACKGROUND OF THE INVENTION

[0002] The most prominent mode of delivery of therapeutic agents is by the oral route by means of solid dosage forms such as tablets and capsules. Oral administration of solid dosage forms is more convenient and accepted than other modes of administration, e.g. parenteral administration. However, the manufacture, dispensing and administration of solid dosage forms are not without associated problems and drawbacks.

[0003] With the manufacture of solid dosage forms, in addition to the active agent, it is necessary to combine other ingredients in the formulations for various reasons, such as to enhance physical appearance, to provide necessary bulk for tableting or capsuling, to improve stability, to improve compressibility or to aid in disintegration after administration. However, these added excipients have been shown to adversely influence the release, stability and bioavailability of the active ingredient. The added excipients are a particular problem with drugs which require a high dose in order to provide a therapeutic effect, e.g., biphosphonate drugs. The inclusion of the additional excipient can make the final tablet extremely large which could result in esophogeal damage due to the physical characteristics of the dosage form if it is not swallowed properly. Esophogeal damage can also be caused by toxicity caused by the drug itself, if the tablet becomes lodged in the throat or has an increased transit time through the esophagus, due to its increased size.

[0004] Further, the tableting of certain drugs has many associated production problems. In particular, many drugs, e.g., acetaminophen, have poor compressibility and cannot be directly compressed into solid dosage forms. Consequently, such drugs must either be wet granulated or manufactured in a special grade in order to be tableted which increases manufacturing steps and production costs.

[0005] The adherence to good manufacturing practices and process controls is essential in order to minimize dosage form to dosage form and batch to batch variations of the final product. Even strict adherence to these practices still is not a guarantee that acceptable variation will occur.

[0006] With the high cost of industrial scale production and governmental approval of solid dosage forms, such formulations are often available in a limited number of strengths, which only meet the needs of the largest sectors of the population. Unfortunately, this practice leaves many patients without acceptable means of treatment and physicians in a quandary with respect to individualizing dosages to meet the clinical needs of their patients.

[0007] The dispensing of oral solid dosage forms also makes the formulations susceptible to degradation and contamination due to repackaging, improper storage and manual handling.

[0008] There are also many patients who are unable or unwilling to take conventional orally administered dosage forms. For some patients, the perception of unacceptable taste or mouth feel of a dose of medicine leads to a gag reflex action that makes swallowing difficult or impossible. Other patients, e.g., pediatric and geriatric patients, find it difficult to ingest typical solid oral dosage forms, e.g., due to tablet size.

[0009] Other patients, particularly elderly patients, have conditions such as achlorhydria which hinders the successful use of oral solid dosage forms. Achlorhydria is a condition wherein there is an abnormal deficiency or absence of free hydrochloric acid in the gastric secretions of the stomach. This condition hinders the disintegration and/or dissolution of oral

solid dosage forms, particularly dosage forms with high or insoluble excipient payloads. Thus, as the present dosage form is in multiparticulate form, it does need to undergo disintegration and/or dissolution to the same extent as solid dosage forms.

[0010] Flavored solutions/suspensions of some therapeutic agents have been developed to facilitate the oral administration of oral agents to patients normally having difficulty ingesting conventional solid oral dosage forms. While liquid formulations are more easily administered to the problem patient, liquid/suspension formulations are not without their own significant problems and restrictions. The liquid dose amount is not as easily controlled compared with tablet and capsule forms and many therapeutic agents are not sufficiently stable in solution/suspension form. Indeed, most suspension type formulations are typically reconstituted by the pharmacist and then have a limited shelf life even under refrigerated conditions. Another problem with liquid formulations which is not as much a factor with tablets and capsules is the taste of the active agent. The taste of some therapeutic agents is so unacceptable that liquid formulations are not a viable option. Further, solution/suspension type formulations are typically not acceptable where the active agent must be provided with a protective coating, e.g. a taste masking coating or an enteric coating to protect the active agent from the strongly acidic conditions of the stomach.

[0011] Due to the disadvantages of known drug delivery discussed above (as well as other disadvantages) there exists a need in the art for the development of a multiparticulate formulation for facilitating delivery of a wide range of therapeutic agents for gastrointestinal deposition and which minimize pulmonary deposition of materials having undesirable or unknown pulmonary toxicology but which are approved for oral delivery. In preferred embodiments, the formulation contains minimal excipient and is used in a multiple dose delivery device which dispenses a unit dose of the powder upon actuation.

OBJECTS OF THE INVENTION

[0012] It is an object of the invention to provide a multiparticulate formulation containing a therapeutic agent for gastrointestinal deposition.

[0013] It is an object of certain embodiments of the invention to provide a multiparticulate formulation having at single coating which aids in the functionality of the formulation.

[0014] It is an object of certain embodiments of the invention to provide a multiparticulate formulation having at least two coatings which aid in the functionality of the formulation.

[0015] It is an object of certain embodiments of the invention to provide a high load multiparticulate formulation with minimal use of excipient.

[0016] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation with improved weight variability, from dose to dose and batch to batch.

[0017] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation which has minimal change in cohesiveness in response to humidity change

[0018] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation which has minimal potential for water coalescence on the surface of the particles.

[0019] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation which has minimal static charge between the particles.

[0020] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which provides a controlled or delayed release of the active

agent contained therein.

[0021] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which tastemasks the active agent therein.

[0022] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which contains a salivary stimulant to facilitate the swallowing of a unit dose of the multiparticulates upon oral delivery.

[0023] It is an object of the certain embodiments of invention to provide a coated multiparticulate formulation which contains a texture modifier to improve mouthfeel upon oral delivery.

[0024] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which has a desired particle range in order to minimize pulmonary aspiration of particles.

[0025] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which has a desired particle range in order to improve functionality of a the formulation in a multiple unit dosing device which delivers a unit dose of the formulation for oral administration or delivery upon actuation.

[0026] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which has improved performance when used in a multiple unit dosing device which delivers a unit dose of the formulation for oral administration or delivery upon actuation.

[0027] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which when divided into unit doses (e.g. with the use of a multiple unit dosing device) has weight uniformity of the formulation which is within the

acceptable range of the weight uniformity of equivalent dosage forms which are tablets or capsules. A detailed discussion of weight uniformity is found in the USP/NF 23/18 section 905, hereby incorporated by reference in its entirety for all purposes.

[0028] It is an object of certain embodiments of the invention to provide methods of preparation of the coated multiparticulate dosage form disclosed herein.

[0029] It is an object of certain embodiments of the invention to provide methods of preparation of the multiple unit delivery systems containing the coated multiparticulate dosage form disclosed herein.

[0030] It is an object of certain embodiments of the invention to provide methods of preparation of multiparticulate dosage forms having a desired particles range.

[0031] It is an object of certain embodiments of the invention to provide methods of administering an active agent comprising administering a coated multiparticulate dosage form disclosed herein.

[0032] It is an object of certain embodiments of the invention to provide methods of administering an active agent comprising administering a coated multiparticulate dosage form disclosed herein via the use of a multiple unit delivery systems.

[0033] The above objects of the invention, and others are achieved by virtue of the present invention, which in certain embodiments is directed to a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug, the core overcoated with a functional coating.

[0034] In certain embodiments, the invention is directed to a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core

overcoated with a functional coating.

[0035] In certain embodiments, the invention is directed to a drug delivery system for delivery of a drug for gastrointestinal deposition. The system comprises a multiple unit dosing device comprising a housing and an actuator, the device containing multiple doses of the multiparticulate formulation disclosed herein, the device upon actuation delivering a unit dose of the multiparticulates for gastrointestinal deposition, the multiparticulates having a mean particle size of greater than 10 μm and preferably less than about 1mm in order to minimize pulmonary deposition of the multiparticulates and such that an effective dose of the drug cannot be delivered into the lower lung of a human patient. The drug delivery system can be used to administer the unit dose of multiparticulates into the oral cavity of the patient (*in-vivo*) or to dispense the unit dose into an intermediate receptacle (*ex-vivo*) for subsequent gastrointestinal deposition. Oral drug delivery systems and devices for oral powders are disclosed in PCT/IB01/00251, hereby incorporated by reference in its entirety for all purposes.

[0036] In certain embodiments, the invention provides a method of preparing a drug delivery system for delivering multiple doses of a drug for gastrointestinal deposition comprising preparing a multiparticulate drug formulation as disclosed herein in a manner wherein the drug particles when placed in the oral cavity and swallowed are deposited to the gastrointestinal tract and not deposited in any substantial amount to the lungs; and placing multiple unit doses of said drug formulation in a device which meters a single unit dose for delivery.

[0037] In certain embodiments, the invention provides a method of treating a patient in need of multiple doses of a drug for gastrointestinal deposition comprising preparing multiparticulates comprising drug particles as disclosed herein in a manner wherein the drug particles when placed in the oral cavity and swallowed are deposited to the gastrointestinal tract and not deposited in any substantial amount to the lungs; placing multiple unit doses of the multiparticulates in a device which meters a single unit dose for delivery; and either (a)