Further, formulations without PEG also appeared to be preferred in order to improve clonazepam stability.

[00205] Addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such formulations. Examples of a suitable anti-oxidants include, but are not limited to, tocopherol and derivatives thereof, ascorbic acid and derivatives thereof, butylhydroxyanisole, butylhydroxytoluene, fumaric acid, malic acid, propyl gallate, sodium sulfite, metabisulfites (including sodium metabisulfite) and derivatives thereof, as well as EDTA disodium, trisodium and the tetrasodium salts. Soluble, organic anti-oxidants are preferred, for example, butylhydroxytoluene.

[00206] Further, the data indicate protective effects resulting from the inclusion of pH modifiers when an aqueous solvent was used. Microbial challenge with 5 organisms (staphylococcus aureas, pseudomonas aeruginosa, escherichia coli, candida albicans and aspergillus niger) showed a log plate count of less than 1/mL observed after a period of 28 days, indicating that the liquid formulation itself is microcidal and therefore a non-sterile product is likely acceptable.

Example 4

Screening Formulations for Nasal Irritation Potential Using a Rat Model

[00207] A number of formulations were tested in a rat irritation model. The first objective was to establish the irritation threshold of Transcutol®. Two formulations were tested containing 20% and 50% Transcutol® in PEG 200. The blood pressure signals integrated as a function of time were as shown in Figure 3.

[00208] In Figure 3, the designations were as follows: CLZ2080 -- 10 mg/mL clonazepam, 20% Transcutol® (TC), 80% Polyethylene Glycol (PEG); CLZ5050 -- 10 mg/mL clonazepam, 50% TC, 50% PEG; CLZ70G30T -- 10 mg/mL clonazepam, 70% GF, 30% TA; CLZ20T80P02T, 10 mg/mL clonazepam, 10% TC, 90% PEG 200 and 0.2% TWEEN 20; Saline (negative control); Acetic Acid (HOAc) 0.3% (positive irritation control); Acetic Acid (HOAc) 1.5% (positive irritation control); Setron (positive irritation control).

[00209] The data shown in Figure 3 demonstrated slight, transient irritation apparent in the test animals. After instillation of compositions, irritation typically lasted

less than 1.5 minutes in rats (range 0.7 to 2.2 minutes). Irritation was generally greater than saline and similar to irritation from 1.5% acetic acid. Veterinary evaluation of the data resulted in the conclusion that nasal irritation from these formulations was not significant.

[00210] Two other clonazepam formulations were tested (70% PEG and 30% GF; and 10% TC, 90% PEG 200 and 0.2% Tween 20) and similar results were obtained. Tween 20 (polyethylene glycol sorbitan monolaurate) was used as a possible irritation reducer.

[00211] One formulation, CLZ5050 appeared to produce more intense irritation than the other formulations as instillation was associated with a blood pressure drop. The drop biased the drawing of a base line and therefore the integration of the signal.

[00212] In a second rat nasal irritation experiment, eight clonazepam formulations and one formulation matrix without clonazepam (K: 30% TA, 70% GF) were tested in the irritation model and compared with irritation results obtained using 0.9% acetic acid. The formulations used in and results from the rat nasal irritation study are presented in Table 11. In the table, Iden. -- is the identifier associated with the formulation; MBP -- integrated mean blood pressure over the duration of the irritation response; T -- duration of irritation response (minutes); TC – Transcutol®; PEG -- polyethylene glyco; TA -- triacetin; GF -- glycofurol; PG -- propylene glycol; H2O -- water; Tw -- TWEEN 20; w/o clz = without clonazepam. Fifty μL of each formulation containing 20 mg/mL clonazepam was administered to each animal.

Table 11

Rat Nasal Irritation Study

Formulation									MBP		$T_{(min)}$	
Iden.	TC	PEG	TA	GF	PG	H2O	Tw	N	aver.	stdev[c]	Avg	err[c]
I	20	80						3	26	8	1.8	0.2
H	50	50						4[a]	25	4	1.9	0.2
K			30	70				3	8	3	0.7	0.1
M		70		30				3	21	9	1.7	0.1
I+Tw	20	80					0.2	3	22	11	1.2	0.2
T				30	70			2[b]	27	(8)	1.2	(0.1)
R_{wa}				30	60	10		3	42	10	1.8	0.5
R				30	60	10[d]	0.2	3	25	1	2.2	0.2
K w/o clz			30	70				3	22	4	1.3	0.2
0.9% HOAc								2	26	11	1.6	(0.3)

a = blood pressure drop must be due to intense irritation. The drop biases the drawing of a base line and therefore the integration of the signal.
b = the third animal in the group reacted very strongly to administration, received cardiac resuscitation. The results from this animal were not included in the data processing.
c = numbers in parentheses are used when $n < 3$.
d = includes citrate buffer pH4, and sodium metabisulphite.

Sodium metabisulfite and citric acid were each present at less than 1% (w/w) basis in the above formulations.

[00213] Acetic acid 0.9% has been found to be tolerated by volunteers in a human trial. The objective of this experiment was to provide a preliminary test a variety of formulations and compare them with respect to irritation. Because a slightly irritating profile would be tolerated for an intranasal formulation against seizure clusters and other acute indications such as panic attacks, the major concern was that volunteers participating in a clinical Phase I trial would not suffer unnecessary pain. The irritation scores based on measurement of blood pressure are presented in Figure 4 and Table 11. In Figure 4, the columns for saline, acetic acid solutions and a setron formulation (i.e., the right-most four columns) represented data from previous experiments and were inserted for comparison. Table 11 also present the duration of the irritation response in minutes. The results showed that all formulations tested gave a relatively short-lived irritation response, in the range from 0.7 to 2.2 minutes.

[00214] To test the irritation of Transcutol®, two formulations were tested containing 20% and 50% Transcutol® with PEG 200 as the cosolvent. Transcutol® at

20% (I) or 50% (H) demonstrated similar irritation scores suggesting that Transcutol® is no more irritating than PEG. A third formulation containing Transcutol® was the same as I but with 0.2% Tween. Comparison of I and I with Tween-20 suggested that Tween did not provide a substantial reduction of irritation in this formulation.

[00215] Formulation K (30% TA, 70% GF), which showed a good pharmacokinetic profile (see Example 5), had the lowest irritation score of the formulations tested in this experiment.

[00216] Formulation K was also tested without clonazepam to obtain information on the effects of clonazepam on irritation. Comparison of the irritation scores of K and K without clonazepam showed that clonazepam appeared to have an irritation reducing effect.

[00217] Formulations M and T contain the same amount of glycofurol but M contains 70% PEG while T contains propylene glycol as the cosolvent. The irritation score of these two does not differ significantly indicating a similar degree of irritation by PG and PEG.

[00218] Formulation R with 10% buffer (citrate/Tween/bisulphite) or with 10% water was the only water containing formulation tested. The formulation with water only appeared to be significantly more irritating than the formulation that contained buffer/Tween/bisulphite. Formulation R with buffer demonstrated similar irritation profile as did the non-aqueous formulations I, H, M and T.

[00219] Acetic acid 0.9% has been tested for irritation in a human trial and was found to be irritating but tolerable. All formulations tested except R with water demonstrate irritation equal or lower than this reference formulation (Figure 4) suggesting that they had minor irritation but were tolerable.

[00220] These nasal irritation data suggested that the clonazepam formulations of the present invention were suitable for intranasal delivery.

Example 5

Pharmacokinetics and Tolerability

[00221] Different clonazepam formulations were delivered intranasally and intravenously to rabbits. Many of the administrated formulations demonstrated intranasal

bioavailability higher than 70% that of the intravenous formulations. Those that contained Transcutol® at concentrations 20-100% demonstrating that Transcutol® was a useful absorption enhancer and solvent for clonazepam

[00222] Additionally, the intranasal clonazepam formulations containing Transcutol® in the concentration range 20-100% yielded pharmacokinetic (PK) profiles with t_{max} lower than 4 minutes. The absorption enhancing effects of Transcutol® were also demonstrated by this performance index.

[00223] Some exemplary pharmacokinetic data for clonazepam formulations is presented in Table 12A (N=1 for each formulation). In the table, Tw or tween is TWEEN20, EtOH is ethanol, Triac or TA is Triacetin, phosph is phosphate buffer, metabisulph is sodium metabisulphite, citr is citrate buffer, AUC is area under the curve T_{max} is minutes, C_{max} is in ng/ml, and F% is bioavailability of the intranasal formulation as compared to the intravenous formulation-- other abbreviations are as used herein above.

[00224]

Table 12A

Example Clonazepam Formulations and Pharmacokinetic Data

Formulation	PEG	TA	TC	GF	PG	Tw	Et OH	H2 O	Dose (mg)	T_{max}	C_{max}	*AUC*	F%
100% Transcutol®			100						0.191	1.4	26	*1048*	125%
30% Triacetin + 70% Transcutol®		30	70						0.201	1.1	50	*1039*	118%
30%Triac.+60%TC+10%H2O		30	60					10	0.190	1.1	29	*1165*	111%
40%PG+60%TC			60		40				0.195	2.9	45	*1182*	110%
30%TA+60%TC+10%citrate		30	60					10	0.187	1.9	31	*1130*	110%
30% Triacetin + 70% Transcutol®		30	70						0.201	3.0	39	*902*	102%
90% TC + 10% H2O			90					10	0.192	3.0	39	*1157*	109%
30%TA+60%TC+10%citrate		30	60					10	0.187	3.0	26	*938*	91%
30% TA + 60%TC + 0.2% tween + 10% citrate pH 4		30	60					10	0.191	1.4	23	*758*	91%
100% Transcutol®			100						0.191	1.6	39	*789*	94%
80% GF + 20% TC			20	80					0.212	2.7	29	*963*	83%
80% GF + 20% TC			20	80					0.212	3.3	34	*980*	84%
30%Triac.+60%TC+10%H2O		30	60					10	0.190	1.5	24	*978*	94%
50% PEG200+50% TC	50		50						0.196	1.6	44	*1105*	102%
40%PG+60%TC			60		40				0.195	3.3	24	*1021*	95%
30%TA+60%TC+10%phosph.		30	60					10	0.187	1.8	18	*826*	80%
100% Glycofurol				100					0.191	15.6	18	*876*	105%
50% GF + 50% TC			50	50					0.218	2.2	38	*1185*	99%
30%TA + 70% GF		30		70					0.191	3.4	20	*811*	77%
90% TC + 10% H2O			90					10	0.192	1.5	21	*826*	78%
95% GF + 5% Tween-20				95		5			0.190	1.4	26	*759*	73%
30%TA+60%TC+10%phosph.		30	60					10	0.187	1.4	23	*679*	66%
50% PEG200+50% TC	50		50						0.196	3.4	30	*839*	78%
10% GF + 0.2% tween + 90%	90			10					0.182	5.7	13	*642*	81%

Formulation	PEG	TA	TC	GF	PG	Tw	Et OH	H2 O	Dose (mg)	T_{max}	C_{max}	*AUC*	F%
PEG 200													
100% GF				100					0.212	3.1	18	*682*	58%
100% GF				100					0.212	1.6	20	*647*	55%
30%TA + 70% GF		30		70					0.191	5.4	15	*707*	67%
10% GF + 0.2% tween + 90% PEG 200	90			10					0.182	3.7	10	*414*	52%
10% TC + 0.2%tween + 90% PEG 200	90		10						0.193	9.9	18	*650*	77%
50%PG+20%TC+20%EtOH+ 10%citr/Tween/metabisulph			20		50		20	10	0.200	15.6	33	*1332*	84%
50%PG+20%TC+20%EtOH+ 10%citr/Tween/metabisulph			20		50		20	10	0.200	1.3	52	*1133*	72%
30%GF+60%PEG200+10%citr/Tween/metabisulph	60			30				10	0.200	3.0	16	*728*	46%
30%GF+60%PEG200+10%citr/Tween/metabisulph	60			30				10	0.200	3.5	42	*773*	49%
100% PEG 300	100								0.201	20.9	17	*690*	79%
100% PEG 200	100								0.195	3.3	15	*475*	56%
10% GF + 90% PEG 200	90			10					0.211	3.0	13	*589*	64%
10% GF + 90% PEG 200	90			10					0.211	5.6	16	*678*	73%
30% TA + 60%TC + 0.2% tween + 10% citrate pH 4		30	60					10	0.191	1.4	23	*482*	58%
10% TC + 0.2%tween + 90% PEG 200	90		10						0.193	46.4	13	*640*	76%
80%PEG200+20%TC	80		20						0.198	3.0	17	*750*	69%
10% GF+80%PEG+10%citr/Tween/ metabisulph	80			10				10	0.200	3.8	25	*840*	53%
30%GF+70%PG				30	70				0.200	4.7	28	*956*	60%
5% GF + 95% PEG 200	95			5					0.200	15.1	14	*622*	71%

Formulation	PEG	TA	TC	GF	PG	Tw	Et OH	H2 O	Dose (mg)	T_{max}	C_{max}	*AUC*	F%
50% GF + 50% TC			50	50					0.218	3.0	10	*298*	25%
70% GF+20% TC+10% H2O			20	70				10	0.214	5.3	20	*655*	56%
30%GF+70%PEG200	70			30					0.189	5.8	9	*445*	43%
30%GF+70%PEG200	70			30					0.189	15.0	14	*653*	63%
10%GF+50%PEG+30%PG+10%citr/Tween/metabisulph	50			10	30			10	0.200	3.4	25	*748*	47%
30%GF+70%PG				30	70				0.200	2.9	14	*585*	37%
30%GF+70%PG				30	70				0.200	3.4	15	*332*	21%
10% GF+80%PEG+10%citr/Tween/metabisulph	80			10				10	0.200	3.1	23	*459*	29%
10%GF+50%PEG+30%PG+10%citr/Tween/metabisulph	50			10	30			10	0.200	3.3	17	*588*	37%
100% PEG 200	100								0.195	21.3	9	*400*	47%
80%PEG200+20%TC	80		20						0.198	10.4	12	*593*	54%
100% PEG 300	100								0.201	30.4	9	*427*	49%
5% GF + 95% PEG 200	95			5					0.200	5.4	10	*297*	34%
95% GF + 5% Tween-20				95		5			0.190	44.8	10	*518*	50%
10% GF+80%PEG+10%citr/Tween/metabisulph	80			10				10	0.200	30.4	14	*636*	40%
70% GF+20% TC+10% H2O			20	70				10	0.214	60.0	6	*270*	23%

Sodium metabisulfite and citric acid were each present at less than 1% (w/w) basis in the above formulations.

[00225] Some clonazepam formulations without Transcutol® also provided a rapid rise in blood levels post-intranasal dosing including, for example, 95% GF, 5% Tween-20, 100% GF, 10%GF, 90% PEG, 100% PEG and 30% TA, 70% GF.

[00226] The pharmacokinetic data presented above illustrated that clonazepam compositions formulated for intranasal administration are pharmaceutically efficacious to deliver clinically relevant amounts of clonazepam into the bloodstream in a short time period -- making such intranasal formulations clinically useful, for example, for the treatment of seizure clusters. Such clonazepam compositions comprise, for example, one or more solvents selected from the group including, but not limited to, Transcutol®(diethylene glycol monoethylether) and similar alkylethers, propylene glycol, triacetin, Glycofurol (ethoxylated furanyl alcohol or tetrahydrofurfuryl alcohol polyethyleneglycol ether) and similar ethoxylated tetrahydrofurfuryl alcohols, as well as polyethylene glycol (e.g., PEG 200, PEG 300, etc.). However, as noted above, free PEG polymers lead to reduced stability of clonazepam formulations.

[00227] The data shown in Table 12 above were reanalyzed. The rabbit pilot PK experiments had been performed in two groups of ten animals, JC01 (Group 1) and JC02 (Group 2). The JC01 experiments were performed in a group of rabbits which were older and heavier than the JC02 group of rabbits. Each group of rabbits had their own set of intravenous clonazepam PK data for the calculations of bioavailability.

[00228] The intranasal formulations were 4 mg/mL. The animals were administered 25 μL of formulation to each nostril, 50 μL in all, with an Eppendorf dosing pipette. The animal was held in a supine position while being dosed and for about 10 seconds after. The intravenous formulation, Rivotril® injectable, was administered as 500μL injected over 30 seconds into the marginal ear vein on opposite site to the blood sampling ear. All rabbits received 0.2 mg clonazepam.

[00229] Five formulations were tested on each study day, where each of the formulations was administered to two rabbits. The data were analyzed before the composition of the formulations administered to the next group of animals was decided.

[00230] Due to the different body weights of the two rabbit groups, the C_{max} and the 60 minute AUC results from the two groups were not directly comparable. The relative bioavailability was corrected for weight differences between the two groups, based on results of the IV administrations to each group. The C_{max} was not directly comparable between the two groups, but was included in the table as a relative indication peak levels within each group.

Table 12B: Example Clonazepam Formulations and Pharmacokinetic Data

Group 1 Rabbits						
ID	Formulation	Rabbit no.	Dose (mg)	t-max	C-max	Relative BA
IV	Intravenous	21-25	0.214			100%
1	100% PEG 300	21	0.201	20.9	27.3	62%
		26	0.201	30.4	14.5	38%
2	100% PEG 200	22	0.195	3.3	26.0	44%
		27	0.195	21.3	14.6	37%
3	100% Glycofurol	23	0.191	-	-	-
		28	0.191	15.6	30.4	83%
4	100% Transcutol	24	0.191	1.4	44.6	99%
		29	0.191	1.6	64.9	74%
5	30% Triacetin + 70% Transcutol	25	0.201	3.0	64.6	81%
		30	0.201	1.1	81.5	93%
6	10% GF + 90% PEG 200	21	0.211	5.6	27.4	61%
		26	0.211	3.0	25.8	58%
7	5% GF + 95% PEG 200	22	0.200	5.4	20.2	32%
		27	0.200	15.1	27.1	65%
8	10% GF + 0.2% tween + 90% PEG 200	23	0.182	3.7	23.9	59%
		28	0.182	5.7	20.1	55%
9	30% TA + 60%TC + 0.2% tween + 10% citrate pH 4	24	0.191	3.0	48.5	90%
		29	0.191	1.4	43.5	53%
10	10% TC + 0.2%tween + 90% PEG 200	25	0.193	46.4	24.0	67%
		30	0.193	9.9	32.8	66%

Group 2 Rabbits						
ID	Formulation	Rabbit no.	Dose (mg)	t-max	C-max	Relative BA
A	IV	33+35	0.214			100%
B	100% GF	31	0.212	3.1	19.9	53%
		32	0.212	1.6	23.2	54%
C	80% GF + 20% TC	34	0.212	2.7	31.2	73%
		36	0.212	3.3	39.7	78%
D	50% GF + 50% TC	37	0.218	2.2	41.1	79%
		38	0.218	3.0	14.4	25%
E	70% GF+20% TC+10% H2O	39	0.214	5.3	25.2	51%
		40	0.214	3.2	9.5	20%
F	90% TC + 10% H2O	31	0.192	3.0	43.5	105%
		32	0.192	1.5	24.6	76%
G	30%Triac.+60%TC+10%H2O	33	0.190	1.5	30.5	84%
		34	0.190	1.1	31.1	103%
H	50% PEG200+50% TC	35	0.196	1.6	47.2	94%
		36	0.196	3.4	34.6	78%
I	80%PEG200+20%TC	37	0.198	3.0	17.9	59%
		38	0.198	10.4	14.1	53%
J	95% GF + 5% Tween-20	39	0.190	44.8	10.9	47%
		40	0.190	1.4	29.6	73%
K	30% Triacetin + 70% Glycofurol	31	0.191	5.4	17.0	69%
		36	0.191	3.4	24.9	84%
L	40%PG + 60%TC	32	0.195	2.9	51.3	111%
		37	0.195	3.3	24.2	85%
M	30%GF+70%PEG200	33	0.189	15.0	17.3	69%
		38	0.189	5.8	12.0	48%
N	30%TA+60%TC+10%citrate	34	0.187	1.9	33.7	105%
		39	0.187	3.0	30.9	94%
O	30%TA+60%TC+10%phosph.	35	0.187	1.8	19.8	76%
		40	0.187	1.4	27.9	72%

P	10% GF + 80% PEG200 + 10% citr/tween/metab	36	0.200	3.8	25	25%
		32	0.200	3.1	23	37%
		31	0.200	30.4	14	49%
Q	10% GF + 50% PEG200 + 30% PG + 10% citr/tween/metab	37	0.200	3.4	25	39%
		33	0.200	3.3	17	39%
R	30% GF + 60% PG + 10% citr/tween/metab	34	0.200	3.0	16	51%
		38	0.200	3.5	42	43%
T	30% GF + 70% PG	35	0.200	4.7	28	49%
		39	0.200	2.9	14	35%
		40	0.200	3.4	15	22%
U	50% PG + 20% EtOH + 20% TC + 10% citr/tween/metab	32	0.200	15.6	33	69%
			0.200	1.3	52	72%

Note: Tw or tween is TWEEN20, EtOH is ethanol, Triac or TA is Triacetin, phosph is phosphate buffer, metabisulph is sodium metabisulphite, citr is citrate buffer.

[00231] As exemplified in Tables 12A and 12B above, the composition may comprise a solvent matrix of two solvents, for example, a first solvent that provides high solublization of clonazepam (for example, TC or GF) that, after application to nasal mucosa, is absorbed by the nasal mucosa leading to clonazepam super saturation, and a second solvent (for example, TA or PG) in which clonazepam has lower solubility relative to the first solvent. In preferred embodiments, the compositions are substantially non-aqueous or anhydrous; however, the compositions may further comprise an aqueous component (for example, of less than about 10% aqueous content, preferably of less than about 5% aqueous content, more preferably of less than about 2% aqueous content, wherein the aqueous content is preferably buffered with a physiologically acceptable buffer to obtain a pH range of about pH 4 to about pH 7, preferably between about pH 4 to about pH 6.5). The benzodiazepine compositions of the present invention may comprise further components as well, for example, anti-oxidants (for example, sodium metabisulfite or butylhydroxytoluene (BHT). Preferred embodiments typically do not include polyethylene glycol polymers as a solvent but may include solvents like tetrahydrofurfuryl alcohol polyethyleneglycol ether (Glycofurol) wherein the solvent molecules contain polyethylene glycol polymers as an intrinsic part of their molecular structure, that is, polyethylene glycol polymers as substituent groups of a larger chemical

structure (also, see, for example, published P.C.T. International Patent Application Nos. WO 03/070273 and WO 03/070280).

[00232] The pharmacokinetics and tolerability of four clonazepam compositions comprising binary solvent systems were further evaluated. The four formulations were as follows in Table 13.

[00233]

Table 13

Compositions of binary solvent systems (10 mg/mL clonazepam)

Composition	Solvent System
I	50% diethyleneglycol monoethylether + 50% triacetin
II	50% diethyleneglycol monoethylether + 50% propylene glycol
III	50% glycofurol + 50% triacetin
IV	50% glycofurol + 50% propylene glycol

[00234] The pharmacokinetics of the formulations in Table 13 were evaluated by nasal administration to rabbits and compared to intravenous (i.v.) administration of clonazepam in rabbits. Sample size for each formulation was N=10 with instillation of 10 mg/mL clonazepam dose adjusted to body weight. A summary of the data is presented in Figure 5.

[00235] The data is further summarized in Table 14.

Table 14

PK Data for Selected Formulations

Formulation		Dose (mg)	T_{max}	C_{max}	AUC	Bioavail.
I	50%TC+50%TA	0.214	20.3	9.02	462	43%
II	50%TC+50%PG	0.214	3.51	24.31	704	66%
III	50%GF+50%TA	0.214	3.24	10.14	454	43%
IV	50%GF+50%PG	0.214	3.26	19.34	604	57%
Intravenous	Injected Rivotril	0.214	1.70	49.70	1061	100%

[00236] The intranasal PK profiles of the formulations presented above demonstrated a rapid absorption of clonazepam such that clinically relevant amounts of clonazepam reach the bloodstream in a short period of time. Short-term bioavailability does not necessarily

need to be high; it is of higher importance that the blood levels become high in as short a time as possible. Lower bioavailability can be balanced out, for example, with higher dose. An advantage of a higher dose and low short term bioavailability may be passage of the drug that is not absorbed intranasally into the gastro-intestinal tract resulting in the remainder of the drug undergoing classical GI absoprtion leading to a sustained release profile.

[00237] As can be seen from the PK data in rabbits, benzodiazepine compositions of the present invention formulated for intranasal delivery may be characterized, for example, by a T_{max} of benzodiazepine, after a single intranasal administration (in one or both nostrils), of 2 hours, often less than 1 hour likely less than 30 minutes or less than 15 minutes. Further, pharmaceutical compositions of benzodiazepines for intranasal delivery, as described herein, may be characterized, for example, by providing at least one of a mean maximum plasma concentration (C_{max}) of benzodiazepine of at least about 3.0 ng/mL or at least about 15% of the concentration of an intravenously delivered dose often 30% of an intravenously delivered dose or 50% or an intravenously delivered dose, and a mean plasma Area Under the Curve over 60 minutes (AUC) value of clonazepam of at least about 400 ng-hr/mL, when a single dose of the composition is administered intranasally to deliver a dose of at least about 0.2 mg of clonazepam. Further, the bioavailability of benzodiazepine compositions of the present invention, after intranasal administration, is typically greater than 30% often greater than 40% and frequently greater than 50% of that of intravenous administration.

[00238] In addition to the PK parameters discussed above, the experiments performed in support of the present invention evaluated the local tolerance in the upper and lower respiratory tract of formulations I-IV containing clonazepam as active drug. This tolerance was assessed in the rabbit as model. Treatments were performed during seven consecutive days before histopathological evaluation of selected tissues.

[00239] The rabbits used in these experiments were as follows: Breed, New Zealand White; Sex, 30 males and 30 females; Weight, Mean body weight 2.466 ± 0.093 (SD) kg for the male rabbits, 2.465 ± 0.114 (SD) kg for the female rabbits. Animals showing any concurrent disease at the time of the treatment were not included. Rabbits were obtained from Charles River Laboratories, L'Arbresle Cedex, France.

[00240] Animals were weighed during the acclimatisation period for allocation, within the 3 days prior to treatment and just before slaughter. The dose-level of 10 mg/mL (1 mg clonazepam in 100 µL solution) was selected to be comparable to an anticipated dose to be administered in humans.

[00241] The treatment groups are detailed in Table 15. Formulation 5 is a vehicle control -- 50 % glycofurol; 50 % propylene glycol (with no clonazepam). Formulation 6 is a saline control (0.9% NaCl in water).

Table 15

Allocation of treatments into groups

Group	Treatment	Number of animals	Concentration of Clonazepam (mg/mL)	Number of treatments
1	Formulation I TC/TA+	5 males 5 females	10	7
2	Formulation II TC/PG+	5 males 5 females	10	7
3	Formulation III GF/TA+	5 males 5 females	10	7
4	Formulation IV GF/PG+	5 males 5 females	10	7
5	Formulation 5 GF/PG-	5 males 5 females	0	7
6	Formulation 6 S-	5 males 5 females	0	7

[00242] The selected route of administration was the route of administration of the final product.

[00243] Whatever the formulation, 0.1 mL of the formulation was daily administered to all animals by nasal instillation during seven consecutive days.

[00244] All administrations were performed in the right nostril using a 1 mL pipette (B13, Adjustable pipettes Pipetman P200 from Gilson) fitted with a plastic cone. The required volume of item was measured with the pipette and placed just inside the nostril of the animal.

[00245] Treatment details were recorded in the raw data including dose administered, formulation identification, date and time of administration.

[00246] Six animals per group, three males and three females at Day 8, and the remaining animals at Day 15, after a seven-day recovery period, were sacrificed by ex-sanguination from abdominal aorta under isoflurane anaesthesia.

[00247] Following euthanasia, macroscopical examination of larynx, trachea, bronchi, lungs and oesophagus were performed.

[00248] The head of the animal, with the larynx and specimens of trachea, bronchi, lungs and oesophagus were taken at necropsy and fixed in formalin for histopathology.

[00249] From head, nasal mucosa, turbinates, in addition to larynx and trachea were sampled after specific preparation and examined. Any observed macroscopic abnormalities or lesions were also sampled and fixed, with a border of surrounding tissue, for histopathology.

[00250] Nasal mucosa and turbinates were examined in the nasal cavities on three head sections corresponding to nasal cavities proximal, nasal cavities turbinates and nasal cavities olfactory.

[00251] Histopathological examinations were performed and the results evaluated by a pathologist. All results were tabulated per group, means and standard deviations were calculated on each organ. Statistical comparisons were performed between group using ANOVA. There were no obvious differences in growth between groups.

[00252] Severity of the eventual modifications observed in the histological preparations were scored by the pathologist as follows: 0, no lesions; 1, slight; 2, moderate; and 3, severe.

[00253] Figure 6 summarizes the histopathology results for the nasal cavities of the animals. Severity scores in group 3 was statistically higher than scores of groups 4, 5 and 6 ($p=0.003$). Irritative modifications like erosion and fibrino-leucocytic material in turbinates lumen were observed mainly in group 3 (2/3 females and 1/3 males), also for group 1 (1/3 females) and group 5 (2/3 males) but not for other treated or control groups. These modifications were not observed in necropsy on day 15. Mild epithelial atrophy on turbinates was noted in necropsy on day 8 and also in necropsy on day 15 mainly for treated

group 1 and slighter for other treated groups. Control group 6 showed no epithelial atrophy. Blood was sometimes observed in aerian lumen for larynx and also nasal cavities both in treated and control groups and are probably of traumatic origin. The best local tolerance was observed for treated group 2 and 4. These results indicate generally good nasal tolerance for the tested formulations.

[00254] Blood or petechia were found in larynx on 15 animals (2 from group 1, 4 from group 2, 3 from group 3, 2 from group 4, 4 from group 5) during necropsy and on 6 animals (1 from group 2, 2 from group 4, 3 from group 5) at histopathology examination. Table 16 presents mean and SD severity scores in each group.

Table 16

Mean and SD severity score on larynx in each group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Mean score	0.0	0.1	0.0	0.2	0.3	0.0
SD	0.0	0.3	0.0	0.4	0.5	0.0

Slight epithelial desquamation were observed on oesophagus from two animals from group 4. Table 17 presents mean and SD severity scores in each group.

Table 17

Mean and SD severity score on oesophagus in each group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Mean score	0.0	0.0	0.0	0.2	0.0	0.0
SD	0.0	0.0	0.0	0.4	0.0	0.0

[00255] Petechia or blood were observed during necropsy on 17 animals (4 from group 1, 3 from group 2, 5 from group 3, 1 from group 4, 4 from group 5). No histopathological lesions were observed in bronchi and trachea.

[00256] Lung modifications were observed during necropsy on 17 animals (1 from group 1, 3 from group 2, 3 from group 3, 1 from group 6). Congestive foci were histologically recorded on two animals from group 2 at Day 15. Table 18 presents mean and SD severity scores in each group.

Table 18

Mean and SD severity score on lungs in each group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Mean score	0.0	0.2	0.0	0.0	0.0	0.0
SD	0.0	0.4	0.0	0.0	0.0	0.0

[00257] Considering the whole respiratory tract, microscopical lesions were mainly observed in the very upper part, the nasal cavities. As no lesions were recorded in the control group, it is likely that all the lesions were related to the treatments. Petechia recorded at necropsy and presence of blood observed during histopathological examination can be due to a trauma induced by the treatment. In the majority of animals (20 out of the 26 presenting petechia or blood at necropsy), lesions recorded at necropsy were associated with histopathological findings. Irritative lesions were observed just after treatment and were not present after a one week recovery. Mild epithelial atrophy was observed after a one week recovery. Considering severity scores, formulation 3 induced significantly the most severe lesions. Local tolerances of the other formulation were nearly similar.

[00258] In conclusion, the results of necropsy and histopathological examination, including comparison of severity scores, suggested that the clonazepam compositions of the present invention comprising formulations for intranasal delivery have acceptable tolerability for pharmaceutical use.

Example 6

Sprayability and Viscosity of Solvent Matrices

[00259] Fourteen representative solvent matrices used for clonazepam formulations were tested for spray pattern and compared with water. The solvent mixtures were made up, spiked with minute amounts of Coomassie Brilliant Blue Dye and 100 µL were subsequently filled into Pfeiffer unit-dose devices (Pfeiffer of America, Princeton, NJ). To measure the spray pattern, the devices were actuated below a sheet of paper that was located 3 cm above the spray nozzle. All measurements were made at ambient room temperature (20-25°C). The smallest (D_{min}) and the largest (D_{max}) diameter of the blue pattern formed on the sheet of paper were measured and the results used to calculate the D_{max}/D_{min} ratio, the area of the

pattern and the average spray angle. The plume area at 3 cm was calculated using the equation for the area of an ellipse using the half of the two diameters as the ellipse radii. Viscosity of all formulations was measured using Brookfield DV-I viscometer (Brookfield Engineering Laboratories, Inc., Middleboro, Massachusetts). The results from the measurements are shown in Table 19. Table 19 presents data related to sprayability and viscosity of solvent mixtures used in clonazepam formulations. Viscosity, plume area at 3 cm, spray angle and D_{max}/D_{min} ratio reflecting the symmetry of the spray plume are presented.

Table 19

Sprayability and Viscosity

Composition	Avg. viscosity (cP)	Plume area at 3 cm (cm^2)	Spray angle (°)	Ratio D_{max}/D_{min}
80% Glycofurol + 20% Transcutol®	11.5	5.93	49.2	1.07
50% Glycofurol + 50% Transcutol®	7.4	8.45	57.3	1.04
95% Glycofurol + 5% H_2O	16.7	5.73	48.6	1.22
70% Glycofurol + 30% Triacetin	14.6	5.78	48.7	1.12
60% Transcutol® + 30% Triacetin + 10% H_2O	5.8	8.71	58.1	1.03
60% Transcutol® + 40% Propylene glycol	8.8	6.42	51.0	1.11
70% PEG200 + 30% H_2O	20.6	4.07	41.6	1.14
80% PEG200 + 20% H_2O	30.0	4.10	43.3	2.04
90% PEG200 + 10% H_2O	41.7	2.46	33.6	1.79
80% PEG200+10% GF+10% H_2O	42.8	3.21	39.2	2.07
50% PEG200+30% PG+10% GF+10% H_2O	35.4	4.55	44.9	1.54
60% PG+30%GF+10% H_2O	23.3	4.92	46.3	1.79
70% PG + 30% GF	31.7	4.32	43.1	1.22
Water	1.0	15.52	73.1	1.10

[00260] While water had a viscosity of 1.0 cP the solvent mixtures tested range from 5.8 (60% Transcutol® + 30% Triacetin + 10% H_2O) to 42.8 cP (80% PEG200+10% GF+10% H_2O). The viscosity of the solvent mixtures had a negative correlation with plume area and spray angle and plume asymmetry as shown in Figure 7, Figure 8 and Figure 9.

[00261] From the data shown in Table 19, Figure 7, and Figure 8 it is evident that the spray angle became smaller with increasing viscosity of solvent matrix in the standard Pfeiffer Unit-dose devices. Figure 9 shows that the plume asymmetry remained within the range 1.0 to 1.2 up to solution viscosity about 20 cP above which irregularity in the plume shape increased. Visual inspection of the appearance of the spray plume of three solutions in the viscosity range from 5.8 to 41.7 revealed that a plume was formed and none of them "squirted."

[00262] These results demonstrated that at 20-25°C all solvent matrices tested spray well from Pfeiffer unit dose devices. The results also suggested that viscosity is a good predictor of sprayability for the formulations of the present invention. As weather may dictate substantially different conditions of use, the effect of temperature on viscosity was determined. A Gilmont falling ball viscometer was filled with diethylene glycol monoethyl ether and calibrated for several hours at each temperature. At -17°C, 8°C, 23°C and 40°C the measured viscosity was 6.6 cP, 5.4 cP, 3.8 cP and 3.1 cP, respectively. Hence, with relatively low dependence of temperature on viscosity, the 100% transcutol formulation can be expected to exhibit good spray characteristic over a wide range of temperatures below 40°C and at least about -15°C to 30°C.

Example 7

Example Compositions, Formulations, and Method of Making

[00263] In one aspect the present invention relates to benzodiazepine compositions formulated for intranasal administration. Unit dosages typically have a volume of between about 25 μL to about 150 μL, preferably about 100 μL. A unit dosage of clonazepam, for example, for the treatment of seizure clusters, is between about 0.1 mg to about 5 mg,

preferably about 1 mg to about 4 mg. Table 20 presents example formulations for nasal administration dosage forms. These example formulations provide 10 mg/mL clonazepam.

Table 20

Composition of Solution Formulations (%w/w)

General Component	Specific Component	Formulation I	Formulation II	Formulation III	Formulation IV
Solvent 1 (high solubli-zation of clonaze-pam	diethylene-glycol monoethyl-ether	49.5	49.5	--	--
	glycofurol	--	--	49.5	49.5
Solvent 2 (low clonaze-pam solubility)	propylene glycol	--	49.5	--	49.5
	triacetin	49.5	--	49.5	--
Drug	Clonazepam	1.0	1.0	1.0	1.0
Total		100	100	100	100

[00264] The following methods of making example compositions of the present invention are generally presented and can be modified by one of ordinary skill in the art in view of the teachings of the present specification. Exemplary dosage forms and methods of manufacturing are generally described.

[00265] The desired amount of clonazepam was dissolved in solvent 1 at ambient temperature with stirring until the solution is clear and homogeneous. Solvent 2 was then added and the solution was stirred until homogeneous.

[00266] Exemplary formulations of the present invention include, but are not limited to, a final concentration of between about 1 w/w% to about 20 w/w% clonazepam, between about 30 w/w% to about 70 w/w% solvent 1, and between about 70 w/w% and about 30 w/w% of solvent 2. Further components may be added as discussed herein above and w/w% composition of the components modified accordingly.

[00267] A typical target dose of intranasal clonazepam is 1 to 2 mg per unit dosage. Normally, 1 mg clonazepam (Rivotril i.v.) is administered intravenously by a health care professional in acute epileptic seizure attack. This could be achieved by intranasally

administering, for example, 100 μL of a 10 mg/mL solution with 100% bioavailability, a 13.3 mg/mL solution with a 75% bioavailability, or a 20 mg/mL formulation with 50% bioavailability.

[00268] Unit or multiple doses may be dispensed into an appropriate delivery device, for example, fixed volume metered dose devices. Devices for intranasal delivery of pharmaceuticals are known in the art (for example, manufactured by Pfeiffer of America, Princeton, N.J. and Valois of America Inc., Greenwich, CN). Devices that have the ability to consistently deliver the pharmaceutical composition of the present invention are preferred. Such devices are operable by a patient or second party, for example, medical personnel. Further, these devices leave virtually no residual clonazepam in the device after use. Accordingly, the device can be easily discarded.

[00269] Intranasal delivery devices may be modified, for example, by increasing the size of the discharge orifice in the nose piece of the applicator in order to achieve appropriate spray plume and nasal penetration. For example, a discharge orifice of about 0.07 mm may be used to accommodate higher viscosity compositions. The intranasal delivery device components may also be sterilized by methods known in the art. However, as the compositions of the present invention are anhydrous, dry heat, aseptic filtering or terminal sterilization may be necessary. However, if the formulation is microcidal, sterilization or aseptic filling will likely not be needed (see Example 3 above)

[00270] Intranasal delivery devices may be filled with single or multi-dose amounts of benzodiazepines. Devices with one or more unit-dose(s) may be sterilized employing methods and technology known in the art. Intranasal delivery devices comprising the benzodiazepine compositions of the present invention may further be sealed with a tamper-proof seal. In addition, appropriate child-proofing control means may also be added to the devices.

[00271] The benzodiazepine compositions of the present invention may be packaged under nitrogen in order to reduce oxidative damage to the clonazepam or to the excipients. Similarly, the manufacturing process may also be carried out under limited oxygen conditions.

Example 8

Human Pharmacokinetic Study

[00272] The human pharmacokinetics, safety, and tolerability of the benzodiazepines compositions of the present invention formulated for intranasal delivery for therapeutic applications are evaluated using standard clinical procedures. Benzodiazepine compositions formulated for intranasal delivery are provided, for example, for application by the participants to intranasal mucosa.

[00273] A primary objective of initial studies in humans is to determine and compare pharmacokinetic profiles of three dosage forms of a benzodiazepine: oral, i.v., and intranasal, following single administration. An example of such a study in humans is a cross-over study performed in 12 healthy male volunteers. Plasma and urine level of clonazepam and 7-amino-clonazepam are determined, for example, using HPLC and UV detection. Secondary objectives of such a study include determination of safety and tolerability of the intranasal clonazepam formulations of the present invention and evaluating their pharmacodynamic effects using qEEG mapping (see, e.g., Example 9, below). Further the initial studies in humans are used to determine local tolerability of intranasal formulation using questionnaire and the Visual Analog Scale (VAS). VAS is a validated instrument that has been used in numerous studies to quantify subjective opening of the nasal passages. In addition, cognitive, sleepiness and mood effects are evaluated using questionnaires and scales (see, e.g., Example 10 below). Further, attention and vigilance may be evaluated using, for example, LEEDS Psychomotor Multiple Choice Reaction Time (MCRT) testing.

Example 9

qEEG Mapping

[00274] EEG profiles are determined for patients dosed intranasally with benzodiazepine compositions of the present invention. Vehicle controls without clonazepam may also be administered. Standard frequencies of the EEG bands are as follows: delta (0.5-305 Hz); theta (4-7.5 Hz); alpha (8-12.5 Hz); and beta (13-32 Hz). The latter two are divided into sub-bands as follows: alpha 1 (8-9.5 Hz) and alpha 2 (10-12.5 Hz); and beta 1 (13-17.5 Hz), beta 2 (18-20.5 Hz), and beta 3 (21-32 Hz)

[00275] The functional correlates of the EEG bands are as follows: delta, sedative potential; theta, cognition; alpha, vigilance/attention; and beta, arousal/anxiety. Increases in beta bands have been shown to be correlated with subjective anxiolysis (Ansseau, M., et al., "Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam," Neuropsychobiology 12(4):255-9 (1984).

[00276] As a control clonazepam may be administered i.v. at selected doses. Placebo is also administered i.v.

[00277] Interkinetic map (absolute energy) of EEG parameters relative to time after administration of clonazepam versus placebo are obtained.

[00278] Sedation effects may also be evaluated using, for example, the Stanford sleepiness scale.

[00279] These results are expected to support the use of clonazepam compositions formulated for intranasal administration for pharmaceutical applications, for example, for treatment of seizure clusters wherein a rapid onset of anti-convulsive effect is seen with minimal adverse effects (such as minimal increases in sedation).

Example 10

Cognitive Effects of Benzodiazepines

[00280] This example describes the pharmacodynamic effects of benzodiazepine compositions formulated for intranasal administration using neurocognitive tests. A selection of tests from a computerized assessment system of Cognitive Drug Research ("CDR," Reading, United Kingdom) is employed. The study is typically a double-blind, randomized, placebo-controlled cross-over design. As a control, the group may receive benzodiazepine intravenous (i.v.) and placebo at selected dosages.

[00281] Cognitive function is typically assessed using an attentional task battery to assess attention and a word recognition task to assess secondary memory. Following training on the cognitive test procedures at screening and on Day −1, CDR assessments are typically completed at pre-dose and 30, 60, 90, 120 and 180 minutes post-dose on Day 1 of each period. The attentional task battery and the Word Recognition task from the CDR

computerized cognitive assessment system are administered. Parallel forms of the tasks are presented at each assessment to allow for repeated assessment by presenting different, but equivalent stimuli.

[00282] Tests may be administered, for example, in the following order: Word Presentation; Simple Reaction Time; Digit Vigilance; Choice Reaction Time; and Word Recognition. Two composite scores were generated from the collected data: Power of Attention, the speed measures from the three attentional tasks all strongly load on a single factor; and Continuity of Attention, the accuracy measures from the attentional tasks Choice Reaction Time and Digit Vigilance both reflect the ability of the subject to sustain attention and avoid error. Summary statistics (n, number; mean; sem, standard error; sd, standard deviation; median; min, minimum; max, maximum; and missing) are typically calculated for each measure at each time point by dose. For each measure, pre-dose (baseline) data is subtracted from the data at each post-dosing time to derive 'difference from baseline' scores. Figures (mean ± sem) are plotted using the unadjusted scores and derived 'difference from baseline' scores.

[00283] Repeated measures analysis of covariance (ANCOVA) are conducted on the data using, for example, SAS PROC MIXED. Fixed terms are fitted to the model for sequence, dose, period, time and the dose*time interaction. A random effect of subjects within sequence are fitted to the model. Pre-dose (baseline) scores are used as a covariate. Significance is typically tested at the 0.05 level.

[00284] For the majority of measures, the selected therapeutic doses of benzodiazepines are expected to show little statistical support for significant impairments. Benzodiazepines are expected to show a pattern of dose dependent impairment of cognition (attention and secondary memory). The size and duration of the impairment will be determined with increasing dose of the benzodiazepine.

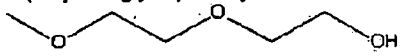
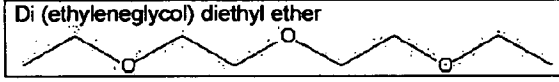
Example 11

Solubility of Clonazepam in Glycol Ethers at 25°C

[00285] A number of glycol ether solvents are believed to be acceptable for solubilizing benzodiazepines in intranasal applications. Four glycol ethers were compared, as shown in the table below.

Table 21

Glycol Ethers

#	Name	CAS	Common	Density
1	1,2-dimethyxoethane 	110-71-4	monoglyme	0.867
2	Di (ethylene glycol) methyl ether 	111-77-3	methyl carbitol	1.023
3	Diethylene glycol monoethyl ether 	111-90-0	Carbitol DEGEE	0.999
4	Di (ethyleneglycol) diethyl ether 	112-36-7	Diethyl carbitol	0.909

[00286] 10 mg of clonazepam was weighed into glass vials used in the Pfeiffer mono-dose spray system (Pfeiffer of America, Princeton, NJ). Four samples of each of four solvents were prepared as follows. 130-μL of each solvent was pipetted into the vial, which was then stoppered with a black chlorobutyl rubber stopper. The samples were then sonicated for 10 minutes and two of each was stored at 25C for at least 12h.

[00287] The vials were removed from the chamber, placed inside polyethylene centrifuge vials, and centrifuged for 2 minutes at 5000 rpm. 10 μL of liquid was then sampled from each vial, accurately weighed, and diluted with 1 mL of acetonitrile. The drug concentration was analyzed by UV using an Agilent HPLC system with no column, 10 μL injection volume, acetonitrile mobile phase, 0.3 mL/min and UV detection at 350nm. The solubilities were calculated from peak area based on calibration with blank and standard solutions, and are shown below.

Table 22

Solubilities of Clonazepam in Glycol Ethers

Solvent	Solubility at 25C, mg/mL
1,2-dimethyxoethane	39.3
Di (ethylene glycol) methyl ether	56.4
Diethylene glycol monoethyl ether (DEGEE)	41.8
Di (ethyleneglycol) diethyl ether	19.0

Example 12

Solubilities of Clonazepam in Glycol Ethers at 3 Temperatures

[00288] Samples were prepared using procedures of Example 11 (25°C solubilities, included in table below for reference). The samples were stored in the refrigerator or freezer for at least 12 hours, and precipitate had substantially settled. The vials were then centrifuged at -5°C and 5°C for the -15°C and 5°C samples, respectively, at 5000 rpm for 2 minutes. The solubilities shown below indicate very little temperature dependence on solubility between 25°C and -15°C for clonazepam in these glycol ethers. These compositions could be stored at temperatures up to 30°C and down to -15°C and retain their stability.

Table 23

Solubilities (mg/mL) of Clonazepam in Glycol Ethers

Solvent	-15C	5C	25C
1,2-dimethyxoethane	35.2	35.7	39.3
Di (ethylene glycol) methyl ether	58.1	53.9	56.4
Diethylene glycol monoethyl ether	43.3	37.7	41.8
Di (ethyleneglycol) diethyl ether	19.5	18.5	19.0

Example 13

Solubilities of Clonazepam in Water-Containing Solvents

[00289] The samples from Example 11, after completing the solubility measurement in 100% solvent, were partly pipetted into another set of glass vials (Pfeiffer mono-dose vials) and mixed with varying proportions of pH6.8 buffered water to form 120μL aqueous mixtures of 20% to 80% glycol ether. All samples immediately showed precipitation. The vials were stored at 25°C for approximately 1 day. Prior to sampling, the vials were centrifuged at 5000 rpm for 2 minutes at 23°C. The results are shown below; neat solvent solubilities from Example 11 are included for reference. Increased water content decreases solubility substantially.

Table 24

Solubilities (mg/mL) of Clonazepam in Solvent/Water Solutions

%Solvent	100	80	60	40	20
Solvent %Water	0	20	40	60	80
1,2-dimethyxoethane	39.3	29.6	9.2	0.64	0.18
Di (ethylene glycol) methyl ether	56.4	18.9	2.8	1.00	0.26
Diethylene glycol monoethyl ether	41.8	21.8	4.5	0.52	0.30
Di (ethyleneglycol) diethyl ether	19.0	38.8	8.5	1.23	0.31

Example 14

Human Pharmacokinetic Study Results

[00290] A human pharmacokinetic study was carried out as described in Example 8.

[00291] 15 young, healthy male volunteers received a single dose of 1 mg clonazepam by oral, intravenous and intranasal routes in a three-period cross-over design. The intranasal formulation of clonazepam produced its median T_{max} at 0.200 hours (approximately 12 minutes) post-dose while the median T_{max} was 2 hours after oral administration and the median T_{max} following intraveneous administration was 0.10 hours.. The mean C_{max} values after administration of 1mg of clonazepam by the oral, intranasal routes were comparable (intranasal route: mean±SD, 7.12±3.81 ng/mL and oral route: mean±SD, 7.64±1.74 ng/mL; and intravenous route: mean±SD, 42.5±10.8). Accordingly, C_{max} of the intranasal route was 93% of that of the oral route and 17% of that of the intravenous route.

[00292] AUCs at 24 hours after administration of 1 mg of clonazepam were similar for the intravenous and oral routes (approximately 106 and 95 ng·h/mL, respectively), while the AUC at 24 hours after intranasal administration (approximately 58 ng·h/mL) was roughly

half that observed after intravenous administration. Accordingly AUC_{in}:AUC_{iv}=1:1.83 and AUC_{in}:AUC_{oral}=1:1.64 and the bioavailability was 55% relative to intravenous and 61% relative to oral.

[00293] Somnolence and nasal discomfort were the most common side effects reported in the study (75.6% and 26.7%, respectively). Somnolence was reported by 10 of 15 (approximately 67%) subjects after intranasal dosing and 13 of 15 (approximately 87%) subjects after oral dosing. Approximately 93% of the subjects reported somnolence or sedation (11/15 for somnolence and 3/15 for sedation) after intravenous dosing. Nasal discomfort was reported by 12 of 15 subjects (approximately 80%) after intranasal dosing. There were no clinically relevant changes in laboratory parameters,

[00294] After administration of 1 mg of clonazepam, 7-Amino-clonazepam concentrations increased continuously over the 24-hour blood sample collection period for all three routes of administration. The mean C_{max} for the intranasal route (1.17 ng/mL) was lower than values observed for the intravenous and oral routes. The mean C_{max} was similar for the intravenous and oral routes (approximately 2 ng/mL). The mean AUC_t for the intranasal route (16.9 ng·h/mL) was lower than values observed for the intravenous and oral routes. The mean AUC_t was similar for the intravenous and oral routes (approximately 30 ng·h/mL).

Example 15

qEEG Mapping Results

[00295] EEG profiles were determined as described in Example 9 for the 15 volunteers described in Example 14. Based on changes from baseline, clonazepam produced EEG changes characteristic of benzodiazepines. Effects were greatest after intravenous administration, followed by intranasal and oral routes of administration. Statistically significant differences between routes of administration occurred at different time points, indirectly demonstrating different time courses for different effects. In general, clonazepam administration by all three routes increased delta and beta activity and decreased alpha and theta activity on the EEG. This pattern of activity was noted soon after administration of clonazepam by the intranasal and intravenous routes (i.e., within the first 3 to 6 minutes after dosing) and occurred later after oral administration (at approximately 2 hours after dosing).

[00296] A post-hoc analysis focusing on the time course of effects for beta-1 relative power established that intranasal administration of clonazepam is efficient, with a magnitude of effect similar to that from oral administration and an intermediate time delay of action between the intravenous and oral routes. Together with the EEG profile in the delta, theta, and alpha bands from mapping analysis, these results are in agreement with previous pharmacodynamic changes reported with various benzodiazepine drugs.

Example 16

Cognitive Effects of Clonazepam

[00297] Psychomotor and subjective test results were obtained as described in Example 10 for the 15 volumteers described in Example 14. Intranasal clonazepam spray was shown to possess a rapid onset of action comparable to the intravenous formulation on objective tests (Leeds Psychomotor Test) and subjective tests (Bond and Lader VAS and Karolinska Sleepiness Scale). Effects with intravenous and intranasal administration were first apparent at approximately 30 minutes while effects with oral administration were first apparent at approximately 2 hours.

We claim:

1. A pharmaceutical composition for transmucosal administration to a mammal, comprising

a solvent system comprising a first solvent in which benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which clonazepam in less soluble than in the first solvent, wherein the solvent system comprises 10% (weight/weight) or less of an aqueous buffer solution with the caveat that the solvent system does not comprise free polyethylene glycol polymers; and

a therapeutically effective amount of a benzodiazepine.

2. A pharmaceutical composition for transmucosal administration to a mammal, comprising

a solvent system comprising an alkyl ether solvent in which clonazepam is soluble, the solvent capable of penetrating nasal mucosal tissue, and

a therapeutically effective amount of benzodiazepine,

wherein the composition is a single phase and homogeneous.

3. The composition of claim 1, wherein the first solvent is diethylene glycol monoethylether or tetrahydrofurfuryl alcohol polyethyleneglycol ether.

4. The composition of claim 1, wherein the first solvent is present at a weight percent of between about 30% to about 70%.

5. The composition of claim 4, wherein the second solvent is glycerol triacetate or propylene glycol.

6. The composition of claim 1 or 2, wherein the benzodiazepine is selected from the group consisting of alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, ketazolam,

loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, tetrazepam, and triazolam.

7. The composition of claim 6, wherein the benzodiazepine is selected from the group consisting of lorazepam and diazepam.

8. The composition of claim 1 or 2, further comprising one or more components selected from the group consisting of surfactant, anti-oxidant, pharmaceutically acceptable polymer, polyalcohol, lipid, mucosa penetration enhancing agent, colorant, flavoring agent, anesthetic agent, co-solvent, and agent to adjust osmolarity.

9. The composition of claim 1 or 2, wherein the composition is formulated to be sprayable between -15°C and 30°C.

10. The pharmaceutical composition of claim 2 wherein the alkyl ether solvent is selected from the group consisting of 1,2-dimethoxyoethane, di(ethylene glycol) methyl ether, diethylene glycol monoethylether and di(ethyleneglycol) diethyl ether.

11. The pharmaceutical composition of claim 10 wherein the alkyl ether solvent is diethylene glycol monoethylether.

12. The pharmaceutical composition of claim 8 wherein the antioxidant is butylhydroxytoluene at a concentration of 100 to 3000 ppm.

13. The composition of claim 1 or 2, wherein the composition is used at a unit therapeutic dose of between about 50 μL and 300 μL or between about 25μL.and 150μL.

14. The composition of claim 7, wherein the therapeutically effective amount of diazepam is between 2.0 mg and 40 mg per unit dose.

15. The composition of claim 7, wherein the therapeutically effective amount of lorazepam is between 0.5 mg and 10 mg per unit dose.

16. A pharmaceutical composition comprising a benzodiazepine for transmucosal administration to a mammal, characterized by (i) a T_{max} of the benzodiazepine, after a single transmucosal administration, of no more than 2 hours and (ii) a bioavailability of the benzodiazepine, after a single transmucosal administration, of no less than 30% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

17. The composition of claim 16 wherein the T_{max} of the benzodiazepine, after a single transmucosal administration, is less than or equal to 30 minutes and the bioavailability of the benzodiazepine, after a single transmucosal administration, is greater than or equal to 55% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

18. A pharmaceutical composition comprising a benzodiazepine for transmucosal administration to a mammal, characterized by (i) a C_{max} of the benzodiazepine, after a single transmucosal administration, of at least about 75% of the C_{max} of an equivalent dose of the benzodiazepine delivered orally, and (ii) a bioavailability of the benzodiazepine, after a single transmucosal administration, of no less than 30% of the bioavailability of an equivalent dose of clonazepam delivered orally.

19. The composition of claim 61 wherein the C_{max} of a benzodiazepine, after a single transmucosal administration, greater than or equal to 90% of the C_{max} of an equivalent dose of the benzodiazepine delivered orally, and a bioavailability of the benzodiazepine, after a single transmucosal administration, is greater than or equal to 55% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

20. The composition of claim 16, 17, 18 or 19 wherein the transmucosal delivery is via the intranasal route.

21. A pharmaceutical composition comprising a benzodiazepine for intranasal administration to a mammal, characterized by (i) a ratio of the AUC of the benzodiazepine, after a single intranasal administration, (AUC_{in}) to the AUC of an equivalent dose of the benzodiazepine delivered orally (AUC_{oral}) of at least about AUC_{in}:AUC_{iv} = 1:1.33, wherein the AUC values are determined over the same time period.

22. A method for administering an active agent to a mammal in need thereof, the method comprising:

delivery of a benzodiazepine to the mammal's bloodstream via nasal mucosa of the mammal, wherein the benzodiazepine is delivered in a dosage form comprising a composition of claims 1 - 21.

23. The method of claim 22, wherein the mammal is suffering from seizure clusters and delivery occurs at the onset of the symptoms of seizures or wherein the mammal is suffering from anxiety states selected from the group consisting of to panic attacks, social phobia, social anxiety and performance anxiety.

24. A method of manufacturing a benzodiazepine composition, comprising

mixing the solvent system and the benzodiazepine of any of claims 1-21 to provide a single-phase, homogeneous solution suitable for intranasal administration of the benzodiazepine.

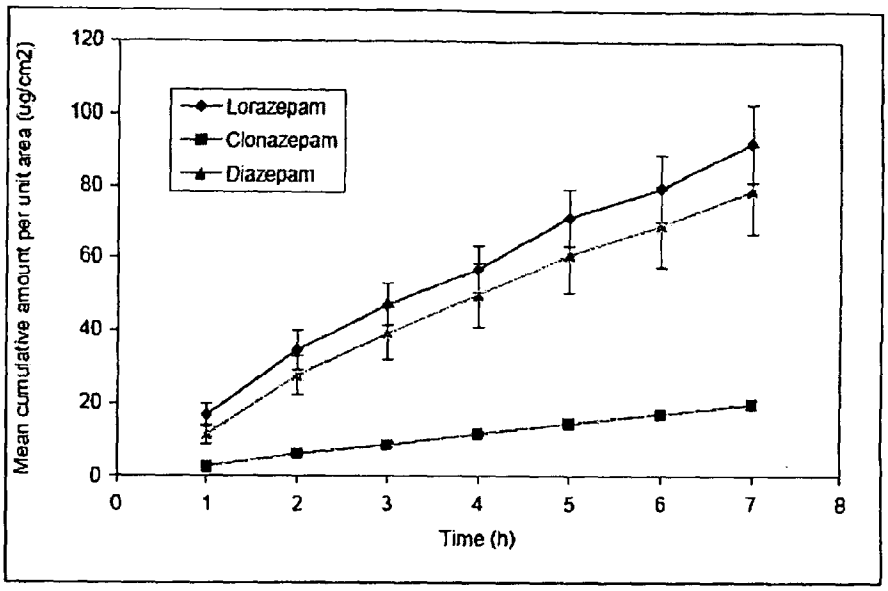


FIGURE 1

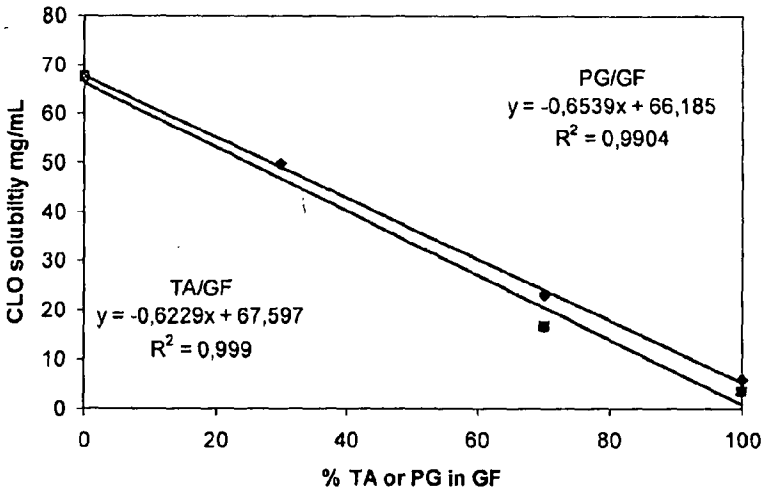


FIGURE 2

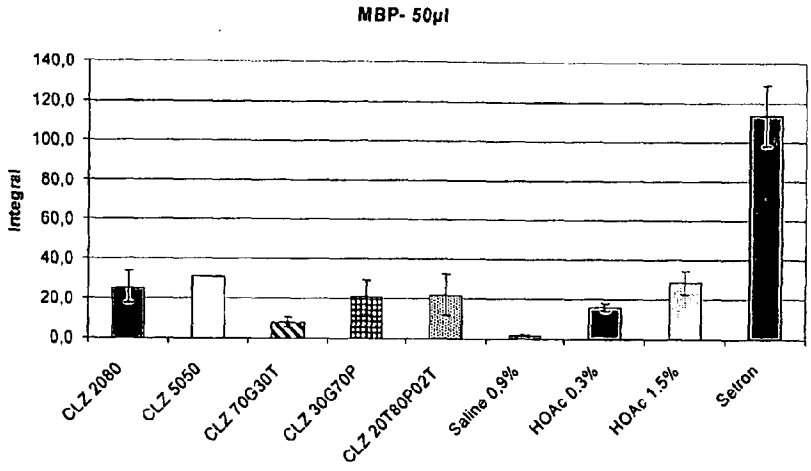


FIGURE 3

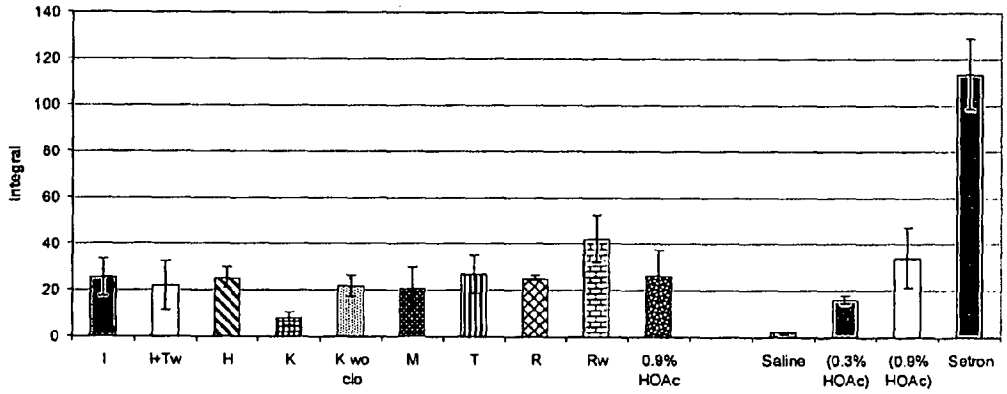


FIGURE 4

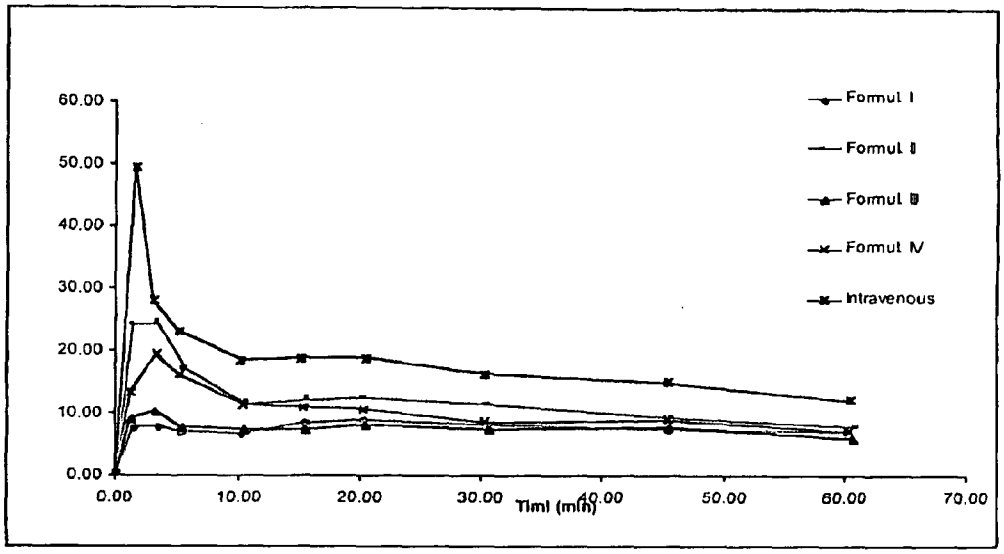


FIGURE 5

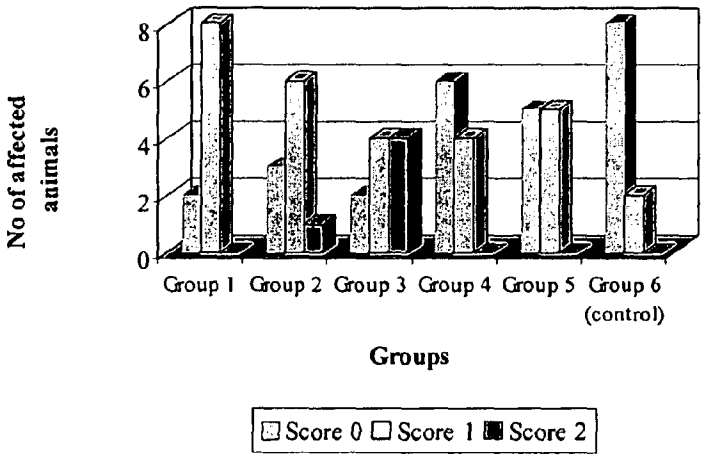


FIGURE 6

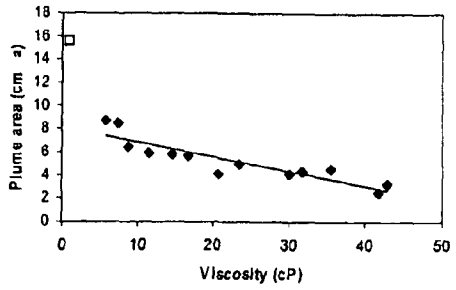


FIGURE 7

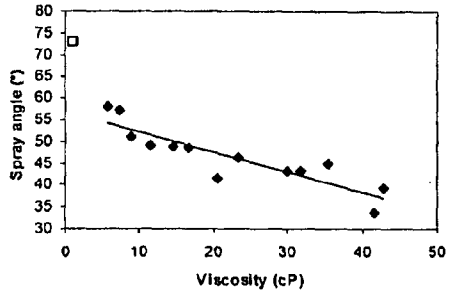


FIGURE 8

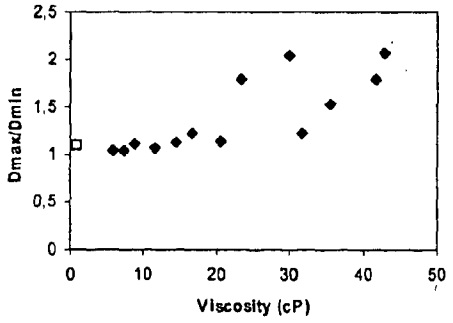


FIGURE 9

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété Intellectuelle
Bureau international

(43) Date de la publication internationale
10 juillet 2003 (10.07.2003)

PCT

(10) Numéro de publication internationale
WO 03/055464 A1

(51) Classification internationale des brevets[7] : A61K 9/00, 47/10, 47/26

(21) Numéro de la demande internationale :
PCT/FR02/04575

(22) Date de dépôt international :
27 décembre 2002 (27.12.2002)

(25) Langue de dépôt : français

(26) Langue de publication : français

(30) Données relatives à la priorité :
01/16934 27 décembre 2001 (27.12.2001) FR

(71) Déposants *(pour tous les États désignés sauf US)* : **BESINS INTERNATIONAL BELGIQUE** [BE/BE]; Groot Bijgaardenstraat 128, B-1620 Drogenbos (BE). **GALENIX INNOVATIONS** [FR/FR]; Allée des Palanques, F-33127 Saint-Jean d'Illac (FR).

(72) Inventeurs; et
(75) Inventeurs/Déposants *(pour US seulement)* : **BESSE, Jérôme** [FR/FR]; Chemin des Vins, Barbat, F-33480 Listrac Medoc (FR). **BESSE, Laurence** [FR/FR]; Chemin des Vins, Barbat, F-33480 Listrac Medoc (FR).

(74) Mandataires : **CATHERINE, Alain** etc.; Cabinet Harle et Phelip, 7, rue de Madrid, F-75008 Paris (FR).

(81) États désignés *(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, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) États désignés *(régional)* : brevet ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Déclaration en vertu de la règle 4.17 :
— *relative à la qualité d'inventeur (règle 4.17.iv)) pour US seulement*

Publiée :
— *avec rapport de recherche internationale*
— *avant l'expiration du délai prévu pour la modification des revendications, sera republiée si des modifications sont reçues*

En ce qui concerne les codes à deux lettres et autres abréviations, se référer aux "Notes explicatives relatives aux codes et abréviations" figurant au début de chaque numéro ordinaire de la Gazette du PCT.

WO 03/055464 A1

(54) Title: MICRONIZED PHARMACEUTICAL OR NUTRACEUTICAL POWDER WITH IMMEDIATE RELEASE

(54) Titre : POUDRE MICRONISEE PHARMACEUTIQUE OU NUTRACEUTIQUE A LIBERATION IMMEDIATE.

(57) Abstract: The invention concerns a micronized pharmaceutical or nutraceutical powder with immediate release having a grain size distribution of not more than 100 μm, and comprising the combination of at least an active substance, at least a wetting agent and at least a diluent.

(57) Abrégé : La présente invention concerne une poudre micronisée pharmaceutique ou nutraceutique à libération immédiate ayant une granulométrie d'au plus 100 μm, et comprenant la combinaison d'au moins une substance active, au moins un agent mouillant et au moins un agent diluant.

POUDRE MICRONISEE PHARMACEUTIQUE OU NUTRACEUTIQUE A LIBERATION IMMEDIATE

La présente invention concerne une poudre micronisée pharmaceutique ou nutraceutique à libération immédiate, pour application mucosale, en particulier buccale.

L'utilisation d'une poudre micronisée selon l'invention, pour préparer une composition pharmaceutique ou nutraceutique, permet une libération rapide (ou « flash ») de la substance active lorsque la composition la comprenant est administrée par voie mucosale, en particulier buccale.

Des formes galéniques permettant une libération rapide d'une substance active sont déjà connues. Il s'agit de comprimés de type « lyoc » ou à délitement rapide dans la bouche comme par exemple la technologie Zydis® (Scherer)®), ou encore des systèmes de type films présentés sous forme de « wafer », c'est-à-dire des films pour application buccale permettant une dissolution plus ou moins rapide des substances actives.

Cependant, ces deux formes galéniques présentent plusieurs inconvénients. Les comprimés souffrent d'une friabilité importante, ce qui rend délicate leur manipulation et par ailleurs leur temps de délitement est très souvent supérieur à 10 secondes. Les films sont difficiles à appliquer du fait de leur très faible épaisseur. En outre, les deux formes galéniques souffrent d'un inconvénient majeur en ce qu'elles ne permettent qu'une charge relativement faible en substance active, des excipients divers et variés étant nécessaires à leur intégrité structurelle.

Les Sociétés Demanderesses ont donc cherché à développer une forme galénique pouvant pallier aux inconvénients rencontrés par les formulations antérieures.

Elles ont ainsi réussi à mettre au point une poudre dont l'utilisation dans une composition pharmaceutique ou nutraceutique permet une libération rapide et immédiate de la substance active seule ou en association, lorsque ladite composition est administrée par voie buccale.

Au sens de la présente invention, on entend par « libération rapide et immédiate » une libération de la totalité de la ou les substances actives en moins de 30 secondes, de préférence moins de 15, et plus préférentiellement encore en moins de 10 secondes.

La poudre selon l'invention, contrairement aux comprimés et films de l'art antérieur, n'est délicate ni dans sa manipulation ni dans son application. Elle permet en outre une charge importante en substance active En effet la charge en substances actives par unité de prises peut être largement supérieure aux 20 mg imposés notamment par la technologie des films de type « WAFER » ou équivalent.

La poudre selon la présente invention présente donc de nombreux avantages par rapport aux formes galéniques connues dans l'art antérieur.

Ainsi, la présente invention concerne une poudre micronisée pharmaceutique ou nutraceutique à libération immédiate ayant une granulométrie d'au plus 100 µm, et comprenant la combinaison d'au moins une substance active, au moins un agent mouillant et au moins un agent diluant.

De préférence, la poudre micronisée à libération immédiate de l'invention comprend, par rapport au poids total de la composition, de 0,001% à 99% en poids de substance(s) active(s), de 1% à 60% en poids d'agent(s) mouillant(s) et de 0,1% à 99% d'agent(s) diluant(s). L'homme du métier adapte les proportions des différents constituants de la poudre micronisée à libération immédiate, selon des techniques conventionnelles de préparation de formulations galéniques comme par exemple celles décrites dans (i) J. Control Release, 1999, Vol. 61 : 175-183, (ii) J. Pharm., 2000, 171-277, (iii) J. Control Release, 2001, Vol. 77 : 1-6 ou encore (iv) J. Pharm. Pharmacol., 1996, Vol. 48 : 255, afin que la poudre possède les caractéristiques physiques, mécaniques et chimiques définies dans la présente description, notamment les caractéristiques de granulométrie, de cinétique de libération de la ou des substances actives ou encore d'humidité résiduelle.

Par substance active, on entend selon l'invention toute substance ayant une activité mesurable de nature thérapeutique ou nutraceutique envers l'organisme, homme ou animal, sur lequel cette substance active est appliquée ou administrée.

Par agent mouillant, on entend selon l'invention un agent accélérant la solubilisation et/ou la dissolution de la ou des substances actives et des autres excipients contenus dans la poudre micronisée. En particulier, un agent mouillant selon l'invention se caractérise en ce qu'il permet un haut indice de mouillabilité de ladite poudre micronisée, comme cela peut être visualisé par mesure de l'angle de contact (α) à l'aide d'un goniomètre, qui est faible et de

préférence compris entre 0 et 90°, préférentiellement entre 0 et 60° et plus préférentiellement entre 0 et 45°

Par agent diluant, on entend selon l'invention un agent utilisé pour compléter la composition de la poudre micronisée contenant la ou les substances actives, jusqu'à obtention d'un volume total prédéterminé contenant une quantité choisie de la ou des substance(s) active(s), le volume de la ou des substances actives elles-mêmes, selon la nature de ces substances actives, étant en général insuffisant pour la réalisation d'une poudre micronisée finale dont le volume désiré comprend la quantité adaptée de ladite ou desdites substances actives.

Selon l'invention, on a montré qu'une poudre micronisée ayant la combinaison des caractéristiques ci-dessus et possédant une granulométrie d'au plus 100 µm, du fait d'une grande surface active, permettait une excellente biodisponibilité de la ou des substances actives qu'elle contient, pour les sites ou récepteurs cellulaires cibles visés sur la muqueuse.

Par « granulométrie » d'une poudre micronisée à libération immédiate selon l'invention, on entend la taille moyenne des grains qui la constituent. La taille moyenne des grains peut être mesurée par toute technique conventionnelle connue en soi. Notamment, l'homme du métier peut avoir recours à une mesure de la granulométrie à laser du type Beckman Coulter® ou Malvern®, comme cela est décrit dans les exemples.

Le demandeur a observé que la distribution de taille des grains de la poudre micronisée à libération immédiate de l'invention suit une courbe de Gauss étroite, la valeur de granulométrie correspondant en conséquence à la taille réelle de la majorité des grains contenue dans ladite poudre.

La poudre micronisée à libération immédiate selon l'invention possède avantageusement une humidité résiduelle comprise entre 0,01% et 15%, et de préférence entre 0,1% et 5%, comme mesuré avec un analyseur d'humidité de type Sartorius® MA 30 commercialisé par la société Sartorius et utilisé selon les recommandations du fabricant, comme cela est illustré dans les exemples. La faible humidité résiduelle de la poudre micronisée à libération immédiate selon l'invention permet d'éviter, ou à tout le moins de réduire fortement, la formation d'agrégats entre les grains contenus dans ladite poudre. En effet, la formation d'agrégats est de nature à affecter la valeur de surface active de la poudre en contact avec les muqueuses, lors de son application, et en

conséquence la valeur de biodisponibilité de la ou des substances actives pour les sites ou récepteurs cibles dans les muqueuses.

On a aussi montré selon l'invention que, dans certaines limites, plus la granulométrie de la poudre micronisée est petite, plus on accroît la biodisponibilité de la ou des substances actives vis-à-vis des sites cibles visés et plus on réduit la durée nécessaire à la libération totale de la ou des substances actives vers les sites ou récepteurs cibles sur la muqueuse.

Ainsi, préférentiellement, la poudre micronisée selon l'invention possède une granulométrie d'au plus 50 µm, et de manière tout à fait préférée d'au plus 10 µm.

A l'exemple 1, on illustre une poudre micronisée à libération immédiate selon l'invention possédant une granulométrie de moins de 3 µm.

On a aussi montré selon l'invention qu'avec une poudre micronisée ayant une granulométrie inférieure à 0,01 µm, la capacité de libération immédiate de la ou des substances active était altérée, notamment du fait d'une agglomération en amas des grains de la poudre, entre eux. Ainsi, avec une poudre micronisée de granulométrie trop fine, on réduit la biodisponilité de la ou des substances actives pour les sites cibles sur les muqueuses, du fait de la rétention de la ou des substances actives au sein de la poudre, au cœur des agglomérats de grains qui se forment. En d'autres termes, contrairement à ce qui pouvait être attendu, une réduction trop grande de la granulométrie de la poudre micronisée, en deçà de 0,01 µm, a pour effet de réduire la surface active de ladite poudre en contact avec les muqueuses, par rapport à une poudre micronisée de granulométrie plus grande, par exemple de 1 µm ou 5 µm.

Selon un mode préférentiel de réalisation de la poudre micronisée à libération immédiate selon l'invention, ladite poudre présente une granulométrie comprise entre 0,01 µm et 100 µm, avantageusement entre 0,1 µm et 100 µm, préférentiellement encore entre 1 µm et 50 µm et de manière tout à fait préférée entre 1 µm et 20 µm.

La poudre micronisée à libération immédiate de l'invention possède une cinétique de dissolution dans un milieu aqueux de moins de trente secondes, et le plus souvent de moins de dix secondes, que ce soit dans des tampons ayant un pH allant de 5 à 9, ou que ce soit dans une solution aqueuse de salive artificielle.

Ainsi, selon une caractéristique avantageuse de la poudre micronisée à libération immédiate de l'invention, ladite poudre permet la libération de la totalité de la ou des substances actives en moins de 30 secondes, avantageusement en moins de 15 secondes, et de manière tout à fait préférée en moins de 10 secondes.

La poudre micronisée à libération immédiate de l'invention est spécifiquement adaptée à la libération rapide d'une substance active, ou d'une combinaison de substances actives, *in situ*, au niveau des muqueuses, en particulier des muqueuses buccales.

Selon un mode de réalisation préféré de la poudre micronisée à libération immédiate, la ou les substance(s) active(s) elle(s)-même(s) est (sont) sous forme micronisée.

Ainsi, selon un mode préférentiel de réalisation de la poudre micronisée selon l'invention, les substances actives sont micronisées avec les autres ingrédients. Ceci accroît encore la capacité de la poudre à libérer rapidement, et de manière homogène, la ou les substances actives, du fait d'une augmentation de la surface de contact de celles-ci avec la muqueuse. Par ailleurs, plusieurs systèmes de conditionnement de la poudre sont particulièrement bien adaptés tel que la pulvérisation de produits micronisés ou l'utilisation de sachets-doses ou capsules thermoformées muni d'un opercule pelable.

Les substances actives de la poudre utilisée selon l'invention peuvent être sélectionnées parmi celles classiquement utilisées dans les familles pharmaco-thérapeutiques suivantes : allergologie, anesthésie/réanimation, cancérologie et hématologie, cardiologie et angiologie, contraception et interruption de grossesse, dermatologie, endocrinologie, gastro-entérohépatologie, gynécologie et obstétrique, immunologie et médicament de transplantation, infectiologie et parasitologie, métabolisme diabète et nutrition, neurologie/psychiatrie, ophtalmologie, oto-rhino-laryngologie, pneumologie, rhumatologie, stomatologie, toxicologie, urologie/néphrologie, ainsi que parmi les antalgiques / antipyrétique et antispasmodiques, anti-inflammatoires, les produits de contraste utilisés en radiologie, les hémostatiques, et les produits de traitement du sang et dérivés.

Avantageusement, les substances actives peuvent être sélectionnées dans le groupe constitué par les substances actives passant la barrière mucosale et atteignant la circulation systémique, telles que les exemples non

limitatifs cités ci-après : l'acétate de cyprotérone, l'acétate de norethistérone, la progestérone, le 3-kéto-désogestrel, le norgestimate, le lévonorgestrel, le désogestrel, le gestodène, les estrogènes naturels tels que l'estradiol ou ses dérivés, les estrogènes synthétiques tels que l'éthinylestradiol, la Δ-4-androstènedione, la testostérone, la dihydrotestostérone ou androstanolone, la DHEA, la trinitrine, le fentanyl, la nitroglycérine, la nicotine (nicotine S(-)), la scopolamine, la clonidine, l'isosorbide dinitrate, l'alclométasone dipropionate, le phloroglucinol, la molsidomine, ainsi que leurs associations.

Elles peuvent également être sélectionnées parmi les substances actives passant la barrière mucosale et ayant une action localisée telles que : l'acétazolamide, l'acyclovir, l'adapalène, l'alclométhasone dipropionate, l'amcinonide, l'améleine, le bamethan sulfate + escine, la bétaméthasone valérate, la bétaméthasone dipropionate, le bufexamac, la caféine, le calcipotriol monohydrate, le cetrimonium bromure, le clobétasol propionate, le crilanomère, la désonide, le dexpanthénol, le diclofénac, le diflucortolone, la valérate, le difluprednate, la diphénydramine chlorhydrate, l'econazole nitrate, l'erythromicine, le flumétasone pivalate, le fluocinolone acétonide, la fluocinodine, le fluocortolone, le fluocortolone hexanoate, le fluocortolone pivalate, l'hydrocortisone, l'hydrocortisone acétate, l'ibacitabine, l'ibuprofène, l'imiquimod, le kétoconazole, le kétoprofène, la lidocaine, la métronidazole, le miconazole nitrate, le minoxidil, le niflumide acide, la penciclovir, le peroxyde benzoyle, la piroxam, la povidone iodé, la promestriène, la pyrazonibutasone, la roxithromycine, la sulfacétalmide, le triamconolone, le tazarotène, le trétinoïne et l'isotrétinoïne, le triclocarban, le vidarabine monophosphate ainsi que leurs associations.

Elles peuvent également être sélectionnées parmi les substances actives suivantes : l'agoniste β-3 adrénergique, l'hormone de croissance, l'oxybutinine, la buprenorphine, le pergolide, le nestorone, le 7α-méthyl-19-nortestérone, la mécamylamine, le salbutamol, le clenbutérol, la sélégiline, la buspirone, la kétotifen, la lidocaïne, le kétorolac, l'eptazocine, l'insuline, l'interféron α, les prostaglandines, l'acide 5 aminolévulinique, la benzodiazepine alprozolam, le diclofenac, le fenoprofen, le flubiprofen, le kétoprofen, la méthylphénidate, la miconazole, le piroxicam, la bruprenorphine, l'alprozolam, la dexmedetomidine, la prazosin (antagoniste α adrénergique), l'alprostadil, le tulobutérol (agoniste β adrénergique), thinylestradiol + norelgestromi, le kétorolac, la physostigmine, le

medindolol (agoniste α adrénergique), la rotigotine (dopamine D2 antagoniste), la thiatolserine ainsi que leurs associations.

Elles peuvent également être sélectionnées parmi les substances actives suivantes : Esomeprazole, Melagatran (en cas de thrombose), Rosuvastatine, Ezetimide, Pitavastatine (Hyperlipidemie), Mitiglinide (Diabète de type II), Cilomilast, Viozan (Asthme), Aripipazole (psychiatrie), Omapatrilat (hypertenseur),Orzel (Cancérologie), Caspofongine acétate, Voriconazole (infections), nouveaux Inhibiteurs COX tels que Etoricoxib (inflammation), Valdecoxib (Arthrites) et Parecoxib, Substance P antagoniste (Dépression), Darifenacine (urologie), Eletriptan (Migraine), Alosetron, Tegaserod, Capravirine (HIV) , Finastéride (inhibiteur de la 5-alpha réductase) ainsi que leurs associations (liste non limitative).

La poudre utilisée selon l'invention peut contenir une ou plusieurs substances actives, en association entre elles.

Pour des applications nutraceutiques, la substance active peut être choisie parmi la liste des matières premières autorisées en tant que compléments alimentaires comme par exemple dans le groupe constitué par les vitamines, les sels minéraux, la levure de bière, etc.

L'agent mouillant peut être un agent mouillant conventionnellement désigné comme tel, par exemple dans la Pharmacopée européenne ou encore dans la Pharmacopée des Etats-Unis d'Amérique (USP) en vigueurou touts autres agents mouillant de qualité pharmaceutique ou nutraceutique. Un agent mouillant contenu dans une poudre micronisée de l'invention englobe également les agents classés dans la Pharmacopée européenne ou dans la Pharmacopée des Etats-Unis d'Amérique (USP) comme agents tensioactifs. En effet, selon un aspect particulier de la poudre micronisée à libération immédiate de l'invention, on utilise aussi les agents tensioactifs comme agents mouillants.

De préférence, un agent mouillant est sélectionné dans le groupe constitué par les polyols tels que le sorbitol, ou encore la glycérine, le PEG, l'hexylène glycol, la triacétine, les huiles végétales hydrogénées telle que l'huile de ricin hydrogénée, les copolymères du polyoxy(éthylène)polyoxy(propylène) tel que le Lutrol® F68, les polyoxyéthylène alkyl éthers tel que le Cremophor®, ainsi que leurs mélanges (liste non limitative).

De préférence, l'agent diluant est sélectionné dans le groupe constitué par le carbonate ou bicarbonate de calcium, sodium, le sucrose, le mannitol, le xylitol, le sorbitol, le lactose, le maltotol, le glucose, la poudre de cellulose ou

cellulose microcristalline, l'amidon et ses dérivés, le phosphate de calcium dibasique, le phosphate de calcium tribasique, le sulfate de calcium, les dextrates, les dextrines, les excipients de dextrose, le fructose, le kaolin, le lactitol, ainsi que leurs mélanges (liste non limitative).

Préférentiellement, la poudre micronisée selon l'invention comprend aussi au moins un agent anti-statique.

On a en effet montré selon l'invention que l'ajout d'au moins un agent anti-statique permettait d'accroître de manière significative la capacité de la poudre micronisée selon l'invention à libérer rapidement la totalité de la ou des substances actives que ladite poudre contient. L'ajout d'au moins un agent anti-statique permet d'éviter, ou à tout le moins de réduire fortement, la formation d'agrégats de poudre qui sont dus à la faible granulométrie de cette dernière. Ainsi, l'ajout d'au moins un agent anti-statique permet l'obtention d'une poudre micronisée de faible granulométrie ne comprenant pas d'agrégats entre les grains, et dont les grains, bien séparés les uns des autres, permettent l'obtention d'une surface de contact maximale de la poudre avec les muqueuses, lors de son application sur ces dernières, et en conséquence une accessibilité ou biodisponibilité maximale de la ou des substances actives pour les sites ou récepteurs cibles correspondants sur les muqueuses.

De préférence, la poudre micronisée à libération immédiate de l'invention comprend, par rapport au poids total de la composition, de 0,01% à 10% d'un ou plusieurs agent(s) anti-statique(s).

De préférence, un agent anti-statique est sélectionné dans le groupe constitué de la silice colloïdale, du silicate de magnésium, du talc, du silicate de calcium et du phosphate de calcium tribasique (liste non limitative).

La poudre utilisée selon l'invention peut également comprendre un liant sélectionné dans le groupe constitué par l'acacia, l'acide alginique, la carboxyméthylcellulose sodique, la cellulose microcristalline, les dextrines, l'éthylcellulose, la gélatine, le glucose, la gomme guar, l'hydroxypropylméthylcellulose, la méthylcellulose, l'oxyde de polyéthylène, la povidone, l'amidon prégélatinisé, ainsi que leurs mélanges (liste non limitative).

La poudre utilisée selon l'invention peut également comprendre, si nécessaire, un promoteur de pénétration, préférentiellement désigné dans la présente description « promoteur d'absorption ». On entend par « promoteur d'absorption», toute molécule favorisant la diffusion d'une substance active à travers la peau ou de la muqueuse de façon réversible, et tout agent de

solubilisation ou agent mouillant favorisant le partage de la substance active entre le véhicule et la couche cornée de l'épiderme ou la muqueuse.

Dans les cas où le promoteur d'absorption est aussi un agent mouillant tel que défini ci-dessus, ledit promoteur d'absorption est ajouté à la composition de la poudre micronisée qui comprend déjà un agent mouillant.

Le promoteur d'absorption peut être sélectionné dans le groupe constitué par les esters d'acide gras aliphatiques comme le myristate d'isopropyle, les acides gras comme l'acide oléique ; les alcools ou polyols tels que l'éthanol, le propylèneglycol et le polyéthylèneglycol ; les composants des huiles essentielles et dérivés terpéniques (comme l'eugenol, le géraniol, le nérol, l'eucalyptol, le menthol) ; les tensioactifs, de préférence non ioniques, tels que le polyoxyéthylène sorbitan (ester d'acide gras), le polyoxyéthylène alkyl éther, le polyoxyéthylène dérivé de l'huile de ricin; les hydratants comme la glycérine, l'urée ; des kératolytiques comme les alpha-hydroxyacides (acide lactique, acide citrique, etc.), le 23-lauryl ether, l'aprotinin, l'azone, le chlorure de benzalkonium, le chlorure de cétylpyridinium, le bromure de cétyltriméthylammonium, les cyclodextrines, le dextran sulfate, l'acide laurique, l'acide laurique, la lysophosphatidylcholine, le menthol, le méthoxysalicylate, le méthyloleate, l'acide oléique, la phosphatidylcholine, le polyoxyethylene, le polysorbate 80, l'EDTA de sodium, le glycocholate de sodium, le glycodeoxycholate de sodium, le lauryl sulfate de sodium, le salycilate de sodium, le taurocholate de sodium, le taurodeoxycholate de sodium, les sulfoxides, les alkyl glycosides, ainsi que leur mélange (liste non limitative). Par ailleurs, afin d'améliorer la compliance du patient, on peut éventuellement ajouter à la composition un agent édulcorant et/ou un agent aromatisant

L'agent édulcorant peut être sélectionné dans le groupe constitué par l'aspartame, les dextrates, le dextrose, le fructose, le mannitol, le saccharinate de sodium ou de calcium, le sorbitol, le sucralose, le sucrose, ainsi que leurs mélanges (liste non limitative).

L'agent aromatisant peut être sélectionné dans le groupe constitué par les arômes d'origine synthétiques, semi-synthétiques ou naturels. On peut citer par exemple la menthe, la menthe poivrée, le citron, la banane, la fraise, la framboise, la mandarine, l'orange, la vanille, les fruit de la passion, le caramel, ainsi que leurs mélanges.

La composition contenant la poudre utilisée selon l'invention est administrée par voie mucosale. Elle peut être appliquée, par exemple, sur la

muqueuse buccale, la muqueuse nasale ou la muqueuse vaginale, et également en application sublinguale.

De manière générale, la poudre micronisée à libération immédiate de l'invention peut être utilisée avec ou dans tout dispositif permettant son application sur la surface d'une muqueuse.

De façon avantageuse, la composition comprenant la poudre utilisée selon l'invention, se présente sous une forme sèche conditionnée dans un pulvérisateur oudans un sachet-dose à 4 soudures ou dans un sachet-dose à 3 soudures tel que le « stick pack qui est un sachet tubulaire avec une soudure longitudinale et une soudure à chaque extrémité du tube, ou dans une capsule thermoformée muni d'un opercule pelable ou encore dans tout autre conditionnement adapté à l'administration de poudre connu de l'homme du métier. Ces conditionnements permettent la délivrance aisée d'une dose précise de matière active.

Tous les procédés connus de l'homme du métier peuvent être utilisés dans le cadre de la réalisation de la poudre utilisée selon l'invention.

On peut citer comme exemple de méthode de préparation d'une poudre : la granulation, par voie humide ou par voie sèche, suivie d'une micronisation.

Ou selon un autre mode de réalisation, la substance active est micronisée puis mélangée avec les excipients sous forme de poudre, et le mélange ainsi obtenu est granulé, par granulation par voie humide ou par voie sèche, puis micronisé.

Avantageusement, pour préparer une poudre micronisée à libération immédiate selon l'invention, on mélange (i) la ou les substances actives, (ii) le ou les agent(s) mouillant(s), (iii) le ou les agent(s) diluant(s), préférentiellement (iv) le ou les agent(s) anti-statique(s) et éventuellement aussi (v) les autres excipients, tels que le ou les agent(s) liant(s) et/ou le ou les promoteur(s) d'absorption dans un dispositif du type mélangeur-granulateur-sécheur, jusqu'à homogénéisation du mélange. Puis, une solution ou suspension de mouillage est incorporée sous agitation afin d'obtenir un granulé humide, qui est ensuite séché afin d'évaporer le solvant de granulation.

La poudre est ensuite micronisée, après calibrage.

Pour la micronisation, on utilise de préférence la méthode conventionnelle à jet d'air, par exemple en utilisant un appareil de micronisation à jet d'air du type ALPINE ou JET MILL, selon les recommandations du fabricant.

Les paramètres préférés pour une micronisation sur un appareil microniseur GALETTE Alpine 200AS sont les suivants :

- Injecteur : 7 à 8 bars ;
- Couronne : 4 à 6 Bars ; et
- Vitesse : 25 kg/h.

Dans un essai particulier réalisé par le demandeur, la poudre avant micronisation avait une taille moyenne de grains (granulométrie)d'environ 160 µm. A près micronisation, la poudre micronisée à libération immédiate obtenue possédait une granulométrie de 2,3 µm.

La substance active seule ou bien le mélange final d'ingrédients peuvent être micronisés.

L'invention est en outre illustrée, sans pour autant être limitée, la figure et les exemples suivants.

La **Figure 1** illustre le profil de distribution de taille des grains de la poudre micronisée à libération immédiate de l'invention préparée à l'Exemple 2, avant et après micronisation.

- En abscisse : Taille des particules, exprimée en µm ;
- En ordonnées : Volume, exprimé en pourcentage.

La **Figure 2** illustre le profil de distribution de taille des grains de la poudre micronisée à libération immédiate de l'invention préparée à l'Exemple 3, avant et après micronisation.

- En abscisse : Taille des particules, exprimée en µm ;
- En ordonnées : Volume, exprimé en pourcentage.

EXEMPLE 1 : POUDRES A UTILISER SELON L'INVENTION

On prépare quatre poudres présentant chacune la composition pondérale suivante :

Tableau 1

Composition	Quantité en %
Phloroglucinol	10
Sorbitol	89
Propylène glycol	1

Tableau 2

Composition	Quantité en %
Testostérone	10
Sorbitol	88
Crémophor RH40	2

Tableau 3

Composition	Quantité en %
Dihydrotestostérone	5
Xylitol	90
Glycérol	3
Tween 80	2

Tableau 4

Composition	Quantité en %
Molsidomine	10
Xylitol	83
Propylène glycol	5
Montanox 80	2

Les différents composants pulvérulents à l'exception de l'agent anti-statique sont mélangés dans un mélangeur-granulateur de type mélangeur-granulateur-sécheur sous vide ROTOLAB ZANCHETTA® ou équivalent jusqu'à homogénéisation du mélange. Ensuite, une solution ou suspension de mouillage comprenant le ou les composant(s) liquide(s) est incorporée sous agitation afin d'obtenir un granulé humide.

Ce granulé est ensuite séché dans des conditions adaptées afin d'évaporer le solvant de granulation. Ce granulé est ensuite séché et calibré

puis micronisé à l'aide d'un appareil de micronisation à jet d'air de type ALPINE ou JETMIL (ou équivalent).

EXEMPLE 2 : POUDRE A LIBERATION IMMEDIATE SELON L'INVENTION

On prépare une poudre présentant la composition pondérale suivante :

Tableau 5

Composition	Quantité en %
Apomorphine	10
Sorbitol	89,01
Propylène glycol	0,90
Silice colloïdale	0,09

Procédé de fabrication :

Les différents composants pulvérulents à l'exception de l'agent anti-statique sont mélangés dans un mélangeur-granulateur de type mélangeur-granulateur-sécheur sous vide ROTOLAB ZANCHETTA ou équivalent jusqu'à homogénéisation du mélange. Ensuite, une solution ou suspension de mouillage comprenant le ou les composant(s) liquide(s) est incorporée sous agitation afin d'obtenir un granulé humide.

Ce granulé est ensuite séché dans des conditions adaptées afin d'évaporer le solvant de granulation, calibré, puis micronisé à l'aide d'un appareil de micronisation à jet d'air de type GALETTE ALPINE 200AS ou JETMIL (ou équivalent)

Paramètre de micronisation :

Injecteur : 8Bars, Couronne : 6Bars, Vitesse : 25Kg/h.

Afin de réduire les phénomènes d'agglomération dus à la faible granulométrie de la poudre micronisée, un agent anti-statique (silice colloïdale) préalablement tamisé est ajouté par mélange progressif dans un mélangeur Turbula.

Contrôles sur granulé avant micronisation

-Granulométrie : réalisée à l'aide d'un granulomètre laser Malvern Mastersizer 2000 équipé d'un vibreur Sirocco 2000

Paramètres : Pression=2bars ; Vibration=80%

Résultat : granulométrie moyenne=157,98µm

-Aptitude à l'écoulement : selon test Pharmacopée européenne 4.2 ; 2.9.16 Ecoulement
masse échantillon=100g, Temps d'écoulement = ∞

-Volume apparent : selon test Pharmacopée Européenne 4.2 ; 2.9.15
masse échantillon=100g
Volume apparent à V0=166 mL
Volume apparent à V10= 156 mL
Volume apparent à V500= 148 mL
V10-V500= 6 mL

-Mesure du taux d'humidité relative : réalisé à l'aide d'un analyseur d'humidité MA 30 Sartorius
Paramètres : masse de l'échantillon=2g, Température=75°C, Temps de dessiccation=automatique
Résultat : Humidité relative= 1,41%

Contrôle sur poudre micronisée finale

-Granulométrie : réalisée à l'aide d'un granulomètre laser Malvern Mastersizer 2000 équipé d'un vibreur Sirocco 2000
Paramètres : Pression=3bars ; Vibration=70%
Résultat : granulométrie moyenne=2,349µm

-Aptitude à l'écoulement : selon test Pharmacopée européenne 4.2 ; 2.9.16 Ecoulement
masse échantillon=100g, Temps d'écoulement = ∞

-Volume apparent : selon test Pharmacopée européenne 4.2 ; 2.9.15
masse échantillon=50g
Volume apparent à V0=178 mL
Volume apparent à V10= 170 mL
Volume apparent à V500= 164 mL
V10-V500= 8 mL

-Mesure du taux d'humidité relative : réalisée à l'aide d'un analyseur d'humidité MA 30 Sartorius
Paramètres : masse de l'échantillon=3g environ, Température=75°C, Temps de dessiccation = automatique, nombre d'essai = 3
Résultat : Humidité relative moyenne = 1,08%

-Cinétique de dissolution in vitro
Conditions opératoires : 1g de poudre micronisée sont dissous à 37°C dans 10g de milieu, sous agitation magnétique à 500 RPM

Tableau 6

Milieu	Temps (s)
Tampon phosphate pH 4,5	4,63
Tampon phosphate pH 8	8,36
Tampon phosphate pH 7,4	5,87
Salive artificielle	2,72

Le profil de distribution de taille des grains de la poudre selon l'Exemple 2, avant et après micronisation, est illustré sur la Figure 1.

EXEMPLE 3 : POUDRE A LIBERATION IMMEDIATE SELON L'INVENTION

On prépare une poudre présentant la composition pondérale suivante :

Tableau 7

Composition	Quantité en %
Testostérone	10

Dextran	87,91
Glycérol	1,99
Silice colloïdale	0,1

Procédé de fabrication :

Les différents composants pulvérulant à l'exception de l'agent anti-statique sont mélangés dans un mélangeur-granulateur de type mélangeur-granulateur-sécheur Lit d'air fluidisé équipé d'une buse top spray ou équivalent jusqu'à homogénéisation du mélange. Ensuite, une solution ou suspension de mouillage comprenant le ou les composant(s) liquide(s) est pulvérisée à l'aide d'une buse de pulvérisation, sur le produit en mouvement afin simultanément de répartir la solution de façon homogène et de le sécher pour évaporer le solvant de granulation.

Ce granulé est calibré, puis micronisé à l'aide d'un appareil de micronisation à jet d'air de type GALETTE ALPINE 200AS ou JETMIL (ou équivalent). Les paramètres de réglage sont identiques à ceux décrits dans l'exemple I.

Afin de réduire les phénomènes d'agglomération dus à la faible granulométrie de la poudre micronisée, un agent anti-statique (silice colloïdale) préalablement tamisé est ajouté par mélange progressif dans un mélangeur Turbula.

Contrôles sur poudre micronisée finale

-Cinétique de dissolution in vitro

Conditions opératoires : 1g de poudre micronisée sont dissous à 37°C dans 10g de milieu, sous agitation magnétique à 500 RPM

Tableau 8

Milieu	Temps (s)
Tampon phosphate pH 4,5	8,9
Tampon phosphate pH 8	7,23
Tampon phosphate pH 7,4	7,74

Salive artificielle	6,78

Le profil de distribution de taille des grains de la poudre selon l'Exemple 3, avant et après micronisation, est illustré sur la Figure 2.

Exemple 4 : POUDRE A LIBERATION IMMEDIATE SELON L'INVENTION

On prépare une poudre présentant la composition pondérale suivante :

Tableau 9

Composition	Quantité en %
Dihydrotestostérone	5
Mannitol	90
Propylène glycol	3
	2

Procédé de fabrication :

Selon exemple 2.

Contrôles sur poudre micronisée finale

-Cinétique de dissolution in vitro

Conditions opératoires : 1g de poudre micronisée sont dissous à 37°C dans 10g de milieu, sous agitation magnétique à 500 RPM

Tableau 10

Milieu	Temps (s)
Tampon phosphate pH 4,5	6,28
Tampon phosphate pH 8	7,71
Tampon phosphate pH 7,4	6,14
Salive artificielle	4,97

REVENDICATIONS

1. Poudre micronisée pharmaceutique ou nutraceutique à libération immédiate ayant une granulométrie d'au plus 100 µm, et comprenant la combinaison d'au moins une substance active, au moins un agent mouillant et au moins un agent diluant.

2. Poudre selon la revendication 1, caractérisée en ce qu'elle possède une granulométrie d'au plus 50 µm.

3. Poudre selon la revendication 1, caractérisée en ce qu'elle possède une granulométrie d'au plus 10 µm.

4. Poudre selon l'une des revendications 1 à 3, caractérisée en ce qu'elle permet la dissolution de la totalité de la ou des substances actives en moins de 30 secondes, lorsqu'elle est administrée par voie mucosale.

5. Poudre selon l'une des revendications 1 à 4, caractérisée en ce que la substance active est sous forme micronisée.

6. Poudre selon l'une quelconque des revendications 1 à 5, caractérisée en ce que la substance active est sélectionnée dans le groupe constitué par l'acétate de cyprotérone, l'acétate de norethistérone, la progestérone, le 3-kéto-désogestrel, le norgestimate, le lévonorgestrel, le désogestrel, le gestodène, les estrogènes naturels tels que l'estradiol ou ses dérivés, les estrogènes synthétiques tels que l'éthinylestradiol, la Δ-4-androstènedione, la testostérone, la dihydrotestostérone ou androstanolone, la DHEA, la trinitrine, le fentanyl, la nitroglycérine, la nicotine (nicotine S(-)), la scopolamine, la clonidine, l'isosorbide dinitrate, l'alclométasone dipropionate, le phloroglucinol, la molsidomine, l'acétazolamide, l'acyclovir, l'adapalène, l'alclométhasone dipropionate, l'amcinonide, l'améleine, le bamethan sulfate + escine, la bétaméthasone valérate, la bétaméthasone dipropionate, le bufexamac, la caféine, le calcipotriol monohydrate, le cetrimonium bromure, le clobétasol propionate, le crilanomère, la désonide, le dexpanthénol, le diclofénac, le diflucortolone, la valérate, le difluprednate, la diphénydramine chlorhydrate, l'econazole nitrate, l'erythromicine, le flumétasone pivalate, le fluocinolone acétonide, la fluocinodine, le fluocortolone, le fluocortolone hexanoate, le fluocortolone pivalate, l'hydrocortisone, l'hydrocortisone acétate, l'ibacitabine, l'ibuprofène, l'imiquimod, le kétoconazole, le kétoprofène, la lidocaine, la métronidazole, le miconazole nitrate, le minoxidil, le niflumide

acide, la penciclovir, le peroxyde benzoyle, la piroxam, la povidone iodé, la promestriène, la pyrazonibutasone, la roxithromycine, la sulfacétalmide, le triamconolone, le tazarotène, le trétinoïne et l'isotrétinoïne, le triclocarban, le vidarabine monophosphate, l'agoniste β-3 adrénergique, l'hormone de croissance, l'oxybutinine, la buprenorphine, le pergolide, le nestorone, le 7α-méthyl-19-nortestérone, la mécamylamine, le salbutamol, le clenbutérol, la sélégiline, la buspirone, la kétotifen, la lidocaïne, le kétorolac, l'eptazocine, l'insuline, l'interféron α, les prostaglandines, l'acide 5 aminolévulinique, la benzodiazepine alprozolam, le diclofenac, le fenoprofen, le flubiprofen, le kétoprofen, la méthylphénidate, la miconazole, le piroxicam, la bruprenorphine, l'alprozolam, la dexmedetomidine, la prazosin (antagoniste α adrénergique), l'alprostadil, le tulobutérol (agoniste β adrénergique), thinylestradiol + norelgestromi, le kétorolac, la physostigmine, le medindolol (agoniste α adrénergique), la rotigotine (dopamine D2 antagoniste), la thiatolserine, Esomeprazole, Melagatran (en cas de thrombose), Rosuvastatine, Ezetimide, Pitavastatine (Hyperlipidemie), Mitiglinide (Diabète de type II), Cilomilast, Viozan (Asthme), Aripipazole (psychiatrie), Omapatrilat (hypertenseur),Orzel (Cancérologie), Caspofongine acétate, Voriconazole (infections), nouveaux Inhibiteurs COX tels que Etoricoxib (inflammation), Valdecoxib (Arthrites) et Parecoxib, Substance P antagoniste (Dépression), Darifenacine (urologie), Eletriptan (Migraine), Alosetron, Tegaserod, Capravirine (HIV) , Finastéride (inhibiteur de la 5-alpha réductase), ainsi que leurs associations.

7. Poudre selon l'une quelconque des revendications 1 à 6, caractérisée en ce que la (les) substance(s) active(s) est (sont) sélectionnée(s) dans le groupe constitué par les vitamines, les sels minéraux, la levure de bière.

8. Poudre selon l'une quelconque des revendications 1 à 7, caractérisée en ce que l'agent mouillant est sélectionné parmi les polyols tels que le sorbitol, ou encore la glycérine, le PEG, l'hexylène glycol, la triacétine, les huiles végétales hydrogénées telle que l'huile de ricin hydrogénée, les copolymères du polyoxy(éthylène)polyoxy(propylène) tel que le Lutrol® F68, les polyoxyéthylène alkyl éthers tel que le Cremophor®, ainsi que leurs mélanges.

9. Utilisation d'une poudre selon l'une quelconque des revendications 1 à 8, caractérisée en ce que l'agent diluant est sélectionné dans le groupe constitué par le carbonate ou bicarbonate de calcium, sodium, le sucrose, le mannitol, le xylitol, le sorbitol, le lactose, le maltotol, le glucose, la

poudre de cellulose ou cellulose microcristalline, l'amidon et ses dérivés, le phosphate de calcium dibasique, le phosphate de calcium tribasique, le sulfate de calcium, les dextrates, les dextrines, les excipients de dextrose, le fructose, le kaolin, le lactitol, ainsi que leurs mélanges.

10. Poudre selon l'une des revendications 1 à 9, caractérisée en ce qu'elle comprend en outre un agent anti-statique.

11. Poudre selon la revendication 10, caractérisée en ce que l'agent anti-statique est sélectionné dans le groupe constitué de la silice colloïdale, le silicate de magnésium, le talc, le silicate de calcium et le phosphate de calcium tribasique, ainsi que leur mélanges.

12. Poudre selon l'une quelconque des revendications 1 à 11, caractérisée en ce qu'elle comprend en outre un agent liant pouvant être sélectionné dans le groupe constitué par l'acacia, l'acide alginique, la carboxyméthylcellulose sodique, la cellulose microcristalline, les dextrines, l'éthylcellulose, la gélatine, le glucose, la gomme guar, l'hydroxypropylméthylcellulose, la méthylcellulose, l'oxyde de polyéthylène, la povidone, l'amidon prégélatinisé, ainsi que leurs mélanges.

13. Poudre selon l'une quelconque des revendications 1 à 12, caractérisée en ce qu'elle comprend en outre un promoteur d'absorption sélectionné dans le groupe constitué par les esters d'acide gras aliphatiques comme le myristate d'isopropyle, les acides gras comme l'acide oléique ; les alcools ou polyols tels que l'éthanol, le propylèneglycol et le polyéthylèneglycol ; les composants des huiles essentielles et dérivés terpéniques (comme l'eugenol, le géraniol, le nérol, l'eucalyptol, le menthol) ; les tensioactifs, de préférence non ioniques, tels que le polyoxyéthylène sorbitan (ester d'acide gras), le polyoxyéthylène alkyl éther, le polyoxyéthylène dérivé de l'huile de ricin; les hydratants comme la glycérine, l'urée ; des kératolytiques comme les alpha-hydroxyacides (acide lactique, acide citrique, etc.), le 23-lauryl ether, l'aprotinin, l'azone, le chlorure de benzalkonium, le chlorure de cétylpyridinium, le bromure de cétyltriméthylammonium, les cyclodextrines, le dextran sulfate, l'acide laurique, l'acide laurique, la lysophosphatidylcholine, le menthol, le méthoxysalicylate, le méthyloleate, l'acide oléique, la phosphatidylcholine, le polyoxyethylene, le polysorbate 80, l'EDTA de sodium, le glycocholate de sodium, le glycodeoxycholate de sodium, le lauryl sulfate de sodium, le salycilate de sodium, le taurocholate de sodium, le taurodeoxycholate de sodium, les sulfoxides, les alkyl glycosides, ainsi que leur mélange

14. Poudre selon l'une quelconque des revendications 1 à 13, caractérisée en ce qu'elle comprend en outre un agent édulcorant et/ou un agent aromatisant.

15. Poudre selon la revendication 14, caractérisée en ce que l'agent édulcorant est sélectionné dans le groupe constitué par l'aspartame, les dextrates, le dextrose, le fructose, le mannitol, le saccharinate de sodium ou de calcium, le sorbitol, le sucralose, le sucrose, ainsi que leurs mélanges.

16. Poudre selon la revendication 14, caractérisée en ce que l'agent aromatisant est sélectionné dans le groupe constitué par par les arômes d'origine synthétiques, semi-synthétiques ou naturels. On peut citer par exemple la menthe, la menthe poivrée, le citron, la banane, la fraise, la framboise, la mandarine, l'orange, la vanille, les fruit de la passion, le caramel, ainsi que leurs mélanges.

17. Poudre selon l'une quelconque des revendications 1 à 16, caractérisée en ce qu'elle se présente sous une forme adaptée à son application sur la muqueuse buccale, la muqueuse nasale ou la muqueuse vaginale.

18. Poudre selon l'une des revendications 1 à 14, caractérisée en ce qu'elle se présente sous une forme adaptée à son application sur la muqueuse buccale par voie sublinguale.

19. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente sous une forme pulvérisable.

20. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente conditionnée dans un sachet-dose.

21. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente conditionnée dans une capsule thermoformée muni d'un opercule pelable.

22. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente dans un conditionnement adapté à l'administration de poudre connu de l'homme du métier.

23. Utilisation d'une poudre selon l'une des revendications 1 à 20, pour la fabrication d'une composition pharmaceutique ou nutraceutique à libération immédiate.

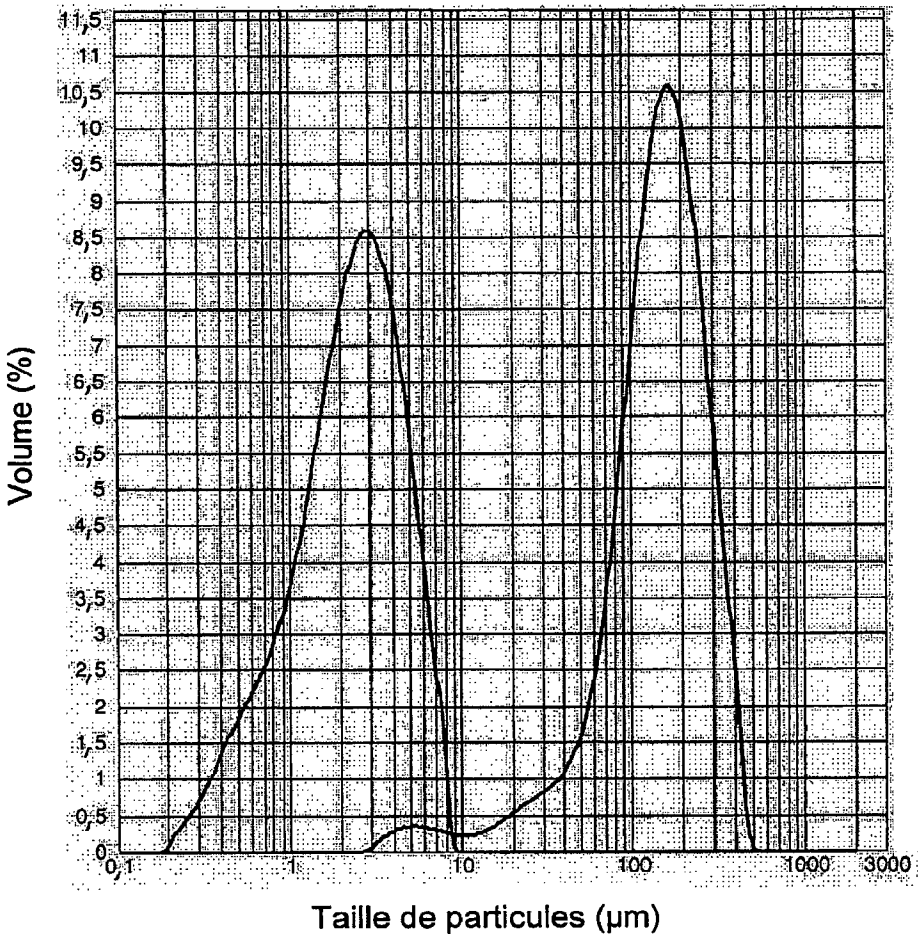

Volume (%)
11,5
11
10,5
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
0,1
1
10
100
1000
3000
Taille de particules (µm)

FIGURE 1

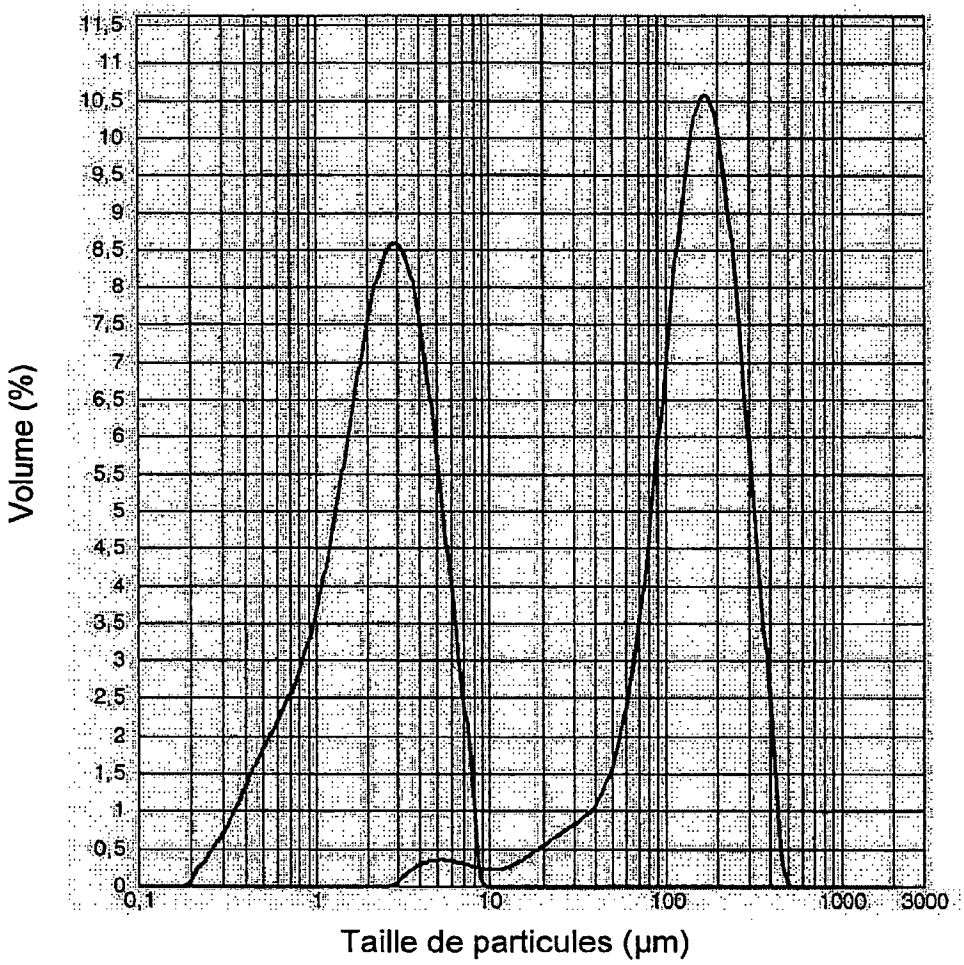

Volume (%)
11,5
11
10,5
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
0,1
1
10
100
1000
3000
Taille de particules (µm)

FIGURE 2

INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/FR 02/04575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K47/10 A61K47/26

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)
WPI Data, PAJ, 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	US 5 073 374 A (J.A. MCCARTY) 17 December 1991 (1991-12-17) claims column 2, line 13 - line 48 column 1, line 23 - line 34 ---	1,6,8,9, 12,13, 17,18,23
X	US 5 157 030 A (A. GALAT) 20 October 1992 (1992-10-20) claims examples --- -/--	1,4,5,8, 9,12,13, 17,19, 22,23

[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
16 April 2003	28/04/2003

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	Scarponi, U

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 24019 A (ORBON) 20 May 1999 (1999-05-20) claims page 4, line 4 - line 10 example 3	1,6,8,9, 13,22,23
X	WO 99 51239 A (DU PONT) 14 October 1999 (1999-10-14) claims 1-5,15-17 page 5, line 3 -page 6, line 14 page 6, line 36 -page 7, line 15 page 9, line 31 -page 10, line 25 examples page 11, line 5 - line 9 page 2, line 31 - line 33	1,4, 8-13,19, 21-23
A	US 5 320 848 A (R.P. GEYER ET AL.) 14 June 1994 (1994-06-14) claims column 4, line 34 - line 35 examples column 5, line 3 - line 68	1-23
A	EP 0 358 951 A (BASF) 21 March 1990 (1990-03-21) claims column 2, line 35 - line 40	1-23
A	US 5 068 467 A (Y. KUNIMI ET AL.) 26 November 1991 (1991-11-26) claims	1-23
A	EP 0 266 113 A (AMERICAN HOME PRODUCTS) 4 May 1988 (1988-05-04) claims examples	1-23
A	WO 01 03672 A (PROGRAPHARM) 18 January 2001 (2001-01-18) claims examples	1-23

INTERNATIONAL SEARCH REPORT

nation on patent family members

Interna | Application No
PCT/FR 02/04575

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5073374	A	17-12-1991	AU	631584 B2	03-12-1992
			AU	4665489 A	26-06-1990
			CA	2004033 A1	31-05-1990
			DK	92991 A	16-05-1991
			EP	0371466 A1	06-06-1990
			EP	0446298 A1	18-09-1991
			JP	4502318 T	23-04-1992
			NO	912001 A	24-05-1991
			NZ	231570 A	25-06-1991
			WO	9006136 A1	14-06-1990
			US	5112616 A	12-05-1992
			ZA	8909070 A	29-08-1990
US 5157030	A	20-10-1992	NONE		
WO 9924019	A	20-05-1999	AU	1307399 A	31-05-1999
			CN	1244794 T	16-02-2000
			EP	0966271 A1	29-12-1999
			JP	2001507722 T	12-06-2001
			WO	9924019 A1	20-05-1999
WO 9951239	A	14-10-1999	AT	223719 T	15-09-2002
			AU	3463799 A	25-10-1999
			BR	9908810 A	19-12-2000
			CA	2321523 A1	14-10-1999
			CN	1296412 T	23-05-2001
			DE	69902893 D1	17-10-2002
			DK	1067936 T3	17-02-2003
			EE	200000589 A	15-04-2002
			EP	1067936 A1	17-01-2001
			ES	2181417 T3	16-02-2003
			HU	0101517 A2	28-11-2001
			JP	2002510634 T	09-04-2002
			NO	20005043 A	06-10-2000
			NZ	507566 A	26-11-2002
			PL	343421 A1	13-08-2001
			PT	1067936 T	31-12-2002
			SK	14612000 A3	10-07-2001
			WO	9951239 A1	14-10-1999
			US	6238695 B1	29-05-2001
			US	2001012518 A1	09-08-2001
US 5320848	A	14-06-1994	US	5380535 A	10-01-1995
			AU	653423 B2	29-09-1994
			AU	2146792 A	08-01-1993
			CA	2103443 A1	29-11-1992
			EP	0587744 A1	23-03-1994
			JP	2948317 B2	13-09-1999
			JP	6511478 T	22-12-1994
			WO	9221328 A1	10-12-1992
EP 358951	A	21-03-1990	DE	3827362 A1	15-02-1990
			AT	75941 T	15-05-1992
			DE	58901404 D1	17-06-1992
			EP	0358951 A1	21-03-1990
			JP	2243630 A	27-09-1990
			US	4950654 A	21-08-1990

INTERNATIONAL SEARCH REPORT

mation on patent family members

Interna | Application No
PCT/FR 02/04575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5068467 A	26-11-1991	JP 1213245 A	28-08-1989
		JP 1828511 C	15-03-1994
		JP 5036424 B	31-05-1993
		AU 2983789 A	24-08-1989
		CA 1333071 A1	15-11-1994
		CN 1035510 A ,B	13-09-1989
		DE 68902657 D1	08-10-1992
		DE 68902657 T2	28-01-1993
		EP 0330352 A1	30-08-1989
		KR 9305255 B1	17-06-1993
EP 266113 A	04-05-1988	US 4760093 A	26-07-1988
		AT 63464 T	15-06-1991
		AU 594203 B2	01-03-1990
		AU 7950987 A	28-04-1988
		CA 1290251 A1	08-10-1991
		DE 3770116 D1	20-06-1991
		EP 0266113 A1	04-05-1988
		ES 2032450 T3	16-02-1993
		GR 3002108 T3	30-12-1992
		IE 61952 B1	30-11-1994
		JP 2542400 B2	09-10-1996
		JP 63112513 A	17-05-1988
		KR 9513751 B1	15-11-1995
WO 0103672 A	18-01-2001	FR 2795962 A1	12-01-2001
		AU 5993600 A	30-01-2001
		BG 106398 A	30-09-2002
		BR 0012250 A	26-03-2002
		CN 1373658 T	09-10-2002
		CZ 20020018 A3	17-04-2002
		EP 1194125 A1	10-04-2002
		WO 0103672 A1	18-01-2001
		HU 0202062 A2	28-12-2002
		JP 2003504324 T	04-02-2003
		NO 20016308 A	21-12-2001
		SK 19392001 A3	04-04-2002
		TR 200200013 T2	21-06-2002
		US 2002098227 A1	25-07-2002

RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale No
PCT/FR 02/04575

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 7 A61K9/00 A61K47/10 A61K47/26

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 7 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	US 5 073 374 A (J.A. MCCARTY) 17 décembre 1991 (1991-12-17) revendications colonne 2, ligne 13 - ligne 48 colonne 1, ligne 23 - ligne 34 --- US 5 157 030 A (A. GALAT) 20 octobre 1992 (1992-10-20) revendications exemples --- -/--	1,6,8,9, 12,13, 17,18,23 1,4,5,8, 9,12,13, 17,19, 22,23

[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

° Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'inven tion revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'inven tion revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
16 avril 2003	28/04/2003

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scarponi, U

Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec,le cas échéant, l'indicationdes passages pertinents	no. des revendications visées
X	WO 99 24019 A (ORBON) 20 mai 1999 (1999-05-20) revendications page 4, ligne 4 - ligne 10 exemple 3	1,6,8,9, 13,22,23
X	WO 99 51239 A (DU PONT) 14 octobre 1999 (1999-10-14) revendications 1-5,15-17 page 5, ligne 3 -page 6, ligne 14 page 6, ligne 36 -page 7, ligne 15 page 9, ligne 31 -page 10, ligne 25 exemples page 11, ligne 5 - ligne 9 page 2, ligne 31 - ligne 33	1,4, 8-13,19, 21-23
A	US 5 320 848 A (R.P. GEYER ET AL.) 14 juin 1994 (1994-06-14) revendications colonne 4, ligne 34 - ligne 35 exemples colonne 5, ligne 3 - ligne 68	1-23
A	EP 0 358 951 A (BASF) 21 mars 1990 (1990-03-21) revendications colonne 2, ligne 35 - ligne 40	1-23
A	US 5 068 467 A (Y. KUNIMI ET AL.) 26 novembre 1991 (1991-11-26) revendications	1-23
A	EP 0 266 113 A (AMERICAN HOME PRODUCTS) 4 mai 1988 (1988-05-04) revendications exemples	1-23
A	WO 01 03672 A (PROGRAPHARM) 18 janvier 2001 (2001-01-18) revendications exemples	1-23

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs au nbres de familles de brevets

Demande internationale No
PCT/FR 02/04575

Document brevet cité au rapport de recherche		Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
US 5073374	A	17-12-1991	AU	631584 B2	03-12-1992
			AU	4665489 A	26-06-1990
			CA	2004033 A1	31-05-1990
			DK	92991 A	16-05-1991
			EP	0371466 A1	06-06-1990
			EP	0446298 A1	18-09-1991
			JP	4502318 T	23-04-1992
			NO	912001 A	24-05-1991
			NZ	231570 A	25-06-1991
			WO	9006136 A1	14-06-1990
			US	5112616 A	12-05-1992
			ZA	8909070 A	29-08-1990
US 5157030	A	20-10-1992	AUCUN		
WO 9924019	A	20-05-1999	AU	1307399 A	31-05-1999
			CN	1244794 T	16-02-2000
			EP	0966271 A1	29-12-1999
			JP	2001507722 T	12-06-2001
			WO	9924019 A1	20-05-1999
WO 9951239	A	14-10-1999	AT	223719 T	15-09-2002
			AU	3463799 A	25-10-1999
			BR	9908810 A	19-12-2000
			CA	2321523 A1	14-10-1999
			CN	1296412 T	23-05-2001
			DE	69902893 D1	17-10-2002
			DK	1067936 T3	17-02-2003
			EE	200000589 A	15-04-2002
			EP	1067936 A1	17-01-2001
			ES	2181417 T3	16-02-2003
			HU	0101517 A2	28-11-2001
			JP	2002510634 T	09-04-2002
			NO	20005043 A	06-10-2000
			NZ	507566 A	26-11-2002
			PL	343421 A1	13-08-2001
			PT	1067936 T	31-12-2002
			SK	14612000 A3	10-07-2001
			WO	9951239 A1	14-10-1999
			US	6238695 B1	29-05-2001
			US	2001012518 A1	09-08-2001
US 5320848	A	14-06-1994	US	5380535 A	10-01-1995
			AU	653423 B2	29-09-1994
			AU	2146792 A	08-01-1993
			CA	2103443 A1	29-11-1992
			EP	0587744 A1	23-03-1994
			JP	2948317 B2	13-09-1999
			JP	6511478 T	22-12-1994
			WO	9221328 A1	10-12-1992
EP 358951	A	21-03-1990	DE	3827362 A1	15-02-1990
			AT	75941 T	15-05-1992
			DE	58901404 D1	17-06-1992
			EP	0358951 A1	21-03-1990
			JP	2243630 A	27-09-1990
			US	4950654 A	21-08-1990

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No
PCT/FR 02/04575

Document brevet cité au rapport de recherche		Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
US 5068467	A	26-11-1991	JP	1213245 A	28-08-1989
			JP	1828511 C	15-03-1994
			JP	5036424 B	31-05-1993
			AU	2983789 A	24-08-1989
			CA	1333071 A1	15-11-1994
			CN	1035510 A ,B	13-09-1989
			DE	68902657 D1	08-10-1992
			DE	68902657 T2	28-01-1993
			EP	0330352 A1	30-08-1989
			KR	9305255 B1	17-06-1993
EP 266113	A	04-05-1988	US	4760093 A	26-07-1988
			AT	63464 T	15-06-1991
			AU	594203 B2	01-03-1990
			AU	7950987 A	28-04-1988
			CA	1290251 A1	08-10-1991
			DE	3770116 D1	20-06-1991
			EP	0266113 A1	04-05-1988
			ES	2032450 T3	16-02-1993
			GR	3002108 T3	30-12-1992
			IE	61952 B1	30-11-1994
			JP	2542400 B2	09-10-1996
			JP	63112513 A	17-05-1988
			KR	9513751 B1	15-11-1995
WO 0103672	A	18-01-2001	FR	2795962 A1	12-01-2001
			AU	5993600 A	30-01-2001
			BG	106398 A	30-09-2002
			BR	0012250 A	26-03-2002
			CN	1373658 T	09-10-2002
			CZ	20020018 A3	17-04-2002
			EP	1194125 A1	10-04-2002
			WO	0103672 A1	18-01-2001
			HU	0202062 A2	28-12-2002
			JP	2003504324 T	04-02-2003
			NO	20016308 A	21-12-2001
			SK	19392001 A3	04-04-2002
			TR	200200013 T2	21-06-2002
			US	2002098227 A1	25-07-2002

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
AEGIS1210-13WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2011/056735	**18 OCTOBER 2011 (18.10.2011)**	18 OCTOBER 2010 (18.10.2010)

Applicant

AEGIS THERAPEUTICS, LLC et al

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/056735

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 11-18
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 11-18 pertain to methods for treatment of the human by therapy and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required addtional 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 and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/056735

A. CLASSIFICATION OF SUBJECT MATTER

A61K 38/08(2006.01)i, A61K 38/04(2006.01)i, C07K 7/06(2006.01)i, C07K 1/04(2006.01)i, A61K 47/42(2006.01)i, A61K 47/48(2006.01)i

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)

A61K 38/08; A61K 31/70; A61K 31/5513; A61K 38/28; A61K 38/02; A61K 31/722; A61K 38/21

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal), PubMed, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008-0299079 A1 (ELIAS MEEZAN et al.) 04 December 2008 See abstract; paragraphs [0010], [0053], [0054], [0058], [0060], [0065], [0069], [0072], [0109].	1-10
X A	US 2010-0209485 A1 (EDWARD T. MAGGIO) 19 August 2010 See abstract; paragraphs [0038], [0039], [0044], [0099], [0110] and claims.	1-6,9,10 7,8
A	US 2009-0258865 A1 (STEVE CARTT et al.) 15 October 2009 See abstract; paragraph [0138].	1-10
A	US 2010-0203119 A1 (MICHAEL LEANE et al.) 12 August 2010 See paragraphs [0060], [0061]; claims 1, 10.	1-10

☐ 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 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
19 JUNE 2012 (19.06.2012)	**20 JUNE 2012 (20.06.2012)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea	PARK, JEONG UNG
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-8131

Form PCT/ISA/210 (second sheet) (July 2009)

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008-0299079 A1	04.12.2008	US 2006-045869 A1	02.03.2006
		US 2006-046962 A1	02.03.2006
		US 2006-046969 A1	02.03.2006
US 2010-0209485 A1	19.08.2010	US 2007-0298010 A1	27.12.2007
		US 2008-0194461 A1	14.08.2008
		US 2008-0268032 A1	30.10.2008
		US 2009-0197816 A1	06.08.2009
		US 2009-0305958 A1	10.12.2009
		US 2009-0326193 A1	31.12.2009
		US 2010-0124567 A1	20.05.2010
		US 2011-0020435 A1	27.01.2011
		US 7425542 B2	16.09.2008
		US 7998927 B2	16.08.2011
		US 8076290 B2	13.12.2011
		US 8084022 B2	27.12.2011
		US 8133863 B2	13.03.2012
		US 8173594 B2	08.05.2012
		WO 2010-151703 A1	29.12.2010
		WO 2010-151707 A1	29.12.2010
US 2009-0258865 A1	15.10.2009	AU 2009-228093 A1	01.10.2009
		CA 2756690 A1	01.10.2009
		EP 2271347 A2	12.01.2011
		JP 2011-516425 A	26.05.2011
		WO 2009-121039 A2	01.10.2009
		WO 2009-121039 A3	01.10.2009
US 2010-0203119 A1	12.08.2010	AT 422356 T	15.02.2009
		DE 602004019405 D1	26.03.2009
		EP 1622601 A1	08.02.2006
		EP 1622601 B1	11.02.2009
		ES 2325020 T3	24.08.2009
		GB 0310919 D0	18.06.2003
		US 2006-0115525 A1	01.06.2006
		WO 2004-100941 A1	25.11.2004

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 32103-714.601	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2008/062961	International filing date *(day/month/year)* 07 May 2008 (07.05.2008)	Priority date *(day/month/year)* 07 May 2007 (07.05.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant QUESTOR PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - ☐ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV — Lack of unity of invention
   - ☐ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☐ Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 10 November 2009 (10.11.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MATTHEW V. GRUMBLING
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	04 AUG 2008
Applicant's or agent's file reference 32103-714.601	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/62961	07 May 2008 (07.05.2008)	07 May 2007 (07.05.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/55 (2008.04)
USPC - 514/220; 514/221

Applicant QUESTOR PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	25 July 2008 (25.07.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 3, 6, 10-13, 17-26, 46-60	YES
	Claims	1, 4, 5, 7-9, 14-16, 27-45, and 61-65	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1 - 65	NO
Industrial applicability (IA)	Claims	1 - 65	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 4, 5, 7-9, and 14-16 lack novelty under PCT Article 33(2) as being anticipated by US 2003/0181411 A1 to Bosch, et. al. (hereinafter 'Bosch').

As to claim 1, Bosch discloses a composition for nasal administration of a medicament (claim 6; para [0147]) comprising
-- a first population of particles having a first effective average particle size (claim 1; para [0070]-[0074]) and
-- a second population of particles having a second effective average particle size (claim 17; para [0070]-[0074]).
Bosch does not specifically disclose that the first effective average particle size is at least 1.5 times that of the second effective average particle size, but said limitation is inherently present in Bosch's disclosure. Bosch discloses that the first population of particles has an average size in the range of about 50 to about 500 nm (claim 1; para [0070]-[0074]) and the second population of particles has a average size in the range of about 2000 to about 10,000 nm (claim 17; para [0070]-[0074]), thereby disclosing the claimed limitation that the first effective average particle size is at least 1.5 times that of the second effective average particle size.

As to claim 4, Bosch further discloses a medicament where the particles in the medicament have an average size of greater than about 2,000 nm (claim 16; para [0043], [0070]).

As to claim 5, Bosch further discloses a medicament wherein the first population of particles is coated with at least one surface acting agent (claim 12, para [0073]).

As to claim 7, Bosch further discloses
-- the first population of particles has an average size in the range of about 50 to about 500 nm (claim 1; para [0070]-[0074]) and
-- the second population of particles has a average size in the range of about 2000 to about 10,000 nm (claim 17; para [0070]-[0074]).

As to claim 8, Bosch further discloses a pharmaceutical composition where the difference between the average particle size of the first and second populations is greater than about 100 nm (para [0116]-[0117]).

As to claim 9, Bosch further discloses a pharmaceutical composition, where the difference between the average particle size of the first and second particle populations is in a range greater than about 10% (para [0116]-[0117]).

As to claim 14, Bosch discloses:
-- a pharmaceutical particulate composition for nasal delivery of a medicament (claim 6; para [0147]) comprising
-- particulates having a multimodal particle size distribution (para [0072]).

As to claim 15, Bosch further discloses a composition where the particulates have a bimodal particle size distribution (claim 1, 17; para [0070]-[0074]).

As to claim 16, Bosch further discloses a composition where the particulates have a trimodal or higher order modal particle size distribution (para [0072]).

Claims 27-45 and 61-65 lack novelty under PCT Article 33(2) as being anticipated by US 2006/0198896 A1 to Liversidge, et. al. (hereinafter 'Liversidge').

As to claim 27, Liversidge discloses
-- an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles (claim 5), wherein:
-- the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 5); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 5).

As to claim 28, Liversidge further discloses a medicament with at least one benzodiazepine, specifically lorazepam (para [0001]).

As to claim 29, Liversidge further discloses an aerosol composition where the droplets of the aerosol have a mass median aerodynamic diameter of from about 2 mc.m to about 10 mc.m (claim 8).

********** SEE SUPPLEMENTAL SHEET TO CONTINUE **********

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 56 is objected to as lacking an antecedent basis for the "the non-aqueous dispersion or suspension." For the purpose of the search, claim 56 was construed as dependent from claim 46, not claim 53.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2):

As to claim 30, Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (para [0154]).

As to claim 31, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 32, Liversidge discloses
-- a method of administering a benzodiazepine drug to a patient (claim 13), comprising:
-- administering to the nose or nasal cavity an effective amount of an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles (claim 13), wherein
-- the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 17); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 16).

As to claim 33, Liversidge further discloses the use of clorazepam (claim 13).

As to claim 34, Liversidge further discloses a method where the nanoparticulate benzodiazepine drug particles have an effective average particle size of less than about 400 nm (claim 16).

As to claim 35, Liversidge further discloses a method where the droplets of the aerosol have a mass median aerodynamic diameter of from about 2 to about 10 mc.m (claim 20).

As to claim 36, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 37, Liversidge discloses a
-- pharmaceutical composition for nasal administration of benzodiazepine (para [0032]), comprising
-- benzodiazepine particles (claim 1) and
-- one or more surface active agents adsorbed to a surface thereof (claim 1).

As to claim 38, Liversidge further discloses the use of clorazepam (claim 1).

As to claim 39, Liversidge further discloses a pharmaceutical composition in the form of an aqueous suspension or dispersion (para [0033]).

As to claim 40, Liversidge further discloses a pharmaceutical composition in the form of a spray powder (para [0032]).

As to claim 41, Liversidge further discloses a pharmaceutical composition where the benzodiazepine particles have a average particle size less than approximately 50 nm to less than approximately 1000 nm (claim 4).

As to claim 42, Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (para [0154]).

As to claim 43, Liversidge discloses
-- a method of administering a benzodiazepine drug to a patient (claim 13), comprising
-- administering to the patient's nose or nasal cavity a pharmaceutical composition (para [0154]);
-- comprising particles of a benzodiazepine drug having a surface active agent adsorbed to a surface thereof (claim 13).

As to claim 44, Liversidge further discloses the use of clorazepam (claim 13).

As to claim 45, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 61, Liversidge discloses:
-- a nanoparticulate composition (claim 1) comprising:
-- (a) a benzodiazepine having an effective average particle size of less than about 2000 nm (claim 1)
-- wherein the benzodiazepine is selected from the group consisting of alprazolam (claim 1)
-- and (b) at least one surface stabilizer (claim 1).

As to claim 62, Liversidge further discloses the use of a surface stabilizer selected from the group consisting of a nonionic surfactant, an ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant (claim 2).

As to claim 63, Liversidge further discloses a composition wherein the surface stabilizer is hypromellose (claim 3).

********** SEE THE FOLLOWING SUPPLEMENTAL BOX TO CONTINUE **********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2) and the preceding Supplemental Box:

As to claim 64, Liversidge further discloses the composition, as above, formulated as an injectable composition (claim 9).

As to claim 65, Liversidge discloses
-- a method of treating a subject in need (claim 13) comprising administering to the subject a nanoparticulate benzodiazepine composition comprising (claim 13);
-- a benzodiazepine having an effective average particle size of less than about 2000 nm (claim 13);
-- wherein the benzodiazepine is alprazolam (claim 13); and
-- at least one surface stabilizer (claim 13).

Claims 2-3, 6, 10-13, 17-26, and 46-60 lack an inventive step under PCT Article 33(3) as being obvious over Bosch, as above, in view of Liversidge.

As to claim 2, Bosch discloses the medicament of claim 1. Liversidge discloses at least one benzodiazepine (para [0001]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using at least one benzodiazepine in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]).

As to claim 3, Liversidge further discloses a medicament with at least one benzodiazepine, specifically lorazepam (para [0001]).

As to claim 6, Bosch further discloses a medicament wherein the composition comprises a third population of particles having a third average particle size distribution different from the first and second populations of particles (para [0072]). Liversidge discloses the use of benzodiazepines as nanoparticles in a medicament (para [0001]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using benzodiazepine in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of several average particle sizes in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a multi-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]).

As to claim 10, the combination of Bosch and Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (Bosch, para [0033], [0147]; Liversidge, para [0154]).

As to claim 11, Liversidge further discloses the use of the medicament for an anticonvulsant effect (para [0001], defined as 'treating status epilepticus').

As to claim 12, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a benzodiazepine plasma concentration maximum Cmax (para [0067]). While neither Liversidge nor Bosch specifically discloses the limitation of obtaining a Cmax twice; such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because the claimed combination is an obvious experimental procedure. A skilled artisan would be motivated to measure the Cmax more than once to attain reliable data.

As to claim 13, neither Liversidge nor Bosch specifically discloses the limitation of obtaining a Cmax twice; first from 1 to 30 minutes after administration of the composition, and second from 5 to 360 minutes after administration of the composition. However, such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because adding the step of measuring the Cmax twice in two discrete time intervals to the disclosures of Liversidge and Bosch is an obvious experimental procedure. A skilled artisan would be motivated to measure the Cmax more than once to attain reliable data. Furthermore, this claim limitation simply recites the definition of "normal experimentation," as applied to the Liversidge and Bosch disclosures.

As to claim 17, Bosch discloses the medicament of claim 14, as above. Liversidge further discloses at least one benzodiazepine (para [0001]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using at least one benzodiazepine in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]).

As to claim 18, Liversidge further discloses a medicament with at least one benzodiazepine, specifically lorazepam (para [0001]).

As to claim 19, Bosch further discloses a medicament where the particles in the medicament have an average size of greater than about 2,000 nm (claim 16; para [0043], [0070]).

As to claim 20, Bosch further discloses a bimodal particle size distribution that fall within the range of:
-- the first population of particles has an average size in the range of about 25 to about 4,000 nm (claim 1; para [0070]-[0074]) and
-- the second population of particles has a average size of about 500 to about 10,000 nm (claim 17; para [0070]-[0074]).

********** SEE THE FOLLOWING SUPPLEMENTAL BOX TO CONTINUE **********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2) and the preceding Supplemental Box:

As to claim 21, Bosch further discloses a bimodal particle size distribution that fall within the range of:
-- the first population of particles has an average size in the range of about 50 to about 2,000 nm (claim 1; para [0070]-[0074]) and
-- the second population of particles has a average size of about 1,000 to about 10,000 nm (claim 17; para [0070]-[0074]).

As to claim 22, the combination of Bosch and Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (Bosch, para [0033], [0147]; Liversidge, para [0154]).

As to claim 23, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 24, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a first Cmax (para [0067]) occurring at a first Tmax after administration (para [0068], [0074]). While neither Liversidge nor Bosch specifically discloses the limitation of obtaining a Cmax and Tmax again at a later time; such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because the claimed combination is an obvious experimental procedure. A skilled artisan would be motivated to measure the Cmax and Tmax more than once to attain reliable data.

As to claim 25, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a benzodiazepine plasma concentration maximum Cmax (para [0067]). While neither Liversidge nor Bosch specifically discloses the limitation of obtaining a shoulder or Cshoulder; such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because the claimed combination is an obvious statistical procedure. A skilled artisan would be motivated to measure the Cshoulder to attain reliable and useful data.

As to claim 26, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a single plasma benzodiazepine concentration maximum Cmax (para [0067]).

As to claim 46, Bosch discloses the medicament of claim 1, as above. Liversidge discloses a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles (para [0036]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles in the medicament taught by Bosch to formulate a medicament utilizing dry nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]). Further, the use of a non-aqueous dispersion is an obvious composition to use in an aerosol, and is also taught by Bosch (para [0187]).

As to claim 47, Liversidge further discloses the use of clorazepam (claim 1).

As to claim 48, Liversidge further discloses
-- droplets of nanoparticulate benzodiazepine particles (para [0036]), with
-- the droplets having a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 5); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 5).

As to claim 49, Liversidge further discloses a non-aqueous dispersion or suspension is adapted for nasal administration (para [0036], [0209]).

As to claim 50, Liversidge further discloses a dispersion or suspension further comprises at least one additional ingredient selected from the group consisting of active pharmaceutical ingredients and enhancers (para [0091]). Bosch also discloses the use of additional ingredient selected from the group consisting of active pharmaceutical ingredients (para [0037]).

As to claim 51, the combination of Bosch and Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (Bosch, para [0033], [0147]; Liversidge, para [0154]).

As to claim 52, Liversidge further discloses administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or nasal cavity a pharmaceutical composition comprising a composition as above (para [0209]).

As to claim 53, Bosch discloses the medicament of claim 1. Liversidge discloses an aqueous dispersion or suspension of nanoparticulate benzodiazepine particles (claim 5). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using an aqueous dispersion or suspension of nanoparticulate benzodiazepine particles in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]). Further, the use of an aqueous dispersion is an obvious composition to use in a spray, and is also taught by Bosch (para [0140]).

********** SEE THE FOLLOWING SUPPLEMENTAL BOX TO CONTINUE **********

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2) and the preceding Supplemental Box:

As to claim 54, Liversidge further discloses the use of clorazepam (claim 1).

As to claim 55, Liversidge further discloses
-- an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles (claim 5), wherein:
-- the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 5); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 5).

As to claim 56, Liversidge further discloses a non-aqueous dispersion or suspension adapted for nasal administration (para [0154]).

As to claim 57, Liversidge further discloses a dispersion or suspension further comprises at least one additional ingredient selected from the group consisting of active pharmaceutical ingredients and enhancers (para [0091]).

As to claim 58, Liversidge further discloses a method of using a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine as above, comprising administering an effective amount of the dispersion or suspension to the nose by administering a therapeutically effective amount of the composition to at least one nostril (para [0154]).

As to claim 59, Liversidge further discloses a method of administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or nasal cavity a pharmaceutical composition comprising a composition as above (para [0154]).

As to claim 60, Liversidge further discloses the use of lorazepam (para [0209]).

Claims 1-64 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Electronic Patent Application Fee Transmittal

Application Number:	13495942
Filing Date:	13-Jun-2012
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Vanessa Agha
Attorney Docket Number:	35401-716.501

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	18721466
Application Number:	13495942
International Application Number:	
Confirmation Number:	7399
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Vanessa Agha
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.501
Receipt Date:	09-APR-2014
Filing Date:	13-JUN-2012
Time Stamp:	19:03:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$90
RAM confirmation Number	5152
Deposit Account	232415
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS.pdf	164631 7f476fee4d6b5bb068e2bfb1ffdfbc7857d4cb6e	yes	13

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	4
Information Disclosure Statement (IDS) Form (SB08)	5	13

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Foreign Reference	EP0396777A1.pdf	873011 e2f535a7bb3ea352e44aca0c6b7e7f244db37fbc	no	15

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
3	Foreign Reference	EP1417972A1.pdf	774989 59fc260877276d1763a836d5e1b8b9771ef118eb	no	13

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
4	Foreign Reference	JP01_151528.pdf	517069 330960b2469e006c48e9691d7de3e44a9e29028d	no	9

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
5	Foreign Reference	WO1991_19481.pdf	2850242 0bb49ff01434e0f6e9fa1a18e6cf63f1b121dba7	no	34

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
6	Foreign Reference	WO1994_05262A1.pdf	2689740 f46c701d7198537f7f1e244e00b0a56f964b9d0c	no	39

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
7	Foreign Reference	WO1995_000151A1.pdf	2327882 [illegible]a7e	no	28

Warnings:					
Information:					
8	Foreign Reference	WO2000_001390A1.pdf	1197779 ac8ab9276ed630bed4bc9dcceba84b106c19bae2	no	18
Warnings:					
Information:					
9	Foreign Reference	WO2005_018565A2.pdf	7063693 28cf77de737b60765a206f1fa94dc8b39c164c91	no	77
Warnings:					
Information:					
10	Foreign Reference	WO2008_027395.pdf	7491199 bfdfd7ede94206a36c21b9a43a31649d13fa3ff6	no	90
Warnings:					
Information:					
11	Foreign Reference	WO2003_055464A1.pdf	2720932 49d8ee9d6ae4535d3e2c8206b167898ed8721c60	no	32
Warnings:					
Information:					
12	Non Patent Literature	Ahsan_2003_Effects_of_the_permeability_.pdf	1535343 5d16a5fa21a63adb21d5f5adadd8f8130668e404	no	8
Warnings:					
Information:					
13	Non Patent Literature	Ahsan_2003_Sucrose_cocoate_a_component_.pdf	1362904 6d9a241cb45417f8f7a1e59fcd386df428f04f11	no	9
Warnings:					
Information:					
14	Non Patent Literature	Albert_1975_Pharmacokinetics_of_diphenhydramine_.pdf	1209170 77257c5f837bbd28b55bc500526c4986bfcf5cf9	no	12
Warnings:					
Information:					
15	Non Patent Literature	Arnold_2004_Correlation_of_tetradecylmaltoside_.pdf	1727509 3e39cb0bbed13729689c3f15680bd413c6c00457	no	9
Warnings:					
Information:					
16	Non Patent Literature	Beam_1977_Blood_Brain_Cerebrospinal_Fluid_Concentrations.pdf	2259141 [illegible]5fe76b	no	7

Warnings:					
Information:					
17	Non Patent Literature	Bhairi_2001_A_guide_to_the_properties_.pdf	2015393 b406602bf75e3a58dd93f78db60c2524ea9bd0ca	no	43
Warnings:					
Information:					
18	Non Patent Literature	Birkett_1990_How_Drugs_are_Cleared_by_the_Liver.pdf	279116 4336e122ade80f801d3e5a1a5bec2330ef524310	no	2
Warnings:					
Information:					
19	Non Patent Literature	Birkett_1991_Bioavailability_and_First_Pass_Clearance.pdf	609661 4f6ed2846f2aae3bd554bd82d9246d2a672dfc5b	no	3
Warnings:					
Information:					
20	Non Patent Literature	CA2723470_OA_07JUN2012.pdf	400068 8bd2c230796385bf8eb3e828724f76e8078b499c	no	3
Warnings:					
Information:					
21	Non Patent Literature	Castro_2005_Ecologically_safe_alkyl_.pdf	1914785 9bca51dd2683c52f685dc92dedf5e58ceb5192d7	no	15
Warnings:					
Information:					
22	Non Patent Literature	Chavanpatil_2005_Nasal_Drug_Delivery_of_Sumatriptan_Succinate.pdf	366815 bd3e67dc254f8a6364699da76296548b10e3820a	no	3
Warnings:					
Information:					
23	Non Patent Literature	Chen_2005_Peptide_Drug_Permeation.pdf	788307 7b90690e6f05f512ae7ca08083ce152216e2d3e8	no	5
Warnings:					
Information:					
24	Non Patent Literature	Chen_Quay_2009_Identification_of_tight_junction_Document_.pdf	2356198 9160ce58454bf530803a13e90230208a6f0eded7	no	14
Warnings:					
Information:					
25	Non Patent Literature	Chiou_1989_Improvement_of_Systemic_Absorption_of_Insulin.pdf	3054624 [illegible]3f0b	no	4

Warnings:					
Information:					
26	Non Patent Literature	Chiou_1989_Systemic_Delivery_of_Insulin_Through_Eyes.pdf	4898377 eb6cca4b8c8bb6bf099bc342d0be6950d4e87225	no	13
Warnings:					
Information:					
27	Non Patent Literature	Communication_from_CN_Pat_Office_AO_.pdf	296944 0750d813ac6a386f4740ac95ee02a7ab083dff0c	no	3
Warnings:					
Information:					
28	Non Patent Literature	Davis_2003_Absorption_Enhancers_for_Nasal_Drug_Delivery.pdf	3814193 bef397ce163fc3b7fc1b1efa939bc44a47c38ce8	no	22
Warnings:					
Information:					
29	Non Patent Literature	DeVry_2000_Effects_of_selected_serotonin_.pdf	2272048 2259b281d6bd0a5bcfab0a916c83ee8f91a45c18	no	13
Warnings:					
Information:					
30	Non Patent Literature	Definition_of_encephalin_2012-09-13_at_the_medical-dictionary_thefreedictionary_.pdf	156482 7d55a3ba8de6b89b96ded49242eb65277911be31	no	1
Warnings:					
Information:					
31	Non Patent Literature	Definition_of_pilus_2013_.pdf	203899 5f6af85616b6ea13362cff6e447283bc2793189d	no	2
Warnings:					
Information:					
32	Non Patent Literature	Definition_of_villus_2013_.pdf	301150 e8ea88a821be822e292b132a22702c96709b0dfc	no	2
Warnings:					
Information:					
33	Non Patent Literature	Drewe_1993_Enteral_absorption_of_octreotide.pdf	999024 49487f200a45375ea539b8094c05e5bc6e3ea1a3	no	6
Warnings:					
Information:					
34	Non Patent Literature	Duquesnoy_1998_Comparative_clinical_pharmacokinetics_.pdf	958392 [illegible]ecb238	no	6

Warnings:					
Information:					
35	Non Patent Literature	Edwards_2004_GLP-1_target_for_.pdf	243316 71f19f4046f7ceb8f2d693843dfcd34388cd3ba6	no	5
Warnings:					
Information:					
36	Non Patent Literature	Eley_2001_In_Vitro_Assessment_of_Alkylglycosides.pdf	923623 59312e0340b9ae2b19aa33e6fcb20262cccf0c1c	no	7
Warnings:					
Information:					
37	Non Patent Literature	EP09835809_ESR_13Nov2012.pdf	247294 6c7c39d135f5cb77f8a1ce113586d00fbe496e84	no	3
Warnings:					
Information:					
38	Non Patent Literature	Fricker_1996_Permeation_enhancement_of_octreotide_.pdf	2640153 a3635c6911c8f61fc57bebeb211280bd4040afeb	no	7
Warnings:					
Information:					
39	Non Patent Literature	Gordon_1985_Nasal_Absorption_of_Insulin-Enhancement.pdf	2132283 f780ecde4b254b01b215a7155c500dc29ec6fdba	no	5
Warnings:					
Information:					
40	Non Patent Literature	Hathcox_1996_Inhibitory_effects_of_sucrose_.pdf	1865291 402d2ea7133fbf13f4aa4b38de14845d220f7955	no	13
Warnings:					
Information:					
41	Non Patent Literature	Hovgaard_1992_Insulin_Stabilization_and_GI_Absorption.pdf	3378595 e405eca24b1e914781027f1e30c72cb9698afc78	no	10
Warnings:					
Information:					
42	Non Patent Literature	Hovgaard_1996_Stabilization_of_insulin_.pdf	1131608 18116f5353710719cd7a682688d7308b61cc1b5d	no	7
Warnings:					
Information:					
43	Non Patent Literature	Hovgaard_1996_Stabilization_of_Insulin_by_Alkylmaltosides.pdf	5161362 [illegible]6c0ba	no	7

Warnings:					
Information:					
44	Non Patent Literature	PCT_US2011_056735_22June2012.pdf	256602 7c6a49ed84350488c0451f7af1ea6b87408b1f86	no	4
Warnings:					
Information:					
45	Non Patent Literature	JP2010507633_OA_23OCT2012.pdf	417839 e916428a870d5c363af85832efa9381569bc8f12	no	10
Warnings:					
Information:					
46	Non Patent Literature	Katzung_1998_Basic_and_Clinical_Pharmacology_7th_Edition.pdf	2862877 4e361efe938493c47b31772eae64b49d59c591d6	no	18
Warnings:					
Information:					
47	Non Patent Literature	Lacy_1999_Drug_Information_Handbook_7th_Edition.pdf	1230625 be208ada19d8b12c08c8b24d13bea6fc305ef7f5	no	6
Warnings:					
Information:					
48	Non Patent Literature	Lahat_1998_Intranasal_midazolam_for_childhood_.pdf	228935 e877e17f3c649d607af1440902bd2a5bb6373ca3	no	1
Warnings:					
Information:					
49	Non Patent Literature	Lehninger_1982_Principles_of_Biochemistry_with_an_Extended_Discussion.pdf	1001727 fbcbb5b237aefcb619238f1e9f9198558d0406da	no	4
Warnings:					
Information:					
50	Non Patent Literature	Maa_2000_Biopharmaceutical_Powder_Particle_.pdf	2627184 309b368b6b33ab9c91668ca5b5fcd142532c3978	no	21
Warnings:					
Information:					
51	Non Patent Literature	Material_Safety_Data_Sheet_for_Anatrace_2012_.pdf	179818 da009e81336d42578a30c8bfe1e49382a07a978a	no	1
Warnings:					
Information:					
52	Non Patent Literature	Mathew_1997_Serotonin_1D_5-HT1D_.pdf	6119017 [illegible]	no	23

Warnings:					
Information:					
53	Non Patent Literature	Matsumura_1990_Surface_activities_biodegradability_.pdf	1239285 90bcbe7e374f937d32fe61785706582a2e9e6307	no	6
Warnings:					
Information:					
54	Non Patent Literature	Moses_1983_Insulin_Administered_Intranasally_as_an_Insulin-Bite_Salt_Aerosol.pdf	1490067 27e2bcbff649cfde9791ed2a9db9f2c453185d19	no	8
Warnings:					
Information:					
55	Non Patent Literature	Murakami_1992_Assessment_of_Enhancing_Ability_of_Medium-Chain.pdf	3431343 86086d9c5ba3e65105b68ea692c78bf1c7dd0209	no	11
Warnings:					
Information:					
56	Non Patent Literature	Ogiso_1991_Percutaneous_Absorption_of_Elcatonin.pdf	1865194 0fafcd89530999b563a9431c3c39f4a11a407dd2	no	5
Warnings:					
Information:					
57	Non Patent Literature	Olesen_2005_The_headaches_.pdf	101788 4591cde660de920ed5f8898adaa8f8d0cacd46c4	no	1
Warnings:					
Information:					
58	Non Patent Literature	Paulsson_2001_Controlled_Drug_Release_from_Gels.pdf	1286706 1330cef474c9a60a9e9d5e4c63590d4809b36f86	no	7
Warnings:					
Information:					
59	Non Patent Literature	PCTUS0862961_IPRP_10NOV2009.pdf	470387 bb41ba5cd9deb4426c99ae15c20880f62a17932f	no	9
Warnings:					
Information:					
60	Fee Worksheet (SB06)	fee-info.pdf	30564 d7aeca516eb8dfcf8b74c609ef65300d77f74712	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	105014193		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt	Group Art Unit: 1612
Serial Number: 13/495,942	Examiner: Adam C. Milligan
Filing Date: 6/13/2012	**CONFIRMATION NO: 7399**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: April 9, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Madam:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☐ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☒ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☒ a fee of $90.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.501).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: 4/9/2014

By: /Matthew V. Grumbling/
Matthew V. Grumbling
Reg. No. 44,427

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 35401-716601	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2009/038696	International filing date *(day/month/year)* 27 March 2009 (27.03.2009)	Priority date *(day/month/year)* 28 March 2008 (28.03.2008)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant HALE BIOPHARMA VENTURES, LLC		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 28 September 2010 (28.09.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Philippe Becamel e-mail: pt12.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
WILSON SONSINI GOODRICH & ROSATI

650 PAGE MILL ROAD PALO ALTO CA 94304 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)* **28 SEPTEMBER 2009 (28.09.2009)**

Applicant's or agent's file reference
35401-716601

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/038696	**27 MARCH 2009 (27.03.2009)**	28 MARCH 2008 (28.03.2008)

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

A61K 31/5513(2006.01)i, A61K 31/355(2006.01)i, A61K 9/16(2006.01)i, A61K 47/10(2006.01)i, A61P 25/22(2006.01)i

Applicant

HALE BIOPHARMA VENTURES, LLC et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302 -701, Republic of Korea Facsimile No. 82-42-472-7140	28 SEPTEMBER 2009 (28.09.2009)	KIM, YONG Telephone No.82-42-481-8164

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/038696

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material
   - ☐ a sequence listing
   - ☐ table(s) related to the sequence listing

   b. format of material
   - ☐ on paper
   - ☐ in electronic form

   c. time of filing/furnishing
   - ☐ contained in the international application as filed.
   - ☐ filed together with the international application in electronic form.
   - ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/038696

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 20-47

because:

☒ the said international application, or the said claims Nos. 20-45
relate to the following subject matter which does not require an international search *(specify)*:

The subject-matter of claims 20-45 does not require an opinion with respect to industrial applicability as it is substantially directed to method for treatment of the human body by therapy (Rules 43 bis.1(b), Rule 67.1(iv)).

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 46, 47
are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 46 and 47 relate to a composition, and are indicated as referring to claims 20 and 21, respectively. However, the claims 20 and 21 relate to a method of treating a patient. Thus claims 46 and 47 are too unclear to make meaningful search possible.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 20-47

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/038696

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-19	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims	None	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: WO 2007043057 A2 (19 April 2007)
D2: WO 2005117830 A1 (15 December 2005)

The present claims 1-19 relate to a pharmaceutical composition for nasal administration comprising (a) a benzodiazepine drug, (b) tocopherols or tocotriols (30-90% (w/w)), (c) alcohols or glycols (10-70% (w/w)) in a pharmaceutically-acceptable formulation for administration ~~to~~ through nasal mucosal membranes of patients.

D1 and D2 are considered to represent the most relevant state of the art. D1 discloses compositions for intranasal administration, which comprises diazepam, water, phospholipids and C2-C4 alcohols or glycols (12-30% (w/w)), tocopherol (0.001-5% (w/w)). D2 discloses a liquid depot formulation comprising a lipid, phospholipid and tocopherol.

1. Novelty and Inventive Step

Although D1 and D2 disclose the compositions for intranasal administration, the constituents and their ratio in the composition of the present claims are different from those of D1 or D2 in that the composition of D1 or D2 contains the phospholipids, and the ratio of tocopherol is 30-90% (w/w) in D1, whereas that of the present claims does not contain the phospholipids, and the ratio of tocopherol is 0.001-5% (w/w).

Moreover, the pharmaceutical composition (solution or suspension) of the present claims exhibits good stability, good pharmacokinetic profile and low toxicity.

Thus, the subject-matter of claims 1-19 is novel and inventive under Article 33(2) and 33(3) PCT.

2. Industrial Applicability

Claims 1-19 appear to be industrially applicable under Article 33(4) PCT.

Electronic Acknowledgement Receipt

EFS ID:	18721538
Application Number:	13495942
International Application Number:	
Confirmation Number:	7399
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Vanessa Agha
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.501
Receipt Date:	09-APR-2014
Filing Date:	13-JUN-2012
Time Stamp:	19:12:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	PCTUS0938696_IPRP_28SEP2010.pdf	220438 2b0580afbcb66a2017cc24a8043129228cf3babf	no	5

Warnings:	
Information:	

2	Non Patent Literature	Phillips_2001_The_challenge_of_gene_.pdf	932670 82bfd5f4b0e48da7c9e29358c056cc9428cd227a	no	6
Warnings:					
Information:					
3	Non Patent Literature	Pillion_1991_Systemic_Absorption_of_Insulin_Delivered_Topically.pdf	6618981 9f6d28a2bab26cdd4bf6816e32433680b5cfb64b	no	7
Warnings:					
Information:					
4	Non Patent Literature	Pillion_2002_Synthetic_long_chain_.pdf	1254954 398ddc1c00f87d724d5054656de9d03f87114f30	no	7
Warnings:					
Information:					
5	Non Patent Literature	Pirollo_2008_Targeted_delivery_of_small_.pdf	850304 062cda9e89a59748f3035593c4441bf7f7179f22	no	4
Warnings:					
Information:					
6	Non Patent Literature	Richards_1971_Inactivation_of_resistant_.pdf	702810 c33f60b5148e20e6f8b2faca36bf8388aa7a39d8	no	5
Warnings:					
Information:					
7	Non Patent Literature	Salzman_1985_Intranasal_Aerosolized_Insulin.pdf	5558987 dcd80fc72ce3e328242f72a45067bb3764ae848e	no	7
Warnings:					
Information:					
8	Non Patent Literature	Sanders_1986_Pharmacokinetics_of_ergotamine_.pdf	718184 334c50f2be8bc2c4bf2b9b14db4cf9b215cb9ad0	no	4
Warnings:					
Information:					
9	Non Patent Literature	Shim_1993_Administration_Route_Dependent_.pdf	2088442 98582d18d2db3b79db2a3f9772e597b795cc3106	no	17
Warnings:					
Information:					
10	Non Patent Literature	Stevens_1995_Use_of_Glucagon_to_Treat_Neonatal.pdf	2095868 594ca9f894ea68517f510f4f9db35ff1df2505be	no	3
Warnings:					
Information:					

11	Non Patent Literature	Swabrick_2002_Encyclopedia_of_Pharmaceutical_Technology_.pdf	281910 550bdc1b2868a61207bd6589fbfd7ca5d09ba76e	no	2
Warnings:					
Information:					
12	Non Patent Literature	Tsuchido_1987_Lysis_of_Bacillus_subtilis_Cells_by_Glycerol.pdf	3166784 a357d422b05fce16bfaf80f6b166989ea2d1d39f	no	4
Warnings:					
Information:					
13	Non Patent Literature	Turker_2004_Nasal_route_and_drug_.pdf	875630 1be06a1417a09125decec785bd82ae5abbbd052c	no	6
Warnings:					
Information:					
14	Non Patent Literature	Turton_1996_A_role_for_glucagon_like_.pdf	1073961 8deb1d2bc5e294c8f7d5196507319b18c3a35564	no	4
Warnings:					
Information:					
15	Non Patent Literature	US12116842_OA_02APR2013.pdf	625390 b15b0b533c6a0c604cdf07ecc0cdc1728526b1d6	no	17
Warnings:					
Information:					
16	Non Patent Literature	US12116842_OA_15NOV2011.pdf	626516 ef70b5070a30a6aa97cc31326cd9ae6877bb8852	no	15
Warnings:					
Information:					
17	Non Patent Literature	US12116842_OA_17DEC2013.pdf	499399 4d48768a56a295e16f9e11adc7e4d523f6f07880	no	12
Warnings:					
Information:					
18	Non Patent Literature	US12116842_OA_25MAY2011.pdf	517557 12c9d30c1ca3bab3abeb3087db8558829b076fed	no	13
Warnings:					
Information:					
19	Non Patent Literature	US12266529_OA_10JUL2012.pdf	672641 a3d74af8d19ca37ff4808fceafec507870f2e8f8	no	16
Warnings:					
Information:					

20	Non Patent Literature	US12266529_OA_16NOV2011.pdf	582557 1860737bfdc59251229a313f543c191552ceb398	no	15
Warnings:					
Information:					
21	Non Patent Literature	US12413439_OA_18MAR2011.pdf	299732 bb2d355f99f84bf7b2484d57c6176bc537d9939a	no	14
Warnings:					
Information:					
22	Non Patent Literature	US12413439_OA_21NOV2011.pdf	303247 5355ce4751949113c695ec02aa4aa21e1a01ac54	no	9
Warnings:					
Information:					
23	Non Patent Literature	Vidal_2005_Making_sense_of_antisense_.pdf	1315281 0b941198eca4158c56abcece7b1943c46cebb8e4	no	7
Warnings:					
Information:					
24	Non Patent Literature	Watanabe_2000_Antibacterial_Carbohydrate_Monoesters.pdf	2614493 1dafe1b4450d02d4b7e581a012e6e526591c1174	no	4
Warnings:					
Information:					
25	Non Patent Literature	Weber_1984_Metabolism_of_orally_.pdf	1325054 891474d8dd14f3351acd4b067c3dc9ebb9e1f408	no	8
Warnings:					
Information:					
26	Non Patent Literature	Webpage_for_Anatrace_products_of_Affymetrix_.pdf	251292 65cc6b535506c2b217edf91061df4ced74e1bda2	no	2
Warnings:					
Information:					
27	Non Patent Literature	Yamamoto_1989_The_Ocular_Route_for_Systemic_Insulin_Delivery.pdf	5620625 8c5158d55c3044989bf2f400bf69e873904644de	no	7
Warnings:					
Information:					
28	Non Patent Literature	Yu_Xinrui_2001_Triptan_Medicament_and_.pdf	973047 2b529955d48494acc7547d8790ec7f368be29953	no	6
Warnings:					
Information:					

Total Files Size (in bytes):	42666754

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 07/24/2014
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 07/24/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	06/13/2012	Steve Cartt	35401-716.501	7399

TITLE OF INVENTION: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	10/24/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 07/24/2014
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	06/13/2012	Steve Cartt	35401-716.501	7399

TITLE OF INVENTION: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	10/24/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLIGAN, ADAM C	1612	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	06/13/2012	Steve Cartt	35401-716.501	7399

21971 7590 07/24/2014

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
MILLIGAN, ADAM C	
ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 07/24/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/495,942	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *claim amendments submitted 4/1/2014* .
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,3-7,10-19,21,22,57-59 and 66*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 9pgs(4/9/2014)
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

The present application is being examined under the pre-AIA first to invent provisions.

Rejoinder of Claims

Claims 1, 3-7, 10-19, 21, 22, 57-59 and 66 are allowable. The restriction requirement between product and process claims, as set forth in the Office action mailed on 5/8/2013, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Specifically, the restriction requirement of 5/8/2013 is fully withdrawn. Claims directed to a method remain withdrawn from further consideration because they do not all require all the limitations of an allowable generic linking claim as required by 37 CFR 1.141. It is also noted that many of the method claims would currently be rejected under 35 U.S.C. 112 for being indefinite due to numerical values being contained in parentheses.

In view of the above noted withdrawal of the restriction requirement, Applicants are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

/ADAM C MILLIGAN/

Primary Examiner, Art Unit 1612

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/14/2014								
1	1	=								
	2	N								
2	3	=								
3	4	=								
4	5	=								
5	6	=								
6	7	=								
	8	N								
	9	N								
7	10	=								
8	11	=								
9	12	=								
10	13	=								
11	14	=								
12	15	=								
13	16	=								
14	17	=								
15	18	=								
16	19	=								
	20	N								
17	21	=								
18	22	=								
	23	N								
	24	N								
	25	N								
	26	N								
	27	N								
	28	N								
	29	N								
	30	N								
	31	N								
	32	N								
	33	N								
	34	N								
	35	N								
	36	N								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/14/2014								
	37	N								
	38	N								
	39	N								
	40	N								
	41	N								
	42	N								
	43	N								
	44	N								
	45	N								
	46	N								
	47	N								
	48	N								
	49	N								
	50	N								
	51	N								
	52	N								
	53	N								
	54	N								
	55	N								
	56	N								
19	57	=								
20	58	=								
21	59	=								
	60	N								
	61	N								
	62	N								
	63	N								
	64	N								
	65	N								
22	66	=								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	Art Unit
	ADAM C MILLIGAN	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	221	7/14/2014	AM

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	9/27/2013	AM
EAST and STN searches (benzodiazepine, tocopherol or tocotrienol,ethanol or benzyl alcohol, alkyl glycoside, nasal)	9/27/2013	AM
Updated EAST and STN searches	7/14/2014	AM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	221	7/14/2014	AM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 7399

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/495,942	06/13/2012 RULE	424	1612	35401-716.501

APPLICANTS

INVENTORS

Steve Cartt, San Carlos, CA;
David Medeiros, South San Francisco, CA;
Garry Thomas Gwozdz, Jim Thorpe, PA;
Andrew Loxley, Philadelphia, PA;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;

**** CONTINUING DATA ***************************

This application is a CIP of 12/413,439 03/27/2009
and claims benefit of 61/497,017 06/14/2011
and claims benefit of 61/570,110 12/13/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
06/21/2012

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☐ Yes ☑ No	/ADAM C MILLIGAN/ Examiner's Signature	☐ Initials	CA	5	65	2

ADDRESS

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050
UNITED STATES

TITLE

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

FILING FEE RECEIVED		
1993	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

CPC						
Symbol					**Type**	**Version**
A61K		9	/	0043	I	2013-01-01
A61K		31	/	355	F	2013-01-01
A61K		31	/	5513	I	2013-01-01
A61K		9	/	008	I	2013-01-01
A61K		45	/	06	I	2013-01-01
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		31	/	5513	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01
A61K		31	/	355	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	22	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612	07/14/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
514	221	A	6	1	K	31 / 55 (2006.01.01)						
CROSS REFERENCE(S)												
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	22	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612	07/14/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	14	17		33		49		65						
	2	15	18		34		50	22	66						
2	3	16	19		35		51								
3	4		20		36		52								
4	5	17	21		37		53								
5	6	18	22		38		54								
6	7		23		39		55								
	8		24		40		56								
	9		25		41	19	57								
7	10		26		42	20	58								
8	11		27		43	21	59								
9	12		28		44		60								
10	13		29		45		61								
11	14		30		46		62								
12	15		31		47		63								
13	16		32		48		64								

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 22	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612 (Primary Examiner)	07/14/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	1	of	9	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2002-0110524 Al	8/15/2002	Cowan et al.	
	2.	US-2002-0141971 Al	10/3/2002	Frey	
	3.	US-2003-0017203 Al	6/23/2003	Crotts et al.	
	4.	US-2003-0040497 Al	2/27/2003	Teng et al.	
	5.	US-2003-0087820 Al	5/1/2003	Young et al.	
	6.	US-2003-0100755 Al	5/29/2003	Sham et al.	
	7.	US-2003-0118547 Al	6/1/2303	Vandenberg	
	8.	US-2003-0118594 Al	6/26/2003	Nag et al.	
	9.	US-2003-0158206 Al	8/21/2003	Billotte et al.	
	10.	US-2003-0170206 Al	9/11/2003	Rasmussen et al.	
	11.	US-2004-0115135 Al	6/17/2004	Quay	
	12.	US-2004-0126358 Al	7/1/2004	Warne et al.	
	13.	US-2004-0147473 Al	7/29/2004	Warriell, Jr.	
	14.	US-2004-0258663 Al	12/23/2004	Quay & El-Shafy	
	15.	US-2005-0130260 Al	6/16/2005	Linden et al.	
	16.	US-2005-0234101 Al	10/20/2005	Stenkamp et al.	
	17.	US-2006-0045869 A1	03/02/2006	Meezan et al.	
	18.	US-2006-0046969 Al	3/2/2006	Maggio	
	19.	US-2006-0106227 Al	5/18/2006	Reddy et al.	
	20.	US-2006-0147386 Al	07-062006	Wermling	
	21.	US-2007-0298010 Al	12/27/2007	Maggio	
	22.	US-2007-0059254 Al	3/15/2007	Singh	
	23.	US-2007-0098805 Al	5/3/2007	Liversidge	
	24.	US-2008-0268032 Al	10/30/2008	Maggio	
	25.	US-2009/0258865 Al	10/15/2009	Cartt et al.	
	26.	US-2010-0203119 Al	8/12/2010	Leane et al.	
	27.	US-2010-0209485 Al	8/19/2010	Maggio	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	2	of	9	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	28.	US-3,547,828	12/15/1970	Mansfield et al.	
	29.	US-3,849,341	11/19/1974	Lambeiti	
	30.	US-4,397,951	8/9/1983	Taki et al.	
	31.	US-4,748,158	5/31/1988	Biermann et al.	
	32.	US-4,868,289	9/1/1989	Magnusson et al.	
	33.	US-4,921,838	5/1/1990	Catsimpoolas et al.	
	34.	US-5,182,258	1/1/1993	Chiou	
	35.	US-5,192,528	3/3/1993	Radhakrishnan et al.	
	36.	US-5,236,707	8/17/1993	Stewart	
	37.	US-5,268,461	12/7/1993	Shoji et al.	
	38.	US-5,308,531	5/3/1994	Urfer et al.	
	39.	US-5,317,010	5/31/1994	Pang et al.	
	40.	US-5,369,095	11/29/1994	Kee et al.	
	41.	US-5,550,220	8/27/1996	Meyer et al.	
	42.	US-5,639,733	6/17/1997	Koike et al.	
	43.	US-5,738,845	4/14/1998	Imakawa	
	44.	US-5,789,375	8/4/1998	Mukae et al.	
	45.	US-5,795,896	8/18/1998	Löfroth et al.	
	46.	US-5,814,607	9/29/1998	John S. Patton	
	47.	US-5,817,634	10/1/1998	Meezan et al.	
	48.	US-5,955,425	9/21/1999	Morley et al.	
	49.	US-6,004,574	12/21/1999	Backstrom et al.	
	50.	US-6,254,854	7/3/2001	Edwards, et al.	
	51.	US-6,316,410	11/13/2001	Barbier et al.	
	52.	US-6,395,300	5/28/2002	Straub et al.	
	53.	US-6,461,591	10/8/2002	Keller et al.	
	54.	US-6,482,834	9/20/2001	Spada, et al.	
	55.	US-6,495,498	12/17/2002	Niemiec et al.	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	3	of	9	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	56.	US-6,524,557	2/25/2003	Backstrom et al.	
	57.	US-6,794,357	9/21/2004	Backstrom et al.	
	58.	US-6,932,962	8/23/2005	Backstrom et al.	
	59.	US-6,991,785	1/31/2006	Frey	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	60.	EP-0396777 A1	11/14/1990	OTSUKA PHARMA CO LTD		
	61.	EP-1417972 A1	5/12/2004	ELI LILLY & COMPANY		
	62.	JP1-151528 (English Abstract and Claims)	6/14/1989	TAIHO YAKUHN KOGYO KK		X
	63.	WO-1991-019481	12/26/1991	ALLERGAN, INC.		
	64.	WO-1994-05262 A1	3/17/1994	F.H. FAUDLING & CO. LTD.		
	65.	WO-1995-000151 A1	1/5/1995	UAB RESEARCH FOUNDATION		
	66.	WO-2000-001390 A1	01/13/2000	RECORDATI S.A. CHEMICAL AND PHARMACEUTICAL COMPANY ET AL.		
	67.	WO-2003-055464	07/10/2003	BESINS INTERNATIONAL BELGIQUE ET AL.		
	68.	WO-2005-018565 A2	03/03/2005	TRANSORAL PHARMACEUTICAL S, INC.		
	69.	WO-2008-027395 A2	3/6/2008	Jazz Pharmaceuticals		

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	4	of	9	Attorney Docket Number	35401-716.501

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	70.	Ahsan et al., "Effects of the permeability enhancers, tetradecylmaltoside and dimethyl-β-cyclodextrin, on insulin movement acress human bronchial epithelial cells", European Journal of Pharmaceutical. Sciences, 2003; 20: 27-34	
	71.	Ahsan et al., "Sucrose cocoate, a component of cosmetic preparations enhances nasal and ocular peptide absorption", Int J Pharm, 2003; 251: 195-203.	
	72.	Albert et al., "Pharmacokinetics of diphenhydramine in man", J. Pharmacokinet, Biopharm., 3(3):159-170 (1975).	
	73.	Arnold et al., "Correlation of tetradecylmaltoside induced increases in nasal peptide drug delivery with morphological changes in nasal eithelial cells", J. Pharm. Sci. 93(9):2205-2213 (2004).	
	74.	Beam et al., "Blood, Brain, Cerebrospinal Fluid Concentrations of Several Antobiotics in Rabbits with Intact and Inflamed Meninges", Antimicrobal Agents and Chemotherapy, December 1977, pp 710-716	
	75.	Bhairi S.M., "A guide to the properties and uses of detergents in biological systems", *Calbiochem,* pp. 1-42 (2001).	
	76.	Birkett et al., "Bioavailability and First Pass Clearance", Australian Prescriber, 1991, pp. 14-16, Vol. 14.	
	77.	Birkett et al., "How Drugs are Cleared by the Liver", Australian Prescriber, 1990, pp. 88-89, Vol. 13, No. 4.	
	78.	CA 2,723,470 Office action dated June 7, 2012	
	79.	Castro et al., "Ecologically safe alkyl glucoside-based gemini surfactants", ARKIVOC, xii:253-267 (2005)	
	80.	Chavanpatil and Vavia, "Nasal drug delivery of sumatriptan succinate", Pharmazie., 2005 May:60(5):347-349.	
	81.	Chen et al., "Peptide Drug Permeation Enhancement By Select Classes of Lipids", presented ath the 45th American Society of Cell Biology, S.F., CA, December 10-14 (2005); 1 page total.	
	82.	Chen-Quay et al., "Identification of tight junction modulating lipids", J. Pharm. Sci., 98(2):606-619 (2009)	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	5	of	9	Attorney Docket Number	35401-716.501

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	83.	Chiou et al., "Improvement of Systemic Absorption of Insulin Through Eyes with Absorption Enhancers", Journal of Pharmaceutical Sciences, October 1989, pp. 815-818, Vol. 78, No. 10	
	84.	Chiou et al., "Systemic Delivery of Insulin Through Eyes to Lower the Glucose Concentration", Journal of Ocular Pharmacology, 1989, pp. 81-91, Vol. 5, No. 1.	
	85.	Chinese Patent Office from Application No. CN200980157305.0 dated January 28, 2013	
	86.	Davis and Illum, "Absorption enhancers for nasal drug delivery", Clin. Pharmacokine., 2003:42(13):107-28	
	87.	De Vry and Schreiber, "Effects of selected serotonin 5-HT(1) and 5-HT(2) receptor agonists on feeding behavior: possible mechanisms of action", Neurosci. Biobehav. Rev., 24(3):341-53 (2000)	
	88.	Definition downloaded 13 September 2012 at the medical-dictionary.thefreedictionary.com/p/encephalin	
	89.	Definition of pilus, Merriam-Webster Medical Dictionary, http://www.merriam-webster.com/medical/pilus, accessed online on 28 May 2013	
	90.	Definition of villus, Merriam-Webster Medical Dictionary, http://www.merriam-webster.com/medical/villus, accessed online on 28 May 2013	
	91.	Drewe et al., "Enteral absorption of octreotide: absorption enhancement by polyoxyethylene-24-cholesterol ether", Br. J. Pharmacol., 108(2):298-303 (1993).	
	92.	Duquesnoy et al., "Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration", Eur. J. Pharm. Sci., 6(2):99-104 (1998)	
	93.	Edwards CM., "GLP-1: target for a new class of antidiabetic agents?", J.R. Soc. Med., 97(6):270-274 (2004).	
	94.	Eley and Triumalashetty, "In vitro assessment of alkylglycosides as permeability enhancers", AAPS PharmsciTech., 2(3): article 19, pages 1-7 (2001).	
	95.	European Search Report (ESR) from EP 09 83 5809 dated 13 November 2012	
	96.	Fricker et al., "Permeation enhancement of octreotide by specific bile salts in rats and human subjects: in vitro, in vivo correlations", Br. J. Pharmacol., 117(1):217-23 (1996)	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	6	of	9	Attorney Docket Number	35401-716.501

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	97.	Gordon et al., "Nasal Absorption of Insulin: Enhancement by Hydrophobic Bile Salts", Proceedings of the National Academy of Sciences of the United States of America, November 1985, pp. 7419-7423, Vol. 82.	
	98.	Hathcox and Beuchat, "Inhibitory effects of sucrose fatty acid esters, alone and in combination with ethylenediaminetetraacetic acid and other organic acids, on viability of Escherichia coli 0157:H7", Food Microbiology, Volume 13, Issue 3, 213-225 (1996).	
	99.	Hovgaard et al., "Insulin Stabilization and GI Absorption", Journal of Controlled Release, March 1992, pp. 99-108, Vol. 19, Issue 1-3.	
	100.	Hovgaard et al., "Stabilization of insulin by alkylmaltosides. A. Spectroscopic evaluation", International Journal of Pharmaceutics, 132(1-2):107-113 (1996).	
	101.	Hovgaard et al., "Stabilization of Insulin by Alkylmaltosides. B. Oral Absorption in Vivo in Rats", International Journal of Pharmaceutics, 1996, pp. 115-121, Vol 132.	
	102.	International Search Report (ISR) from PCT/US2011/056735 dated June 22, 2012	
	103.	JP2010-507633 Office Action dated October 23, 2012	X
	104.	Katzung, B., "Basic and Clinical Pharmacology, 7th Edition", Appleton & Lange: Stamford, Connecticut, 1998, pp. 34-49	
	105.	Lacy, C, et al., "Drug Information Handbook, 7th Edition 1999-2000" Lexi-Comp, Inc., 1999, pp. 163-164.	
	106.	Lahat et al., "Intranasal midazolam for childhood seizures", The Lancet, 1998; 352: 620	
	107.	Lehninger et al., "Principles of Biochemistry with an Extended Discussion of Oxygen-Binding Proteins", 1982, pp. 150-151, Worth Publishers, Inc.	
	108.	Maa and Prestrelski, "Biopharmaceutical powders: particle formation and formulation considerations", Curr. Pharm. Biotechnol., 1(3):283-302 (2000).	
	109.	Material Safety Data Sheet for Anatrace, Inc. product n-DODECYL-β-d-MALTOPYRANOSIDE, ANAGRADE, Dated: 01/25/1994 and Revised: 07/15/2004, hhtp://media.affymetrix.com/estore/browse/level_three)category_and_products.jsp?category=35843&categoryldClicked=35843&expand=true&parent=35900, access online on 13 December 2012	
	110.	Mathew N.T., "Serotonin 1D (5-HT1D) agonists and other agents in acute migraine", Neurol. Clin., 15(1):61-83 (1997).	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	7	of	9	Attorney Docket Number	35401-716.501

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	111.	Matsumura et al., "Surface activities, biodegrabalbility and antimicrobial properties of n-alkyl glucosides, mannosides and galactosides", Journal of the America Oil Chemists' Society, 67(12):996-1001 (1990)	
	112.	Moses et al., "Insulin Administered Intranasally as an Insulin-Bite Salt Aerosol - Effectiveness and Reproducibility in Normal and Diabetic Subjects", Diabetes, November 1983, pp. 1040-1047, Vol. 32.	
	113.	Murakami et al., "Assessment of Enhancing AbititY of Medium-Chain Alkyl Saccharides as New Absorption Enhancers in Rat Rectum", International Journal of Pharmaceutics, February 1992, pp. 159-169, Vol. 79, Issue 1-3]	
	114.	Ogiso et al., "Percutaneous Absorption of Elcatonin Chemical and Hypocalcemic Effect in Rat", Chemical & Pharmaceutical Bulletin, February 1991, pp. 449-453, Vol. 39, Issue 2, The Pharmaceutical Society of Japan, Tokyo, Japan.	
	115.	Olesen et al., "The Headaches", *Lippincott Williams & Wilkins,* page 474 (2005)	
	116.	Paulsson and Edsman, "Controlled drug release from Gels using surfactant aggregates. II Vesicles formed from mixtures of amphiphilic drugs and oppositely charged surfactants", Pharm, Res., 18(11):1586-1592 (2001).	
	117.	PCT/US08/62961 International Preliminary Report on Patentability dated 11/10/2009	
	118.	PCT/US09/38696 International Preliminary Report on Patentability dated 9/28/2010	
	119.	Phillips, A., "The challenge of gene therapy and DNA delivery", J. Pharm Pharmacology 53: 1169-1174, 2001	
	120.	Pillion et al., "Synthetic long-chain alkyl maltosidee and alkyl sucrose esters as enhancers of nasal insulin absorption", J. Pharm. Sci., 91:1456-1462 (2002).	
	121.	Pillion et al., "Systemic Absorption of Insulin Delivered Topically to the Rat Eye", Investigative Ophthalmology & Visual Science, November 1991, pp. 3021-3027, Vol. 32, Issue 12.	
	122.	Pirollo et al., "Targeted Delivery of Small Interfering RNA: Approaching Effective Cancer Therapies", Cancer Res. 68(5): 1247-1250, 2008	
	123.	Richards R.M., "Inactivation of resistant Pseudomonas aeruginosa by antibacterial combinations", J. Pharm. Pharmacol., 23:136S-140S (1971)	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	8	of	9	Attorney Docket Number	35401-716.501

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	124.	Salzman et al., "Intranasal Aerosolized Insulin", The New England Journal of Medicine, April 25, 1985, pp. 1078-1084, Vol. 312, Issue 17	
	125.	Sanders et al., "Pharmacokinetics of ergotamine in healthy volunteers following oral and rectal dosing", Eur. J. Clin. Pharmacol., 30(3):331-334 (1986).	
	126.	Shim and Kim, "Administration Route Dependent Bioavailability of Interferon-α and Effect of Bile Salts on the Nasal Absorption", Drug Development and Industrial Pharmacy, 19(10):1183-1199 (1993).	
	127.	Stevens and Guillet, "Use of Glucagon to Treat Neonatal Low-Output Congestive Heart Failure after Maternal Labetalol Therapy", The Journal of Pediatrics, July 1995, pp. 151-153, Volume 127, Issue 1.	
	128.	Swarbrick et al., Encyclopedia of Pharmaceutical Technology, Informa Health Care, 2nd edition, Vol. 1, page 918 (2002).	
	129.	Tsuchido et al,, "Lysis of Bacillus subtilis Cells by Glycerol and Sucrose Esters of Fatty Acids", Applied and Environmental Microbiology. Vol. 53, No.3, 505-508, 1987.	
	130.	Türker et al., "Nasal route and drug delivery systems", Pharm. World Sci., 26(3):137-42 (2004).	
	131.	Turton et al., "A role for glucagon-like peptide-1 in the central regulation of feeding", Nature, 1996; 379:69-72	
	132.	U.S. Serial No. 12/116,842 Office action mailed May 25, 2011	
	133.	U.S. Serial No. 12/116,842 Office action mailed April 2, 2013	
	134.	U.S. Serial No. 12/116,842 Office action mailed November 15, 2011	
	135.	U.S. Serial No. 12/116,842 Office action mailed December 17, 2013	
	136.	U.S. Serial No. 12/266,529 Office action mailed July 10, 2012	
	137.	U.S. Serial No. 12/266,529 Office action mailed November 16, 2011	
	138.	U.S. Serial No. 12/413,439 Office action mailed March 18, 2011	
	139.	U.S. Serial No. 12/413,439 Office action mailed November 21, 2011	
	140.	Vidal et al., "Making sense of antisense", European Journal of Cancer, 41:2812-2818, 2005	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	9	of	9	Attorney Docket Number	35401-716.501

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	141.	Watanabe et al., "Antibacterial Carbohydrate Monoesters Suppressing Cell Growth of Streptoccus mutans in the Presence of Sucrose", Current Microbiology, September 2000, pp. 210-213, Vol. 41, No. 3.	
	142.	Weber and Benning, "Metabolism of orally administered alkyl beta-glycosides in the mouse", J. Nutr., 114:247-254 (1984).	
	143.	Webpage for Anatrace products of Affymetrix, http://www.affymetrix.com/estore/browse/level_three_category_and_products.jsp?category=35843&categoryIdClicked=35843&expand=true&parent=35900, accessed online on 13 December 2012	
	144.	Yamamoto et al., "The Ocular Route for Systemic Insulin Delivery in the Albino Rabbit", The Journal of Pharmacology and Experimental Therapeutics, April 1989, pp. 249-255, Vol. 249; No. 1.	
	145.	Yu Xinrui et al., "Triptan Medicament and Migraine", World Pharmacy (Synthetic Drug and Biochemical Drug Formulation Fascicule), 22(2):91-92 (2001)	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	06/13/2012	Steve Cartt	35401-716.501	7399

21971 7590 09/04/2014

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
MILLIGAN, ADAM C	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/04/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Corrected Notice of Allowability	Application No. 13/495,942	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,3-7,10-19,21,22,57-59 and 66*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

The present application is being examined under the pre-AIA first to invent provisions.

Examiner's Amendment

This application is in condition for allowance except for the presence of claims 23-56 and 60-65 directed to an invention non-elected without traverse. Accordingly, **claims 23-56 and 60-65 have been cancelled**.

Any inquiry concerning this communication should be directed to ADAM C. MILLIGAN at telephone number (571)270-7674.

/ADAM C MILLIGAN/

Primary Examiner, Art Unit 1612

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	08/22/2014								
1	1	=								
	2	-								
2	3	=								
3	4	=								
4	5	=								
5	6	=								
6	7	=								
	8	-								
	9	-								
7	10	=								
8	11	=								
9	12	=								
10	13	=								
11	14	=								
12	15	=								
13	16	=								
14	17	=								
15	18	=								
16	19	=								
	20	-								
17	21	=								
18	22	=								
	23	-								
	24	-								
	25	-								
	26	-								
	27	-								
	28	-								
	29	-								
	30	-								
	31	-								
	32	-								
	33	-								
	34	-								
	35	-								
	36	-								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13495942	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	08/22/2014								
	37	-								
	38	-								
	39	-								
	40	-								
	41	-								
	42	-								
	43	-								
	44	-								
	45	-								
	46	-								
	47	-								
	48	-								
	49	-								
	50	-								
	51	-								
	52	-								
	53	-								
	54	-								
	55	-								
	56	-								
19	57	=								
20	58	=								
21	59	=								
	60	-								
	61	-								
	62	-								
	63	-								
	64	-								
	65	-								
22	66	=								

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	June 13, 2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	1	of	1	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-6,165,484	12/26/2000	Raad et al.	
	2.	US-6,316,029	11/13/2001	Jain et al.	
	3.	US-7,008,920	3/7/2006	Kimura et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	4.	WO-2006-025882 A2	3/9/2006	The UAB Research Foundation et al.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	5.	Fix, "Oral controlled release technology for peptides: status and future prospects", Pharmaceutical Research 1996 Dec;13(12):1760-1764.	
	6.	Hussain et al, "Absorption enhancers in pulmonary protein delivery." J Control Release. 2004 Jan 8;94(1):15-24.	
	7.	Kissel et al., "Tolerability and absorption enhancement of intranasally administered octreotide by sodium taurodihydrofusidate in healthy subjects." Pharm Res. 1992 Jan;9(1):52-57.	
	8.	Kite et al., "Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro." J Clin Microbiol. 2004 Jul;42(7):3073-3076.	
	9.	Liu et al., "Interaction between chitosan and alkyl P-D-glucopyranoside and its effect on their antimicrobial activity", Carbohydrate Polymers. 2004; 56: 243-250.	
	10.	U.S. Serial No. 12/413,439 Office action mailed June 19, 2014	

Examiner Signature		Date Considered	

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal

Application Number:	13495942
Filing Date:	13-Jun-2012
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/J C
Attorney Docket Number:	35401-716.501

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	20437864
Application Number:	13495942
International Application Number:	
Confirmation Number:	7399
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/J C
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.501
Receipt Date:	16-OCT-2014
Filing Date:	13-JUN-2012
Time Stamp:	16:36:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$90
RAM confirmation Number	3212
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Foreign Reference	WO2006025882A2.pdf	3225121 7bae7d1475dd3735aba5ea14f1a39f599b2d80c2	no	70
Warnings:					
Information:					
2	Non Patent Literature	FIX-Oral-controlled-1760.pdf	584804 1bd94ffbd9cd445a7757b631ecc291dca53253ba	no	5
Warnings:					
Information:					
3	Non Patent Literature	HUSSAIN-Absorption-enhancers-15.pdf	941677 22c3a1ef69e2ba8aab912ca999eb5836fd04af0f	no	10
Warnings:					
Information:					
4	Non Patent Literature	KISSEL-Tolerability-52.pdf	866837 115caf77aedc7c3d63bb9231957d96405c96307c	no	6
Warnings:					
Information:					
5	Non Patent Literature	KITE-in-vivo-generated-biofilms-3073.pdf	392692 6353a3263a77f3401baf5b24c993fcce05218546	no	4
Warnings:					
Information:					
6	Non Patent Literature	LIU-Interaction-between-243.pdf	639619 c90738835bdc608889208d078451e459cd518d61	no	8
Warnings:					
Information:					
7		35401-716-501-IDS-10-16-2014.pdf	69518 e3dd32be643ad02b2f37d4f09f2ceef3491da8e8	yes	6

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	5
Information Disclosure Statement (IDS) Form (SB08)	6	6

Warnings:					
Information:					
8	Non Patent Literature	US12413439_OA_19June2014.pdf	321754 [illegible]	no	8

Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	30558 620941cb3b52bbe28171e4781f198c5889429200	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	7072580	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 March 2006 (09.03.2006)

PCT

(10) International Publication Number
WO 2006/025882 A2

(51) International Patent Classification:
A61K 38/17 (2006.01) *A61K 31/70* (2006.01)

(21) International Application Number:
PCT/US2005/016944

(22) International Filing Date: 11 May 2005 (11.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/604,296	25 August 2004 (25.08.2004)	US
60/609,890	14 September 2004 (14.09.2004)	US
60/632,038	30 November 2004 (30.11.2004)	US
60/637,284	17 December 2004 (17.12.2004)	US
60/649,958	3 February 2005 (03.02.2005)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	60/604,296 (CIP)
Filed on	25 August 2004 (25.08.2004)
US	60/609,890 (CIP)
Filed on	14 September 2004 (14.09.2004)
US	60/632,038 (CIP)
Filed on	30 November 2004 (30.11.2004)
US	60/637,284 (CIP)
Filed on	17 December 2004 (17.12.2004)
US	60/649,958 (CIP)
Filed on	3 February 2005 (03.02.2005)

(71) Applicants *(for all designated States except US)*: **THE UAB RESEARCH FOUNDATION** [US/US]; 701 20th Street South,, Birmingham, AL 35294-0111 (US). **AEGIS THERAPEUTICS LLC** [US/US]; 16870 W. Bernardo Drive, Suite 390, San Diego, CA 92127 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MEEZON, Elias** [US/US]; 1202 Cheval Lane, Birmingham, AL 35216 (US). **PILLION, Dennis, J.** [US/US]; 1100 Regent Drive, Hoover, AL 35226 (US). **MAGGIO, Edward, T.** [US/US]; 18775 Bernardo Trails Drive, San Diego, CA 92128 (US).

(74) Agent: **HAILE, Lisa, A.**; DLA Piper Rudnick Gray Cary US LLP, 4365 Executive Drive, Suite 1100, San Diego, CA 92121-2133 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (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*

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: ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

(57) Abstract: A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.

WO 2006/025882 A2

ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

CROSS REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/649,958 filed February 3, 2005, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/637,284 filed December 17, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/632,038 filed November 30, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/609,890 filed September 14, 2004, now pending; and the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/604,296 filed August 25, 2004, now pending. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] The invention relates generally to non-irritating, non-toxic compositions providing enhanced bioavailability and more specifically to alkyl glycoside or saccharide alkyl ester compositions for delivery of therapeutic agents to a subject.

BACKGROUND INFORMATION

[0003] Therapeutic agents are often combined with various surfactants. Yet, surfactants are frequently irritating to the skin and other tissues, including mucosal membranes such as those found in the nose, mouth, eye, vagina, rectum, esophagus, intestinal tract, and the like. Many surfactants also cause proteins to denature, thus destroying their biological activity. Another serious limitation to the development and use of such agents is the ability to deliver them safely, non-invasively, efficiently and stably to the site of action. Therefore, an ideal enhancing surfactant will stabilize the therapeutic agent, be non-toxic and non-irritable to the skin or mucosal surfaces, and enhance the passage or absorption of the therapeutic agent through various membrane barriers without damaging the structural integrity and biological function of the membrane and increase bioavailability of the agent.

SUMMARY OF THE INVENTION

[0004] The present invention is based, in part, on the development of a therapeutic composition containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug. In particular, the drug enhancing agents of the invention contain a non-toxic surfactant consisting of at least an alkyl glycoside and/or saccharide alkyl ester. One advantage of the therapeutic compositions of the invention is that they permit administration and delivery of the therapeutic agents with high bioavailabilities at concentrations of enhancing agents that are dramatically below their so-called "no observable adverse effect levels" (their NOAEL's) . Accordingly, the present invention provides compositions, including alkyl glycosides and/or saccharide alkyl esters and a therapeutic agent (e.g. small molecule organic drug molecules, low molecular weight peptides such as Exenatide, GLP-1 and the like , proteins, and non-peptide therapeutic polymers such as low molecular weight heparin and inhibitory RNA), methods of administering and using the compositions e.g. via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or cerebral spinal fluid (CSF) delivery route, and methods of ameliorating a disease state in a subject by administration of such compositions

[0005] In one aspect, the present invention relates to a surfactant composition having at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed, mixed or blended with a therapeutic agent, a drug, or biologically active compound, the surfactant stabilizes the biological activity and increases the bioavailability of the drug.

[0006] Accordingly, in one aspect, the invention provides a therapeutic composition having at least one biologically active compound and at least one surfactant, wherein the surfactant further consists of at least one alkyl glycoside and/or saccharide alkyl ester or sucrose ester and wherein the therapeutic composition stabilizes the biologically active compound for at least about 6 months, or more, and from about 4°C to about 25°C.

[0007] The invention also provides a method of administering a therapeutic composition having a surfactant including at least one alkyl glycoside and/or saccharide alkyl ester admixed, mixed, or blended with at least one therapeutic agent, or a drug, or biologically active compound, and administered or delivered to a subject, wherein the

alkyl has from about 10 to 24, 10 to 20, 10 to 16, or 10 to 14 carbon atoms, wherein the surfactant increases the stability and bioavailability of the therapeutic agent.

[0008] In yet another aspect, the invention provides a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by, administering the compound via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route when admixed, mixed or blended with an absorption increasing amount of a suitable surfactant, wherein the surfactant is a nontoxic and nonionic hydrophobic alkyl joined by a linkage to a hydrophilic saccharide. Such low molecular weight compounds include but are not limited to, nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

[0009] The present invention also provides a method of treating diabetes including administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell), a blood glucose reducing amount of a therapeutic composition, for example, an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of incretin mimetic agent or insulin and lowering the level of blood glucose and treating diabetes in the subject.

[0010] The present invention also provides a method of treating congestive heart failure in a subject including administering to the subject in need thereof via the oral, ocular, nasal, nasolacrimal, or inhalation delivery route, a therapeutically effective amount of a composition comprising a GLP-1 peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

[0011] In another aspect, the invention provides a method of treating obesity or diabetes associated with obesity in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or CSF delivery route, a therapeutically effective amount of a composition comprising a PYY peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic,

nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

[0012] In another aspect, the invention provides a method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject by administering via the oral, ocular, nasal, nasolacrimal, inhalation or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the compound is not insulin, calcitonin, or glucagon when the route of administration is oral, ocular, nasal, or nasolacrimal.

[0013] The present invention also provides a method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject by administering via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kilo Daltons (kD), with the proviso that the subject does not have diabetes when delivery is via the oral, ocular, nasal or nasolacrimal routes.

[0014] In one aspect of the invention, there is provided a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of Exenatide (exendin-4) in a pharmaceutically acceptable carrier.

[0015] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of GLP-1 in a pharmaceutically acceptable carrier.

[0016] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of nicotine in a pharmaceutically acceptable carrier.

[0017] In one aspect, the invention provides a pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of interferon in a pharmaceutically acceptable carrier.

[0018] In one aspect, the invention provides pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of PYY in a pharmaceutically acceptable carrier.

[0019] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of parathyroid hormone in a pharmaceutically acceptable carrier.

[0020] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of a peptide having a molecular weight of about 1-75 kD in a pharmaceutically acceptable carrier, with the proviso that the peptide is not insulin, calcitonin, and glucagon.

[0021] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount erythropoietin in a pharmaceutically acceptable carrier.

[0022] In one aspect, the invention provides a method of increasing absorption of a compound into the CSF of a subject having administered intranasally the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide.

[0023] In yet another aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group

joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

[0024] In one aspect, the invention provides a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering, via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral

cavity (sublingual or Buccal cell) or CSF delivery route (a) the compound; (b) an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide; and (c) a mucosal delivery-enhancing agent.

[0025] In one aspect, the invention provides a method of controlling caloric intake by administering a composition having a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

[0026] In another aspect, the invention provides a method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

[0027] Still, in another aspect, the invention provides a controlled release dosage composition comprising:

(a) a core comprising:

(i) at least one therapeutic agent or drug;

(ii) at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is impermeable, permeable, semi-permeable or porous and becomes more permeable upon sustained contact with contents of the gastrointestinal tract.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Figure 1 is a graph showing the intranasal percent bioavailability compared to intravenous injection and the subject-to-subject coefficients of variation for MIACALCIN® (salmon calcitonin) with and without alkyl glycoside.

[0029] Figure 2 is a graph showing the effect of intranasal administration of insulin/0.25%TDM (filled circles) and intranasal administration of insulin alone (open circles) in reducing blood glucose levels.

[0030] Figure 3 is a graph showing the effect of intranasal (closed triangles) and intraperitoneal (IP) injection (closed circles) administration of exendin-4/0.25%TDM and

IP injection of saline alone, minus TDM (open circles) in reducing blood glucose levels following oral administration of glucose (i.e., in a so-called "glucose tolerance test").

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention may be understood more readily by reference to the following detailed description of specific embodiments and the Examples included therein.

[0032] The present invention is based on the discovery that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are stable, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject.

[0033] A "therapeutic composition" can consist of an admixture with an organic or inorganic carrier or excipient, and can be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, or other form suitable for use. The carriers, in addition to those disclosed above, can include glucose, lactose, mannose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition, auxiliary stabilizing, thickening or coloring agents can be used, for example a stabilizing dry agent such as triulose.

[0034] A "drug" is any therapeutic compound, or molecule, or therapeutic agent, or biologically active compound, including but not limited to nucleic acids, small molecules, proteins, polypeptides or peptides, etc. The term "nucleic acids" also denotes DNA, cDNA, RNA, siRNA, RNAi, etc. which encode translated and untranslated regions or inhibits translated or untranslated regions of structural genes encoding a peptide or protein of the invention. For example, a nucleic acid of the invention can include 5' and 3' untranslated regulatory nucleotide sequences as well as translated sequences associated with the structural gene, e.g. GLP-1.

[0035] A peptide of the invention may be any medically or diagnostically useful peptide or protein of small to medium size (i.e. up to about 15 kD, 30 kD, 40 kD, 50 kD, 60 kD, 70 kD, 80 kD, 90 kD, 100 kD, for example). The mechanisms of improved polypeptide absorption are described in U.S. Patent No. 5,661,130 which is hereby incorporated by reference in its entirety. Invention compositions can be mixed with all such peptides, although the degree to which the peptide benefits are improved may vary according to the molecular weight and the physical and chemical properties of the peptide, and the particular surfactant used. Examples of polypeptides include vasopressin, vasopressin polypeptide analogs, desmopressin, glucagon, corticotropin (ACTH), gonadotropin, calcitonin, C-peptide of insulin, parathyroid hormone (PTH), growth hormone (HG), human growth hormone (hGH), growth hormone releasing hormone (GHRH), oxytocin, corticotropin releasing hormone (CRH), somatostatin or somatostatin polypeptide analogs, gonadotropin agonist or gonadotrophin agonist polypeptide analogs, human atrial natriuretic peptide (ANP), human thyroxine releasing hormone (TRH), follicle stimulating hormone (FSH), prolactin, insulin, insulin like growth factor-I (IGF-I) somatomedin-C (SM-C), calcitonin, leptin and the leptin derived short peptide OB-3, melatonin, GLP-1 or Glucagon-like peptide-1,, GiP, neuropeptide pituitary adenylate cyclase, GM-1 ganglioside, nerve growth factor (NGF), nafarelin, D-tryp6)-LHRH, FGF, VEGF antagonists, leuprolide, interferon (e.g., α,β, γ) low molecular weight heparin, PYY, LHRH antagonists, Keratinocyte Growth Factor (KGF) , Glial-Derived Neurotrophic Factor (GDNF), ghrelin, and ghrelin antagonists. Further, in some aspects, the peptide or protein is selected from a growth factor, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, or a polypeptide involved in the blood coagulation cascade.

[0036] Other drugs or therapeutic compounds, molecules and/or agents include compounds or molecules of the central nervous system affecting neurotransmitters or neural ion channels (i.e. antidepressants (bupropion)), selective serotonin 2c receptor agonists, anti-seizure agents (topiramate, zonisamide), some dopamine antagonists, and cannabinoid-1 receptor antagonists (rimonabant)); leptin/insulin/central nervous system pathway agents (i.e. leptin analogues, leptin transport and/or leptin receptor promoters, ciliary neurotrophic factor (Axokine), neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin, cocaine and amphetamine regulated transcript

promoters, alpha-melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor-gamma receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin); gastrointestinal-neural pathway agents (i.e. agents that increase glucagon-like peptide-1 activity (extendin-4, liraglutide, dipeptidyl peptidase IV inhibitors), protein YY3-36, ghrelin, ghrelin antagonists, amylin analogues (pramlintide)); and compounds or molecules that may increase resting metabolic rate "selective" beta-3 stimulators/agonist, melanin concentrating hormone antagonists, phytostanol analogues, functional oils, P57, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11B-hydroxysteroid dehydrogenase type 1 activity, corticotropin-releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, and gastrointestinal lipase inhibitors (ATL962).

[0037] The therapeutic composition of the invention includes a drug and a drug absorption enhancing agent, for example, a surfactant. The term "surfactant" is any surface active agent that modifies interfacial tension of water. Typically, surfactants have one lipophilic and one hydrophilic group in the molecule. Broadly, the group includes soaps, detergents, emulsifiers, dispersing and wetting agents, and several groups of antiseptics. More specifically, surfactants include stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and glycerin monostearate; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

[0038] Preferably, the surfactant of the invention consists of at least one suitable alkyl glycoside. As used herein, "alkyl glycoside" refers to any sugar joined by a linkage to any hydrophobic alkyl, as is known in the art. Any "suitable" alkyl glycoside means one that fulfills the limiting characteristics of the invention, i.e., that the alkyl glycoside be nontoxic and nonionic, and that it increases the absorption of a compound when it is administered with the compound via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route. Suitable compounds can be determined using the methods set forth herein.

[0039] Alkyl glycosides of the invention can be synthesized by known procedures, i.e., chemically, as described, e.g., in Rosevear et al., *Biochemistry* 19:4108-4115 (1980) or Koeltzow and Urfer, *J. Am. Oil Chem. Soc.*, 61:1651-1655 (1984), U.S. Pat. No. 3,219,656 and U.S. Pat. No. 3,839,318 or enzymatically, as described, e.g., in Li et al., *J. Biol. Chem.*, 266:10723-10726 (1991) or Gopalan et al., *J. Biol. Chem.* 267:9629-9638 (1992).

[0040] Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl- α- or β-D-maltoside, -glucoside or -sucroside (synthesized according to Koeltzow and Urfer; Anatrace Inc., Maumee, Ohio; Calbiochem, San Diego, Calif.; Fluka Chemie, Switzerland); alkyl thiomaltosides, such as heptyl, octyl, dodecyl-, tridecyl-, and tetradecyl-β-D-thiomaltoside (synthesized according to Defaye, J. and Pederson, C., "Hydrogen Fluoride, Solvent and Reagent for Carbohydrate Conversion Technology" in Carbohydrates as Organic Raw Materials, 247-265 (F. W. Lichtenthaler, ed.) VCH Publishers, New York (1991); Ferenci, T., J. Bacteriol, 144:7-11 (1980)); alkyl thioglucosides, such as heptyl- or octyl 1-thio α- or β-D-glucopyranoside (Anatrace, Inc., Maumee, Ohio; see Saito, S. and Tsuchiya, T. Chem. Pharm. Bull. 33:503-508 (1985)); alkyl thiosucroses (synthesized according to, for example, Binder, T. P. and Robyt, J. F., Carbohydr. Res. 140:9-20 (1985)); alkyl maltotriosides (synthesized according to Koeltzow and Urfer); long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers; (synthesized according to Austrian Patent 382,381 (1987); Chem. Abstr., 108:114719 (1988) and Gruber and Greber pp. 95-116); derivatives of palatinose and isomaltamine linked by amide linkage to an alkyl chain (synthesized according to Kunz, M., "Sucrose-based Hydrophilic Building Blocks as Intermediates for the Synthesis of Surfactants and Polymers" in Carbohydrates as Organic Raw Materials, 127-153); derivatives of isomaltamine linked by urea to an alkyl chain (synthesized according to Kunz); long chain aliphatic carbonic acid ureides of sucrose β-amino-alkyl ethers (synthesized according to Gruber and Greber, pp. 95-116); and long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers (synthesized according to Austrian Patent 382,381 (1987), Chem. Abstr., 108:114719 (1988) and Gruber and Greber, pp. 95-116).

[0041] Surfactants of the invention consisting of an alkyl glycoside and/or a sucrose ester have characteristic hydrophile-lipophile balance (HLB) numbers, which can be calculated or determined empirically (Schick, M. J. Nonionic Surfactants, p. 607 (New York: Marcel Dekker, Inc. (1967)). The HLB number is a direct reflection of the hydrophilic character of the surfactant, i.e., the larger the HLB number, the more hydrophilic the compound. HLB numbers can be calculated by the formula: (20 times MW hydrophilic component)/(MW hydrophobic component+MW hydrophilic component), where MW=molecular weight (Rosen, M. J., Surfactants and Interfacial Phenomena, pp. 242-245, John Wiley, New York (1978)). The HLB number is a direct expression of the hydrophilic character of the surfactant, i.e., the larger the HLB number, the more hydrophilic the compound. A preferred surfactant has an HLB number of from about 10 to 20 and an even more preferred range of from about 11 to 15.

[0042] As described above, the hydrophobic alkyl can thus be chosen of any desired size, depending on the hydrophobicity desired and the hydrophilicity of the saccharide moiety. For example, one preferred range of alkyl chains is from about 9 to about 24 carbon atoms. An even more preferred range is from about 9 to about 16 or about 14 carbon atoms. Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

[0043] The surfactants of the invention can also include a saccharide. As use herein, a "saccharide" is inclusive of monosaccharides, oligosaccharides or polysaccharides in straight chain or ring forms, or a combination thereof to form a saccharide chain. Oligosaccharides are saccharides having two or more monosaccharide residues. The saccharide can be chosen, for example, from any currently commercially available saccharide species or can be synthesized. Some examples of the many possible saccharides to use include glucose, maltose, maltotriose, maltotetraose, sucrose and trehalose. Preferable saccharides include maltose, sucrose and glucose.

[0044] The surfactants of the invention can likewise consist of a sucrose ester. As used herein, "sucrose esters" are sucrose esters of fatty acids and is a complex of sucrose

and fatty acid. Sucrose esters can take many forms because of the eight hydroxyl groups in sucrose available for reaction and the many fatty acid groups, from acetate on up to larger, more bulky fatty acids that can be reacted with sucrose. This flexibility means that many products and functionalities can be tailored, based on the fatty acid moiety used. Sucrose esters have food and non-food uses, especially as surfactants and emulsifiers, with growing applications in pharmaceuticals, cosmetics, detergents and food additives. They are biodegradable, non-toxic and mild to the skin.

[0045] The surfactants of the invention have a hydrophobic alkyl group linked to a hydrophobic saccharide. The linkage between the hydrophobic alkyl group and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic (Horton), amide (Carbohydrates as Organic Raw Materials, F. W. Lichtenthaler ed., VCH Publishers, New York, 1991), ureide (Austrian Pat. 386,414 (1988); Chem. Abstr. 110:137536p (1989); see Gruber, H. and Greber, G., "Reactive Sucrose Derivatives" in Carbohydrates as Organic Raw Materials, pp. 95-116) or ester linkage (Sugar Esters: Preparation and Application, J. C. Colbert ed., (Noyes Data Corp., New Jersey), (1974)). Further, preferred glycosides can include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of about 9-16 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. Again, these compositions are amphipathic and nontoxic, because they degrade to an alcohol and an oligosaccharide.

[0046] The above examples are illustrative of the types of glycosides to be used in the methods claimed herein, but the list is not exhaustive. Derivatives of the above compounds which fit the criteria of the claims should also be considered when choosing a glycoside. All of the compounds can be screened for efficacy following the methods taught herein and in the examples.

[0047] The compositions of the present invention can be administered in a format selected from the group consisting of a tablet, a capsule, a suppository, a drop, a spray, an aerosol and a sustained release or delayed burst format. The spray and the aerosol can be achieved through use of an appropriate dispenser. The sustained release format can be an ocular insert, erodible microparticulates, swelling mucoadhesive particulates, pH sensitive microparticulates, nanoparticles/latex systems, ion-exchange resins and other polymeric gels and implants (Ocusert, Alza Corp., California; Joshi, A., S. Ping and K. J.

Himmelstein, Patent Application WO 91/19481). These systems maintain prolonged drug contact with the absorptive surface preventing washout and nonproductive drug loss. The prolonged drug contact is non-toxic to the skin and mucosal surfaces.

[0048] The surfactant compositions of the invention are stable. For example, Baudys et al. in U.S. Patent No. 5,726,154 show that calcitonin in an aqueous liquid composition comprising SDS (sodium dodecyl sulfate, a surfactant) and an organic acid is stable for at least 6 months. Similarly, the surfactant compositions of the present invention have improved stabilizing characteristics when admixed with a drug. No organic acid is required in these formulations. For example, the composition of the invention maintains the stability of proteins and peptide therapeutics for about 6 months, or more, when maintained at about 4°C to 25°C.

[0049] The stability of the surfactant compositions are, in part, due to their high no observable adverse effect level (NOAEL). The Environmental Protection Agency (EPA) defines the no observable adverse effect level (NOAEL) as the exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Hence, the term, "no observable adverse effect level" (or NOAEL) is the greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions.

[0050] The Food and Agriculture Organization (FAO) of the United Nations of the World Health Organization (WHO) has shown that some alkyl glycosides have very high NOAELs, allowing for increased consumption of these alkyl glycosides without any adverse effect. This report can be found on the world wide web at inchem.org/documents/jecfa/jecmono/v10je11.htm. For example, the NOAEL for sucrose dodecanoate, a sucrose ester used in food products, is about 20-30 grams/kilogram/day, e.g. a 70 kilogram person (about 154 lbs.) can consume about 1400 - 2100 grams (or about 3 to 4.6 pounds) of sucrose dodecanoate per day without any observable adverse effect. Typically, an acceptable daily intake for humans is about 1% of the NOAEL, which translates to about 14–21 grams, or 14 million micrograms to 21 million micrograms, per day, indefinitely. Definitions of NOAELs and other related

definitions can be found on the world wide web at epa.gov/OCEPAterms. Thus, although some effects may be produced with alkyl glycoside levels anticipated in the present invention, the levels are not considered adverse, or precursors to adverse effects.

[0051] Accordingly, a subject treated with surfactant compositions of the invention having at least one alkyl glycoside, e.g. tetradecylmaltoside (TDM; or Intravail A), at a concentration of about 0.125% by weight of alkyl glycoside two times per day, or three times per day, or more depending on the treatment regimen consumes about 200 to 300 micrograms per day total of TDM. So, the effective dose of the TDM is at least 1000X fold lower than (i.e., 1/1000) of the NOAEL, and falls far below 1% of the NOAEL, which is the acceptable daily intake; or in this case about 1/50,000 of the acceptable daily intake.. Stated another way, alkyl glycosides of the present invention have a high NOAEL, such that the amount or concentration of alkyl glycosides used in the present invention do not cause an adverse effect and can be safely consumed without any adverse effect.

[0052] The surfactant compositions of the invention are also stable because they are physiologically non-toxic and non-irritants. The term, "nontoxic" means that the alkyl glycoside molecule has a sufficiently low toxicity to be suitable for human administration and consumption. Preferred alkyl glycosides are non-irritating to the tissues to which they are applied. Any alkyl glycoside used should be of minimal or no toxicity to the cell, such that it does not cause damage to the cell. Yet, toxicity for any given alkyl glycoside may vary with the concentration of alkyl glycoside used. It is also beneficial if the alkyl glycoside chosen is metabolized or eliminated by the body and if this metabolism or elimination is done in a manner that will not be harmfully toxic. The term, "non-irritant" means that the agent does not cause inflammation following immediate, prolonged or repeated contact with the skin surface or mucous membranes.

[0053] Moreover, one embodiment of the surfactant compositions, in particular, the sucrose esters, serve as anti-bacterial agents. An agent is an "anti-bacterial" agent or substance if the agent or its equivalent destroy bacteria, or suppress bacterial growth or reproduction. The anti-bacterial activity of sucrose esters and their fatty acids have been reported. Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508.

Watanabe et al. (2000) describe that galactose and fructose laureates are particularly effective carbohydrate monoesters. Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213. Hence, the present invention is not limited to the sucrose ester described herein, but encompasses other carbohydrate esters, including galactose and fructose esters, that suppress bacterial growth and reproduction.

[0054] The surfactant compositions of the invention are typically present at a level of from about 0.01% to 20% by weight. More preferred levels of incorporation are from about 0.01% to 5% by weight, from about 0.01% to 2% by weight, from about 0.01% to 1%, most preferably from about 0.01% to 0.125% by weight. The surfactant is preferably formulated to be compatible with other components present in the composition. In liquid, or gel, or capsule, or injectable, or spray compositions the surfactant is most preferably formulated such that it promotes, or at least does not degrade, the stability of any protein or enzyme in these compositions. Further, the invention optimizes the concentration by keeping the concentration of absorption enhancer as low as possible, while still maintaining the desired effect.

[0055] The compositions of the invention when administered to the subject, yield enhanced mucosal delivery of the biologically active compound(s), or drug, with a peak concentration (or Cmax) of the compound(s) in a tissue, or fluid, or in a blood plasma of the subject that is about 15%, 20%, or 50% or greater as compared to a Cmax of the compound(s) in a tissue (e.g. CNS), or fluid, or blood plasma following intramuscular injection of an equivalent concentration of the compound(s) to the subject.

[0056] The measure of how much of the drug or compound(s) reaches the bloodstream in a set period of time, e.g. 24 hours can also be calculated by plotting drug blood concentration at various times during a 24-hour or longer period and then measuring the area under the curve (AUC) between 0 and 24 hours. Similarly, a measure of drug efficacy can also be determined from a time to maximal concentration (tmax) of the biologically active compound(s) in a tissue (e.g. CNS) or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours. The therapeutic compositions of the invention increase the speed of onset of drug action (i.e., reduce Tmax) by a factor of about 1.5-fold to 2-fold.

[0057] Also, the therapeutic compositions or formulations of the invention can be administered or delivered to a subject in need systemically or locally. Suitable routes may, for example, include oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), transmucosal administration, vaginal, rectal, parenteral delivery, including intramuscular, subcutaneous, intravenous, intraperitoneal, or CSF delivery. Moreover, the mode of delivery e.g. liquid, gel, tablet, spray, etc. will also depend on the method of delivery to the subject.

[0058] Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof, and can contain a surfactant, emollient, lubricant, stabilizer, dye, perfume, preservative, acid or base for adjustment of pH, a solvent, emulsifier, gelling agent, moisturizer, stabilizer, wetting agent, time release agent, humectant, or other component commonly included in a particular form of pharmaceutical composition. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, and oils such as olive oil or injectable organic esters. A pharmaceutically acceptable carrier can contain physiologically acceptable compounds that act, for example, to stabilize or to increase the absorption of the specific inhibitor, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. A pharmaceutically acceptable carrier can also be selected from substances such as distilled water, benzyl alcohol, lactose, starches, talc, magnesium stearate, polyvinylpyrrolidone, alginic acid, colloidal silica, titanium dioxide, and flavoring agents.

[0059] Additionally, to decrease susceptibility of alkyl saccharides or saccharide alkyl esters to hydrolytic cleavage of the drug, various oxygen atoms within the drugs can be substituted for by sulfur (Defaye, J. and Gelas, *J. in Studies in Natural Product Chemistry* (Atta-ur-Rahman, ed.) Vol. 8, pp. 315-357, Elsevier, Amsterdam, 1991). For example, the heteroatom of the sugar ring can be either oxygen or sulfur, or the linkage between monosaccharides in an oligosaccharide can be oxygen or sulfur (Horton, D. and Wander, J. D., "Thio Sugars and Derivatives," The Carbohydrates: Chemistry and Biochemistry,

2d. Ed. Vol. IB, (W. Reyman and D. Horton eds.), pp. 799-842, (Academic Press, New York), (1972)). Oligosaccharides can have either α (alpha) or β (beta) anomeric configuration (see Pacsu, E., et al. in Methods in Carbohydrate Chemistry (R. L. Whistler, et al., eds.) Vol. 2, pp. 376-385, Academic Press, New York 1963).

[0060] A composition of the invention can be prepared in tablet form by mixing a therapeutic agent or drug and one alky glycoside and/or saccharide alkyl ester according to the invention, and an appropriate pharmaceutical carrier or excipient, for example mannitol, corn starch, polyvinylpyrrolidone or the like, granulating the mixture and finally compressing it in the presence of a pharmaceutical carrrier such as corn starch, magnesium stearate or the like. If necessary, the formulation thus prepared may include a sugar-coating or enteric coating or covered in such a way that the active principle is released gradually, for example, in the appropriate pH medium.

[0061] The term "enteric coating," is a polymer encasing, surrounding, or forming a layer, or membrane around the therapeutic composition or core. Also, the enteric coating can contain a drug which is compatible or incompatible with the coating. One tablet composition may include an enteric coating polymer with a compatible drug which dissolves or releases the drug at higher pH levels (e.g., pH greater than 4.0, greater than 4.5, greater than 5.0 or higher) and not at low pH levels (e.g., pH 4 or less); or the reverse.

[0062] In a preferred embodiment, the dose dependent release form of the invention is a tablet comprising:

(a) a core comprising:

(i) a therapeutic agent or drug;

(ii) a surfactant comprising at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is an impermeable, permeable, semi-permeable or porous coating and becomes more permeable or porous upon contacting an aqueous environment of a defined pH.

[0063] The term "membrane" is synonymous with "coating," or equivalents thereof. The terms are used to identify a region of a medicament, for example, a tablet, that is impermeable, permeable, semi-permeable or porous to an aqueous solution(s) or bodily

fluid(s), and/or to the therapeutic agent(s) or drug(s) encapsulated therein. If the membrane is permeable, semi-permeable or porous to the drug, the drug can be released through the openings or pores of the membrane in solution or *in vivo*. The porous membrane can be manufactured mechanically (e.g., drilling microscopic holes or pores in the membrane layer using a laser), or it can be imparted due to the physiochemical properties of the coating polymer(s). Membrane or coating polymers of the invention are well known in the art, and include cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in U.S. Pat. Nos. 3 ,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,11210 which are incorporated herein by reference.

[0064] Further, the enteric coating according to the invention can include a plasticizer, and a sufficient amount of sodium hydroxide (NaOH) to effect or adjust the pH of the suspension in solution or *in vivo*. Examples of plasticizers include triethyl citrate, triacetin, tributyl sebecate, or polyethylene glycol. Other alkalizing agents, including potassium hydroxide, calcium carbonate, sodium carboxymethylcellulose, magnesium oxide, and magnesium hydroxide can also be used to effect or adjust the pH of the suspension in solution or *in vivo*.

[0065] Accordingly, in one embodiment, an enteric coating can be designed to release a certain percentage of a drug or drugs in certain mediums with a certain pH or pH range. For example, the therapeutic composition of the invention may include at least one enteric coating encasing or protecting at least one drug which is chemically unstable in an acidic environment (e.g., the stomach). The enteric coating protects the drug from the acidic environment (e.g., pH < 3), while releasing the drug in locations which are less acidic, for example, regions of the small and large intestine where the pH is 3, or 4, or 5, or greater. A medicament of this nature will travel from one region of the gastrointestinal tract to the other, for example, it takes about 2 to about 4 hours for a drug to move from the stomach to the small intestine (duodenum, jejunum and ileum). During this passage or transit, the pH changes from about 3 (e.g., stomach) to 4, or 5, or to about a pH of 6 or 7 or greater. Thus, the enteric coating allows the core containing the drug to remain substantially

intact, and prevents premature drug release or the acid from penetrating and de-stabilizing the drug.

[0066] Examples of suitable enteric polymers include but are not limited to cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof. One skilled in the art will appreciate that other hydrophilic, hydrophobic and enteric coating polymers may be readily employed, singly or in any combination, as all or part of a coating according to the invention.

[0067] The therapeutic compositions of the invention in the form of a tablet can have a plurality of coatings, for example, a hydrophilic coating (e.g., hydroxypropylmethyl-cellulose), and/or a hydrophobic coating (e.g., alkylcelluloses), and/or an enteric coating. For example, the tablet core can be encases by a plurality of the same type of coating, or a plurality of different types of coating selected from a hydrophilic, hydrophobic or enteric coating. Hence, it is anticipated that a tablet can be designed having at least one, but can have more than one layer consisting of the same or different coatings dependent on the target tissue or purpose of the drug or drugs. For example the tablet core layer may have a first composition enclosed by a first coating layer (e.g. hydrophilic, hydrophobic, or enteri-coating), and a second same or different composition or drug having the same or

different dosage can be enclosed in second coating layer, etc. This layering of various coatings provides for a first, second, third, or more gradual or dose dependent release of the same or different drug containing composition.

[0068] In a preferred embodiment, a first dosage of a first composition of the invention is contained in a tablet core and with an enteric-coating such that the enteric-coating protects and prevents the composition contained therein from breaking down or being released into the stomach. In another example, the first loading dose of the therapeutic composition is included in the first layer and consists of from about 10% to about 40% of the total amount of the total composition included in the formulation or tablet. In a second loading dose, another percentage of the total dose of the composition is released. The invention contemplates as many time release doses as is necessary in a treatment regimen. Thus, in certain aspects, a single coating or plurality of coating layers is in an amount ranging from about 2% to 6% by weight, preferably about 2% to about 5%, even more preferably from about 2% to about 3% by weight of the coated unit dosage form.

[0069] Accordingly, the composition preparations of the invention make it possible for contents of a hard capsule or tablet to be selectively released at a desired site the more distal parts of the gastro-intestinal tract (e.g. small and large intestine) by selecting the a suitable pH-soluble polymer for a specific region. Mechanical expulsion of the composition preparations may also be achieved by inclusion of a water absorbing polymer that expands upon water absorption within a hard semi-permeable capsule thus expelling composition through an opening in the hard capsule.

[0070] Drugs particularly suited for dose dependent time release include but are not limited to insulin like growth factor-I (IGF-I), somatomedin-C (SM-C; diabetes, nerve function, renal function), insulin (diabetes), calcitonin (osteoporosis), leptin (obesity; infertility), leptin derived short peptide (OB-3), hGH (AIDs wasting, dwarfism), human parathyroid hormone (PTH) (osteoporosis), melatonin (sleep), GLP-1 or Glucagon-like peptide-1 (diabetes), GiP (diabetes), pituitary adenylate cyclase-activating polypeptide (PACAP) and islet function (diabetes), GM-1 ganglioside, (Alzheimers), nerve growth factor (NGF), (Alzheimers), nafarelin (endometriosis), Synarel® (nafarelin acetate nasal solution), (D-tryp6)-LHRH (fertility), FGF (duodenal ulcer, macular degeneration, burns,

wounds, spinal cord injuries, repair of bone and cartilage damage), VEGF antagonists (to block the receptor), VEGF (agonist) neonatal distress syndrome; ALS), leuprolide (prostate and breast cancer), interferon-alpha (chronic hepatitis C), low molecular weight heparin (blood clotting, deep vein thrombosis), PYY (obesity), LHRH antagonists (fertility), LH (luteinizing hormone), ghrelin antagonists (obesity), KGF (Parkinson's), GDNF (Parkinsons), G-CSF (erythropoiesis in cancer), Imitrex (migraine), Integrelin (anticoagulation), Natrecor® (congestive heart failure), human B-type natriuretic peptide (hBNP), SYNAREL® (Searl; nafarelin acetate nasal solution), Sandostatin (growth hormone replacement), Forteo (osteoporosis), DDAVP® Nasal Spray (desmopressin acetate), Cetrotide® (cetrorelix acetate for injection), Antagon™ (ganirelix acetate), Angiomax (bivalirudin; thrombin inhibitor), Accolate® (zafirlukast; injectable), Exendin-4 (Exanatide; diabetes), SYMLIN® (pramlintide acetate; synthetic amylin; diabetes), desmopressin, glucagon, ACTH (corticotrophin), C-peptide of insulin, GHRH and analogs (GnRHa), growth hormone releasing hormone, oxytocin, corticotropin releasing hormone (CRH), atrial natriuretic peptide (ANP), thyroxine releasing hormone (TRHrh), follicle stimulating hormone (FSH), prolactin, tobramycin ocular (corneal infections), Vasopressin, desmopresin, Fuzeon (Roche; HIV fusion inhibitor MW 4492), and Eptifibatide.

[0071] Further, it will be understood by one skilled in the art, that the specific dose level and frequency of dosage for any particular subject in need of treatment may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0072] It has been shown that alkyl glycosides, particularly alkylmaltosides and more specifically, dodecylmaltoside (DDM) and tetradecylmaltoside (TDM), stabilize insulin in solution and prevent aggregation of the peptide. Hovgaard et al., "Insulin Stabilization and GI absorption," *J. Control. Rel.*, 19 (1992) 458-463, *cited in* Hovgaard et al., "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132 (1996) 107-113 (hereinafter, "Hovgaard-1"). Further, Hovgaard-1 shows that even after 57 days, the DDM-insulin complex remained stable and possessed

nearly full biological activity. It is postulated that the stability of the complex is due to the length of the alkyl group (number of carbon atoms) and the higher ratio of DDM to insulin ratio the better (e.g. 4:1 and 16:1; see FIG. 1 in Hovgaard 1). However, according to Hovgaard-1, although the DDM-insulin complex was stable, the same stability was not shown for other maltosides. Yet, in a related study, Hovgaard et al.(1996) demonstrated that when DDM-insulin was orally administered to animals *in vivo*, bioavailability of the complex was weak (e.g. 0.5% - 1% bioavailability). Hovgaard et al., "Stabilization of insulin by alkylmaltoside. B. Oral absorption in vivo in rats," *Int. J. Pharmaceutics* 132 (1996) 115-121 (Hovgaard-2). Hence, an improved aspect of the invention is that the surfactant increases the bioavailability of a drug to the target tissues, organs, system etc., as well as increase drug stability.

[0073] Accordingly, one aspect of the invention is to provide therapeutic compositions having at least one drug and one surfactant, wherein the surfactant further consists of at least one alkyl glycoside and/or saccharide alkyl ester formulation which enhances the bioavailability of the drug. Determining the bioavailability of drug formulations is described herein. As used herein, "bioavailability" is the rate and extent to which the active substance, or moiety, which reaches the systemic circulation as an intact drug. The bioavailability of any drug will depend on how well is adsorbed and how much of it escapes being removed from the liver.

[0074] To determine absolute bioavailability, the tested drug and mode of administration is measured against an intravenous reference dose. The bioavailability of the intravenous dose is 100% by definition. For example, animals or volunteering humans are given an intravenous injections and corresponding oral doses of a drug. Urinary or plasma samples are taken over a period of time and levels of the drug over that period of time are determined.

[0075] The areas under the curve (AUC), of the plasma drug concentration versus time curves, are plotted for both the intravenous and the oral doses, and calculation of the bioavailability of both formulations is by simple proportion. For example, if the same intravenous and oral doses are given, and the oral AUC is 50% of the intravenous AUC, the bioavailability of the oral formulation is 50%. Note that the bioavailability of any drug is due to many factors including incomplete absorption, first pass clearance or a

combination of these (discussed more below). Further, the peak concentration (or C_{max}) of the plasma drug concentration is also measured to the peak concentration (C_{max}) of the plasma drug concentration following intramuscular (IM) injection of an equivalent concentration the drug. Moreover, the time to maximal concentration (or t_{max}) of the plasma drug is about 0.1 to 1.0 hours.

[0076] To determine the relative bioavailability of more than one formulation of a drug (e.g. an alkyl glycoside or saccharide alkyl ester drug formulation), bioavailability of the formulations are assessed against each other as one or both drugs could be subject to first pass clearance (discussed more below) and thus undetected. For example, a first oral formulation is assessed against a second oral formulation. The second formulation is used as a reference to assess the bioavailability of the first. This type of study provides a measure of the relative performance of two formulations in getting a drug absorbed.

[0077] Bioavailabilities of drugs are inconsistent and vary greatly from one drug to the next. For example, the bioavailability of MIACALCIN® (salmon calcitonin from Novartis) nasal spray, a prescription medication for the treatment of postmenopausal osteoporosis in women, has a mean bioavailability of about 3% (range is 0.3%-30.6%; see FIG. 1). The MIACALCIN® product information sheet can be found on the world wide web at miacalcin.com/info/howWorks/index.jsp and drugs.com/PDR/Miacalcin_Nasal_Spray.html. The data on MIACALCIN®, which was obtained by various investigators using different methods and human subjects, show great variability in the drug's bioavailability, e.g. in normal volunteers only ~3% of the nasally administered dose is bioavailable, as compared to the same dose administered by intramuscular injection (MIACALCIN® product insert). This represents two orders of a magnitude in variability and is undesirable to the consumer.

[0078] Poor bioavailability of a drug can also be observed in NASCOBAL® (Nastech), or cyanocobalamin, which is used for the treatment and maintenance of the hematologic status of patients who are in remission following intramuscular vitamin B_{12} therapies. The gel formulation was administered intranasally and the bioavailability of B_{12} was compared to intramuscular B_{12} injections. The peak concentrations of B_{12} (or the Tmax) was reached in 1-2 hours after intranasal administration, and relative to the

intramuscular injection, the bioavailability of B_{12} nasal gel was found to be about 8.9% (90% confidence intervals, 7.1% to 11.2%).

[0079] The alkyl glycosides or sucrose esters of the present invention include any compounds now known or later discovered. Drugs which are particularly well suited for admixture with the alkyl glycosides and/or saccharide alkyl esters of the invention are those that are difficult to administer by other methods, e.g. drugs that are degraded in the gastrointestinal (GI) tract or those that are not absorbed well from the GI tract, or drugs that can be self-administered via the ocular, nasal, nasolacrimal, inhalation, or CSF delivery route instead of traditional methods such as injection. Some specific examples include peptides, polypeptides, proteins, nucleic acids and other macromolecules, for example, peptide hormones, such as insulin and calcitonin, enkephalins, glucagon and hypoglycemic agents such as tolbutamide and glyburide, and agents which are poorly absorbed by enteral routes, such as griseofulvin, an antifungal agent. Other compounds include, for example, nicotine, interferon (e.g., alpha, beta, gamma), PYY, GLP-1, synthetic exendin-4 (Exenatide), parathyroid hormone, and human growth hormone or other low molecular weight peptides and proteins.

[0080] Alternatively, bioavailability of a drug can be determined by measuring the levels of the drug's first pass clearance by the liver. Alkyl glycosides and/or saccharide alkyl ester compositions of the invention administered intranasally or via oral cavity (sublingual or Buccal cell) do not enter the hepatic portal blood system, thereby avoiding first pass clearance by the liver. Avoiding first past clearance of these formulations by the liver is described herein. The term, "first pass liver clearance" is the extent to which the drug is removed by the liver during its first passage in the portal blood through the liver to the systemic circulation. This is also called first pass metabolism or first pass extraction.

[0081] The two major routes of drug elimination from the body are excretion by the kidneys whereby the drug is unchanged; and elimination by the liver, whereby the drug is metabolized. The balance between these two routes depends on the relative efficiency of the two processes. The present invention describes herein elimination by the liver or liver clearance. First pass liver clearance is described by Birkett et al (1990 and 1991), which

is incorporated by reference in its entirety. Birkett et al., *Aust Prescr,* 13(1990):88-9; and Birkett et al., *Austra Prescr* 14:14-16 (1991).

[0082] Blood carrying drug from the systemic circulation enter the liver via the portal vein, and the liver in turn extracts a certain percentage or ratio (i.e. 0.5 or 50%) of that drug. The remainder left over (i.e. 0.2 or 20%) re-enters the systemic circulation via the hepatic vein. This rate of clearance of the drug is called the hepatic extraction ratio. It is the fraction of the drug in the blood which is irreversibly removed (or extracted) during the first pass of the blood through the liver. If no drug is extracted, the hepatic extraction ratio is zero. Conversely, if the drug is highly extracted in the first pass through the liver, the hepatic extraction ratio may be as high as 100% or 1.0. In general, clearance of the drug by the liver depends then on the rate of delivery of that drug to the liver (or the hepatic blood flow), and on the efficiency of removal of that drug (or the extraction ratio).

[0083] Therefore, the net equation used to determine hepatic clearance is:

(hepatic clearance – blood flow) = (unbound fraction * intrinsic clearance) / blood flow + (unbound fraction * intrinsic clearance) **(1)**

[0084] The "unbound fraction" of drug is dependent on how tightly the drug is bound to proteins and cells in the blood. In general, it is only this unbound (or free) drug which is available for diffusion from the blood into the liver cell. In the absence of hepatic blood flow and protein binding, the "intrinsic clearance" is the ability of the liver to remove (or metabolize) that drug. In biochemical terms, it is a measure of liver enzyme activity for a particular drug substrate. Again, although intrinsic clearance can be high, drugs cannot be cleared more rapidly than that presented to the liver. In simple terms, there are two situations: where liver enzyme activity is very high or very low (i.e. high extraction ratio or low extraction ratio).

[0085] When liver enzyme activity is low, the equation simplifies to:

hepatic clearance = unbound fraction * intrinsic clearance **(2)**

[0086] Clearance then is independent of blood flow, but instead depends directly on the degree of protein binding in the blood and the activity of drug metabolizing enzymes towards that drug.

[0087] In contrast, when liver enzyme activity is high, the equation is:

hepatic clearance = liver blood flow (3)

[0088] In this scenario, because the enzymes are so active the liver removes most of the drug presented to it and the extraction ratio is high. Thus, the only factor determining the actual hepatic clearance is the rate of supply of drug to the liver (or hepatic blood flow)..

[0089] First pass liver clearance is important because even small changes in the extraction of drugs can cause large changes in bioavailability. For example, if the bioavailability of drug A by oral administration is 20% by the time it reaches the systemic circulation, and the same drug A by intravenous administration is 100%, absent no other complicating factors, the oral dose will therefore have to be 5 times the intravenous dose to achieve similar plasma concentrations.

[0090] Secondly, in some instances where liver enzyme activity is very high, drug formulations should be designed to have the drug pass directly through to the systemic circulation and avoid first pass liver clearance all together. For example, drugs administered intranasally, sublingual, buccal, rectal, vagina, etc. directly enter the systemic circulation and do not enter the hepatic portal blood circulation to be partially or fully extracted by the liver. Alternatively, where drugs cannot be administered by the above means, a tablet with at least one enteric-coating layer to prevent release of the drug in the stomach (i.e. highly acidic environment) is provided. Thus, an objective of the invention is to administer drugs using these alternative routes.

[0091] Additionally, first pass liver clearance is an important factor because many patients are on more than one drug regimen, and this may cause drug interactions which increase or decrease liver enzyme activity; thereby increasing or decreasing metabolism (increasing or decreasing the hepatic extraction ratio) of the drug of interest.

[0092] Hence, therapeutic compositions of the invention can be administered directly to the systemic circulatory system and avoid first pass liver clearance. .Avoiding first pass clearance assures that more of the drug will be available to the system. Stated another way, by avoiding first pass liver clearance, the bioavailability of the drug is increased.

[0093] The present invention also relates to methods of increasing absorption of a low molecular compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation, or the CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

[0094] The composition formulation is appropriately selected according to the administration route, such as oral administration (oral preparation), external administration (e.g., ointment), injection (preparations for injection), and mucosal administration (e.g., buccal and suppository) etc. For example, excipients (e.g., starch, lactose, crystalline cellulose, calcium lactate, magnesium aluminometasilicate and anhydrous silicate), disintegrators (e.g., carboxymethylcellulose and calcium carboxymethylcellulose), lubricants (e.g., magnesium stearate and talc), coating agents (e.g., hydroxyethylcellulose), and flavoring agents can be used for oral and mucosal formulations; whereas, solubilizers and auxiliary solubilizers capable of forming aqueous injections (e.g., distilled water for injection, physiological saline and propylene glycol), suspending agents (e.g., surfactant such as polysorbate 80), pH regulators (e.g., organic acid and metal salt thereof) and stabilizers are used for injections; and aqueous or oily solubilizers and auxiliary solubilizers (e.g., alcohols and fatty acid esters), tackifiers (e.g., carboxy vinyl polymer and polysaccharides) and emulsifiers (e.g., surfactant) are used for external agents. The drug and the alkyl glycoside can be admixed, mixed, or blended along with the above excipients, disintegrators, coating polymers, solubilizers, suspending agents, etc., prior to administration, or they can be administered sequentially, in either order. It is preferred that they be mixed prior to administration.

[0095] The term, "mucosal delivery-enhancing agent" includes agents which enhance the release or solubility (e.g., from a formulation delivery vehicle), diffusion rate, penetration capacity and timing, uptake, residence time, stability, effective half-life, peak or sustained concentration levels, clearance and other desired mucosal delivery characteristics (e.g., as measured at the site of delivery, or at a selected target site of activity such as the bloodstream or central nervous system) of a compound(s) (e.g., biologically active compound). Enhancement of mucosal delivery can occur by any of a variety of mechanisms, including, for example, by increasing the diffusion, transport, persistence or stability of the compound, increasing membrane fluidity, modulating the

availability or action of calcium and other ions that regulate intracellular or paracellular permeation, solubilizing mucosal membrane components (e.g., lipids), changing non-protein and protein sulfhydryl levels in mucosal tissues, increasing water flux across the mucosal surface, modulating epithelial junction physiology, reducing the viscosity of mucus overlying the mucosal epithelium, reducing mucociliary clearance rates, and other mechanisms.

[0096] Exemplary mucosal delivery enhancing agents include the following agents and any combinations thereof:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for

enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

[0097] Additional mucosal delivery-enhancing agents include, for example, citric acid, sodium citrate, propylene glycol, glycerin, ascorbic acid (e.g., L-ascorbic acid), sodium metabisulfite, ethylenediaminetetraacetic acid (EDTA) disodium, benzalkonium chloride, sodium hydroxide, and mixtures thereof.

[0098] Therapeutic agents or drugs of the present invention can be peptides or proteins, medically or diagnostically useful, of small to medium size, e.g. up to about 15 kD, 30 kD, 50 kD, 75 kD, etc., or a protein having between about 1-300 amino acids or more. The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.

[0099] The mechanisms of improved drug absorption according to the invention are generally applicable and should apply to all such peptides or protein, although the degree to which their absorption is improved may vary according to the molecular weight (MW) and the physico-chemical properties of the peptide or protein, and the particular enhancer used. Examples of peptides or protein include vasopressin, vasopressin polypeptide analogs, desmopressin, glucagon, corticotropin (ACTH), gonadotropin, calcitonin, C-peptide of insulin, parathyroid hormone (PTH), growth hormone (HG), human growth hormone (hGH), growth hormone releasing hormone (GHRH), oxytocin, corticotropin releasing hormone (CRH), somatostatin or somatostatin polypeptide analogs, gonadotropin agonist or gonadotrophin agonist polypeptide analogs, human atrial natriuretic peptide (ANP), human thyroxine releasing hormone (TRH), follicle stimulating hormone (FSH), and prolactin.

[0100] One preferred composition of the invention is the peptide drug is Exenatide (or exendin-4) and an alkyl glycoside. Exenatide is a synthetic version of exendin-4, and has been used in clinical trials by Amylin™ Pharmaceuticals. Exendin-4 is a low molecular weight peptide that is the first of a new class of therapeutic medications known as incretin mimetic agents or hormones. Incretin hormones are any of various gastrointestinal (GI)

hormones and factors that act as potent stimulators of insulin secretion, e.g. as gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), or Exenatide, or exendin-4, or equivalents thereof.

[0101] Exendin-4 is a naturally occurring 39-amino acid peptide isolated from salivary secretions of the Gila Monster Lizard. Eng et al., "Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas," *J. Biol. Chem.* 267(15):7402-7405(1992). Exenatide exhibits similar glucose lowering actions to glucagons like peptide, or GLP-1. Exenatide is being investigated for its potential to address important unmet medical needs of many people with type 2 diabetes. Clinical trials suggest that Exenatide treatment decreases blood glucose toward target levels and is associated with weight loss. The effects on glucose control observed with Exenatide treatment are likely due to several actions that are similar to those of the naturally occurring incretin hormone GLP-1 (see Example 7). These actions include stimulating the body's ability to produce insulin in response to elevated levels of blood glucose, inhibiting the release of glucagon following meals and slowing the rate at which nutrients are absorbed into the bloodstream. In animal studies Exenatide administration resulted in preservation and formation of new beta cells, the insulin-producing cells in the pancreas, which fail as type 2 diabetes progresses.

[0102] Use of Exenatide, incretin mimetic agents or equivalents thereof can be used to treat various forms of diabetes including but not limited to brittle diabetes, chemical diabetes or impaired glucose tolerance, gestational diabetes, diabetes insipidus, diabetes insipidus central, diabetes insipidus nephrogenic, diabetes insipidus pituitary, latent diabetes, lipatrophic diabetes, maturity-onset diabetes of youth (MODY), diabetes mellitus (DM), diabetes mellitus adult-onset (type 2 DM), diabetes mellitus insulin-dependent (IDDM, or type 1 DM), diabetes mellitus non-insulin dependent (NIDDM), diabetes mellitus juvenile or juvenile-onset, diabetes mellitus ketosis-prone, diabetes mellitus ketosis-resistant, diabetes mellitus malnutrition-related (MRDM), diabetes mellitus tropical or tropical pancreatic, diabetes mellitus, preclinical diabetes, or diabetes induced by various drugs e.g. thiazide diabetes, steroid diabetes, or various diabetes animal model including but not limited to alloxan diabetes and puncture diabetes.

[0103] In another aspect, therapeutic compositions of the invention are used to treat obesity. Obesity is a common problem in both adults and adolescents. For example, PYY3-36 (or AC162352) is a hormone that plays a critical role in decreasing appetites. The gut hormone fragment peptide PYY3–36 (PYY) reduces appetite and food intake when infused into subjects of normal weight. Similar to the adipocyte hormone, leptin, PYY reduces food intake by modulating appetite circuits in the hypothalamus. However, in obese patients there is a resistance to the action of leptin, thereby limiting leptin's therapeutic effectiveness. Still other studies show that PYY reduces food intake. Injection of PYY revealed that they eat on average 30% less than usual, resulting in weight loss. Hence, PYY 3-36 has potential as a treatment for obesity. Amylin™ Pharmaceuticals submitted an Investigational New Drug application for PYY 3-36 in 2003.

[0104] Compounds whose absorption can be increased by the method of this invention include any compounds now known or later discovered, in particular drugs, or therapeutic compounds, molecules or agents that are difficult to administer by other methods, for example, drugs that are degraded in the gastrointestinal (GI) tract or that are not absorbed well from the GI tract, or drugs that subjects could administer to themselves more readily via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route than by traditional self-administration methods such as injection. Some specific examples include peptides, polypeptides, proteins and other macromolecules, for example, peptide hormones, such as insulin and calcitonin, enkephalins, glucagon and hypoglycemic agents such as tolbutamide and glyburide, and agents which are poorly absorbed by enteral routes, such as griseofulvin, an antifungal agent. Other compounds include, for example, nicotine, interferon (e.g., alpha, beta, gamma), PYY, GLP-1, synthetic exendin-4 (Exenatide), parathyroid hormone (PTH), and human growth hormone or other low molecular weight peptides and proteins.

[0105] Further, the therapeutic compositions of the invention also contemplate non-peptide drugs or therapeutic agents. For example, in U.S. Pat. No. 5,552,534, non-peptide compounds are disclosed which mimic or inhibit the chemical and/or biological activity of a variety of peptides. Such compounds can be produced by appending to certain core species, such as the tetrahydropyranyl ring, chemical functional groups which cause the compounds to be at least partially cross-reactive with the peptide. As will be recognized,

compounds which mimic or inhibit peptides are to varying degrees cross-reactivity therewith. Other techniques for preparing peptidomimetics are disclosed in U.S. Pat. Nos. 5,550,251 and 5,288,707. The above U.S. patents are incorporated by reference in their entirety.

[0106] The method of the invention can also include the administration, along with the alkyl glycoside and a protein or peptide, a protease or peptidase inhibitor, such as aprotinin, bestatin, alpha$_1$ proteinase inhibitor, soybean trypsin inhibitor, recombinant secretory leucocyte protease inhibitor, captopril and other angiotensin converting enzyme (ACE) inhibitors and thiorphan, to aid the protein or peptide in reaching its site of activity in the body in an active state (i.e., with degradation minimal enough that the protein is still able to function properly). The protease or peptidase inhibitor can be mixed with the alkyl glycoside and drug and then administered, or it can be administered separately, either prior to or after administration of the glycoside or drug.

[0107] The invention also provides a method of lowering blood glucose level in a subject comprising administering a blood glucose-reducing amount of a composition comprising insulin and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of insulin and lowering the level of blood glucose. A "blood glucose-reducing amount" of such a composition is that amount capable of producing the effect of reducing blood glucose levels, as taught herein. Preferred is an amount that decreases blood glucose to normoglycemic or near normoglycemic range. Also preferred is an amount that causes a sustained reduction in blood glucose levels. Even more preferred is an amount sufficient to treat diabetes, including diabetes mellitus (DM) by lowering blood glucose level. Thus, the instant method can be used to treat diabetes mellitus. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

[0108] Also provided is a method of raising blood glucose level in a subject by administering a blood glucose-raising amount comprising glucagons and at least one alkyl glycoside and/or saccharide alkyl ester. When the composition includes insulin, it can be used to cause the known effect of insulin in the bloodstream, i.e., lower the blood glucose levels in a subject. Such administration can be used to treat diabetes mellitus, or related

diseases. A "blood glucose-raising amount" of glucagon in such a composition is that amount capable of producing the effect of raising blood glucose levels. A preferred amount is that which increases blood glucose to normoglycemic or near-normoglycemic range. Another preferable amount is that which causes a sustained rising of blood glucose levels. Even more preferred, is that amount which is sufficient to treat hypoglycemia by raising blood glucose level. Thus, this method can be used to treat hypoglycemia. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

[0109] Similarly, when this composition includes glucagon, it can be used to cause the known effect of glucagon in the bloodstream, i.e., to raise the blood glucose levels in a subject. Such administration can therefore be used to treat hypoglycemia, including hypoglycemic crisis.

[0110] The invention also provides methods for ameliorating neurological disorders which comprises administering a therapeutic agent to the cerebral spinal fluid (CSF). The term "neurological disorder" denotes any disorder which is present in the brain, spinal column, and related tissues, such as the meninges, which are responsive to an appropriate therapeutic agent. The surprising ability of therapeutic agents of the present invention to ameliorate the neurological disorder is due to the presentation of the therapeutic agent to persist in the cerebro-ventricular space. The ability of the method of the invention to allow the therapeutic agent to persist in the region of the neurological disorder provides a particularly effective means for treating those disorders.

[0111] It will be understood, however, that the specific dose level and frequency of dosage for any particular subject in need of treatment may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. Generally, however, dosage will approximate that which is typical for known methods of administration of the specific compound. For example, for intranasal administration of insulin, an approximate dosage would be about 0.5 unit/kg regular porcine insulin (Moses et al.). Dosage for compounds affecting blood glucose levels optimally would be that

required to achieve proper glucose levels, for example, to a normal range of about 5-6.7 mM. Additionally, an appropriate amount may be determined by one of ordinary skill in the art using only routine testing given the teachings herein (see Examples).

[0112] Furthermore, the compositions of the invention can be administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained release format. The spray and the aerosol can be achieved through use of the appropriate dispenser. The sustained release format can be an ocular insert, erodible microparticulates, swelling mucoadhesive particulates, pH sensitive microparticulates, nanoparticles/latex systems, ion-exchange resins and other polymeric gels and implants (Ocusert, Alza Corp., California; Joshi, A., S. Ping and K. J. Himmelstein, Patent Application WO 91/19481). These systems maintain prolonged drug contact with the absorptive surface preventing washout and nonproductive drug loss.

[0113] The present invention is more particularly described in the following examples which are intended as illustrative only since numerous modifications and variations therein will be apparent to those skilled in the art. The following examples are intended to illustrate but not limit the invention.

EXAMPLE 1

ALKYL GLYCOSIDE AND/OR SUCROSE ESTER FORMULATIONS DO NOT CAUSE MUCOSA IRRITATION OR DISRUPTION

[0114] The nasal mucosa is highly vascularized and hence optimal for high drug permeation. Moreover, absorption of drug(s) through the nasal mucosa is available to the central nervous system (CNS). Although local application of drugs is desirable, a challenge for this method of administration is mucosal irritancy.

[0115] A formulation consisting of an alkyl glycoside (0.125% TDM) in a commercial over-the-counter (OTC) nasal saline was administered *in vivo* to human nasal epithelium over a period of over one month. The 0.125% TDM formulation is compared to the control, namely the same commercial (OTC) nasal saline, over the same period of time. Results show that during and after 33 days of daily TDM administration (i.e., the duration of the study), there is no observable irritation of the nasal mucosa (data not shown). Thus,

compositions of the invention are non-toxic and non-irritable providing repeated and long-term intranasal administration, which is beneficial for those patients with chronic and ongoing disease(s).

[0116] A similar test was performed using sucrose dodecanoate, a sucrose ester. Sucrose dodecanoate is administered *in vivo* to human nasal epithelium and during and after 47 days (i.e., the duration of the study), no observable irritation was detected (data not shown). Thus, these results show that alkyl glycosides and sucrose esters of the invention are non-toxic and do not cause mucosa irritation when administered daily over a long period of time.

EXAMPLE 2

ALKYL GLYCOSIDE AND/OR SUCROSE ESTER COMPOSITIONS STABILIZE DRUGS BY INCREASING DRUG BIOAVAILABILITY AND REDUCING DRUG BIOAVAILABILITY VARIANCE

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

[0118] Figure 1 is a graph comparing the bioavailability of the drug MIACALCIN® (salmon calcitonin from Novartis) with and without alkyl glycoside (TDM). MIACALCIN® is a nasal spray and administered directly onto the nasal epithelium or nasal mucosa. Figure 1 shows that MIACALCIN® minus alkyl glycoside has very low bioavailability levels in humans (MIACALCIN® product specification insert), as

compared to the MIACALCIN® with alkyl glycoside as administered to rats. More specifically, intranasal delivery of MIACALCIN® with 0.125% and 0.250% alkyl glycoside (TDM) resulted in about 43% to about 90% bioavailability, respectively. The bioavailability of intranasal administration of MIACALCIN® without alkyl glycoside is only about 3% in humans, and was undetectable in rats, suggesting that the rat is a stringent model for estimating intranasal drug absorption in humans. Thus, the alkyl glycoside of the invention enhances absorption and increases bioavailability of the drug.

[0119] Furthermore, besides increasing the bioavailability of the drug, the alkyl glycoside compositions of the invention effectively decrease the bioavailability variance of the drug. Figure 1 shows that administration of MIACALCIN® with alkyl glycoside (0.125% or 0.25%) intranasally has a bioavailability variance of +/- 8%, whereas the bioavailability variance without alkyl glycoside is 0.3% to 30%, or a two orders of magnitude change. The increase in bioavailability and the decrease in the bioavailability variance ensures patient-to-patient variability is also reduced. The results as shown in FIG. 1 are administered intranasally, however, similar results are expected for oral, buccal, vaginal, rectal, etc. delivery and at different alkyl glycoside concentrations.

[0120] Thus, contrary to the art, the alkyl glycoside compositions of the invention, in the range of about 0.01% to about 6% result in increased bioavailability and reduced bioavailability variance. This has not otherwise been reported.

EXAMPLE 3

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS INSULIN PRODUCES HYPOGLYCEMIC EFFECTS *IN VIVO*

[0121] Normal rats were anesthetized with a mixture of xylazine/ketamine to elevate their blood glucose levels. The elevated levels of D-glucose that occur in response to anesthesia provide an optimal system to measure the systemic hypoglycemic action of drug administration, e.g. insulin-containing eye drops. This animal model mimics the hyperglycemic state seen in diabetic animals and humans. In the experimental animal group, anesthetized rats are given eye drops containing insulin. Blood glucose levels from the experimental group are compared to anesthetized animals which received eye drops without insulin. The change in blood glucose levels and the differential systemic responses reflects the effect of insulin absorbed via the route of administration, e.g. ocular route.

[0122] Adult male Sprague-Dawley rats (250-350g) were fed *ad libitum*, and experiments were conducted between 10:00 a.m. and 3:00 p.m. Rats were anesthetized with a mixture of xylazine (7.5 mg/kg) and ketamine (50 mg/kg) given intraperitoneally (IP) and allowed to stabilize for 50-90 min before the administration of eye drops. Anesthesia of a normal rat with xylazine/ketamine produces an elevation in blood glucose values which provides an optimal state to determine the systemic hypoglycemic action of insulin-containing eye drops. Blood D-glucose values were measured by collecting a drop of blood from the tail vein at 5-10 min intervals throughout the experiment and applying the blood to glucometer strips (Chemstrip bG) according to directions provided with the instrument (Accu-Chek II, Boehringer Mannheim Diagnostics; Indianapolis, Ind.). Blood D-glucose values ranged from 200 to 400 mg/dl in anesthetized nondiabetic rats.

[0123] At time 0, after a 50-90 min stabilization period, rats were given 20 µl of eye drops composed of phosphate-buffered saline (PBS) with or without 0.2% regular porcine insulin and 0.125%-0.5% of the absorption enhancing alkyl glycoside (e.g. TDM) to be tested. Eye drops were instilled at time 0 using a plastic disposable pipette tip with the eyes held open, and the rat was kept in a horizontal position on a warming pad (37°C.) throughout the protocol. The rats were given additional anesthesia if they showed signs of awakening. Rats received in each eye 20 µl of 0.125-0.5% absorption enhancer in

phosphate buffered saline, pH 7.4 with (experimental) or without (control) 0.2% (50 U/ml) regular porcine insulin (Squibb-Novo, Inc.) for a total of 2 U per animal. Octyl-β-D-maltoside, decyl-β-D-maltoside, dodecyl-μ-D-maltoside, tridecyl-β-D-maltoside and tetradecyl-β-D-maltoside were obtained from Anatrace, Inc. (Maumee, Ohio). Hexylglucopyranoside, heptylglucopyranoside, nonylglucopyranoside, decylsucrose and dodecylsucrose were obtained from Calbiochem, Inc. (San Diego, Calif.); Saponin, BL-9 and Brij 78 were obtained from Sigma Chemical Co. (St. Louis, Mo.).

[0124] The D-glucose levels in the blood remained elevated when the animals received eye drops containing: 1) saline only; 2) 0.2% regular porcine insulin in saline only; or 3) absorption enhancer only. However, when rats received eye drops containing 0.2% regular porcine insulin and several alkylmaltoside or alkylsucrose compounds, a pronounced decrease in blood D-glucose values occurred and was maintained for up to two hours. Insulin administered ocularly with 0.5% dodecyl-β-D-maltoside (see Table I) or 0.5% decyl-β-D-maltoside (see Table III) results in a prompt and sustained fall in blood glucose levels which are maintained in the normoglycemic (80-120 mg/dl) or near-normoglycemic (120-160 mg/dl) range for the two hour duration of the experiment. Hence, at least two alkylmaltosides are effective in achieving sufficient absorption of insulin delivered via the ocular route to produce a prompt and sustained fall in blood glucose levels in experimentally hyperglycemic animals. The surfactant compositions of the invention are therefore useful to achieve systemic absorption of insulin and other peptides/proteins, e.g., glucagon and macromolecular drugs and heparin delivered via the ocular route in the form of eye drops.

[0125] Several other alkylmaltosides are also effective as absorption enhancers for ocular administration of insulin including 0.5% tridecylmaltoside (see Table III) and 0.125% (Table II) and 0.5% tetradecyl maltoside. These studies show that alkylmaltosides with the longer alkyl chains (or number of carbon atoms), e.g., dodecyl-, tridecyl- and tetradecyl-β-D-maltosides, are more effective. The increase in the number of carbon atoms also contributes to the greater hydrophobic/hydrophilic structural balance and absorption enhancing effect. The shorter alkyl chains (fewer carbon atoms) e.g., decylmaltoside, or no, e.g., octylmaltoside, produce less absorption enhancing activity. It is noted that the most effective alkylmaltosides produce effects comparable to or greater

than those seen with other absorption enhancers such as saponin, and with the added advantage that they can be metabolized to nontoxic products following systemic absorption.

[0126] The effects of the alkylmaltosides as absorption enhancers are dose-dependent, as can be seen by examining the effects of different concentrations ranging from 0.125-0.5% in producing a hypoglycemic effect when combined with insulin. Whereas, 0.5% and 0.375% dodecylmaltoside appear equally effective in achieving systemic absorption of insulin and reduction of blood glucose levels, 0.25% has a smaller and more transient effect and 0.125% is ineffective (Table I). Similarly, tridecylmaltoside also shows a dose-dependent effect in lowering blood glucose concentrations when combined with insulin, but the effect achieved with even 0.25% of the absorption enhance is sustained for the two hour time course of the experiment. Thus, dose-dependent effects of the alkylmaltosides suggest that they achieve enhancement of protein absorption via the ocular route in a graded fashion proportional to the concentration of the agent.

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

[0127] The absorption enhancing effects of the alkyl saccharides were not confined to the alkylmaltosides alone since dodecylsucrose (0.125%, 0.25%, 0.375%) also shows a dose-dependent effect in producing ocular absorption of insulin and reduction in blood glucose levels. This effect is observed even at 0.125% alkyl saccharide (from 335 mg/dl.+-.26 mg/dl at time 0 min. to 150 mg/dl +-.44 mg/dl at time 120 min.). 0.5% decylsucrose was also effective in reducing blood glucose levels, but as shown for the alkylmaltosides, a reduction in the length of the alkyl chain, and hence the hydrophobic properties of the molecule, appears to reduce the potency of the alkylsucrose compounds. However, a significant and sustained reduction in blood glucose levels is achieved with 0.5% decylsucrose (from 313 mg/dl.+-.15 mg/dl at time 0 min. to 164 mg/dl+-.51 mg/dl at time 120 min.). The absorption enhancing abilities of alkyl saccharides with two distinct disaccharide moieties suggests that it is the physicochemical properties of the compounds which are crucial to their activity and that other alkyl saccharides, e.g., dodecyllactose, have the right balance of properties to be equally or more effective as absorption enhancers while retaining the metabolic and nontoxic properties of the alkylsaccharide enhancing agents. These alkyl saccharides are anticipated by the invention.

[0128] Studies with alkylglucosides were also conducted; 0.5% hexylglucoside and 0.5% heptylglucoside were ineffective at promoting insulin absorption from the eye, but 0.5% nonylglucoside effectively stimulated insulin absorption and reduced blood glucose levels (from 297 mg/dl to 150 mg/dl). This result once further supports that the alkyl chain length, as well as the carbohydrate moiety, play critical roles in effectively enhancing insulin absorption.

[0129] It should be noted that no damaging effects (i.e. non-irritants) to the ocular surface were observed with any of the alkylmaltoside or alkylsucrose agents employed in these studies. Furthermore, the prompt and sustained hypoglycemic effects produced by these agents in combination with insulin suggest that these absorption enhancers do not adversely affect the biological activity of the hormone, in keeping with their nondenaturing, mild surfactant properties.

[0130] Thus, therapeutic compositions on the invention consisting of at least an alkyl glycoside and a drug are stable and the alkyl glycosides enhance the absorption of the drug.

EXAMPLE 4

OCULAR AND INTRANASAL ADMINISTRATION OF TDM PLUS INSULIN PRODUCES HYPOGLYCEMIC EFFECTS *IN VIVO*

[0131] Since previous Examples showed that administration via eye drops of an absorption enhancer with drug e.g. insulin results in significant absorption of the drug via the nasolacrimal drainage system, therapeutically effective administration of insulin with alkylmaltosides, alkylsucrose and like agents by intranasal administration is tested herein.

[0132] Tetradecylmaltoside (TDM) in combination with insulin also produced a drop in blood D-glucose levels when administered in the form of a drop intranasally as well as via a drop by the ocular route. Eye drops containing 0.2% regular porcine insulin with 0.125% tetradecylmaltoside are administered to rats as previously described. The administration of the composition produces a prompt and prominent drop in blood glucose levels. The drop in blood glucose levels decrease even more by administration of a nose drop containing the same concentration of insulin with 0.5% tetradecylmaltoside

(Table II). Thus, intranasal delivery and administration of the alkyl saccharide with drug results in lowering of blood glucose levels.

TABLE II

Effect of Insulin Eye Drops, Containing 0.125% Tetradecyl Maltoside and Nose Drops Containing 0.5% Tetradecyl Maltoside on Blood Glucose Values in Rats

Time (min)	Blood Glucose (mg/dl)
-20	319
-10	311
Eye drops added	
0	322
15	335
30	276
45	221
60	212
75	167
90	174
105	167
120	208
Nose Drops Added	
135	129
150	74
165	76
180	68

EXAMPLE 5

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS INSULIN PRODUCES HYPERGLYCEMIC EFFECTS *IN VIVO*

[0133] Previous studies demonstrated that insulin absorption from the eye is stimulated by saponin, BL-9 and Brij-78. BL-9 and Brij-78 are ineffective at stimulating the absorption of glucagon from the eye, whereas saponin is effective. Glucagon absorption from the eye was measured in rats given eye drops containing various

surfactants plus glucagon (30 μg) (Eli Lilly, Indianapolis, Indiana) by monitoring an elevation in blood D-glucose levels. In these experiments, rats were anesthetized with sodium pentobarbital rather than xylazine/ketamin. This modification of the procedure resulted in basal blood glucose levels in the normoglycemic range and made it possible to readily monitor the hyperglycemic action of any glucagon absorbed from the eye.

[0134] Paired animals that receive eye drops containing the surfactant alone, or glucagon alone, were compared to animals receiving eye drops with the surfactant plus glucagon. When eyedrops containing 0.5% saponin plus glucagon are administered to rats, the level of D-glucose in blood rises significantly, but no such effect is observed with eye drops containing 0.5% BL-9 or 0.5% Brij-78 plus glucagon. Interestingly, when eye drops containing dodecylsucrose, decylmaltose or tridecylmaltose plus glucagon are administered to rats which were previously treated with eye drops containing these surfactant agents plus insulin, the glucagon is absorbed and blood D-glucose values increase significantly (Table III). This result confirms that ocular administration of certain alkylsaccharides can enhance the absorption of drugs, including glucagon and insulin. Moreover, it is now possible to treat for a hypoglycemic crisis using a formulation with at least an alkyl saccharide of the invention.

TABLE III

Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats

	Surfactant Agent		
	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
Time (min)	Blood Glucose Concentration (mg/dl)		
-20	266	249	255
-10	305	287	307
	Insulin Eye Drops Added		
0	351	337	323
10	347	304	309
20	252	292	217
30	161	221	131
40	120	164	100
50	105	138	87
60	114	114	107
70	113	104	115
80	104	110	79
90	86	120	85
100	113	92	76
110	107	81	74
120	112	87	75
	Glucagon Eye Drops Added		
130	111	95	82
140	143	99	121
150	202	132	148
160	247	157	173
170	242	171	162
180	234	180	162
190	211	189	156

EXAMPLE 6

INTRANASAL ADMINISTRATION OF 0.25% TDM PLUS INSULIN DECREASES BLOOD GLUCOSE LEVELS *IN VIVO*

[0135] Intranasal administration of drugs or agents are possible in animal models e.g. mice and rats, although the nasal opening in is very small. In the experiments and results described herein, an anesthesia-induced hyperglycemia model was used (described in Examples above). Hyperglycemic animals were induced by an intraperitoneal (IP) injection containing xylazine-ketamine and blood glucose levels were monitored over a period of time. Immediately after the xylazine-ketamine injection, there was an increase

in the blood glucose levels as shown in FIG. 2 (closed dark circles), and blood glucose levels were about 450 mg/dl. The increase in blood glucose levels was attributed to the inhibition of pancreatic insulin secretion. Blood glucose levels peak to about 482 mg/dl by 30 minutes after the xylazine-ketamine injection (FIG. 2). Then, at approximately 33 minutes after the xylazine-ketamine injection, 6 μL of insulin (Humalog) in 0.25% tetradecylmaltoside (TDM; or Intravail A) was administered intranasally using a long thin micropipette tip, and blood glucose levels were monitored at about 15 minute intervals. After administration of the 0.25% TDM/insulin composition, there was a rapid decrease in blood glucose levels, reaching a low of about 80 mg/dl at about the 60 minute time point, or about 30 minutes after the insulin administration (FIG. 2). At about the 75 minute time point, blood glucose levels gradually returned to the baseline level in a normoglycemic mouse, or about 80-100 mg/dl.

[0136] The results above were compared with animals treated with insulin alone (same dosage), minus 0.25% TDM (FIG.2, open circles). The insulin only treatment showed blood glucose levels do not start to decline until at about the 120 minute time mark, or about 110 minutes after the insulin administration. Further, the blood glucose levels observed in animals treated with insulin alone never return to normoglycemic levels, as was observed in those animals receiving insulin plus 0.25%TDM (FIG. 2).

[0137] Thus, these results again demonstrate that compositions of the invention consisting of certain alkyl glycosides or alkyl saccharides plus a drug, e.g. insulin, effectively lower blood glucose levels, and that these effects are measurable shortly after administration of the drug.

EXAMPLE 7

INTRANASAL ADMINISTRATION OF 0.25% TDM (INTRAVAIL A) + EXENDIN-4 DECREASES BLOOD GLUCOSE LEVELS *IN VIVO*

[0138] The ob/ob mouse model was utilized for the studies described herein. Friedman, J. M. , *Nature* 404, 632-634 (2000). All animals received an intraperitoneal (IP) injection of a bolus of 2 g/kg glucose for purposes of determining glucose tolerance. At time 0 the experimental animals were given about 100 micrograms/kg of exendin-4/0.25% TDM (exendin-4 from American Peptide) either as 10 µl of nasal drops (FIG. 3; closed triangles), or by IP injection (FIG. 3; closed circles), or by and IP injection of saline alone (no drug, no TDM; FIG. 3; open circles). Control animals were previously performed and received no drugs. The results of this study are shown in FIG. 3.

[0139] Figure 3 shows that glucose tolerance of the animals were different since blood glucose levels vary at time 0 when the animals received the glucose bolus. Regardless, of the glucose tolerance level at time 0, immediately after injection of the glucose bolus, blood glucose levels increased in all three animals. The blood glucose level of the animal receiving the IP injection of saline alone does not decrease as rapidly as the experimental animals receiving the drug. Moreover, the animal receiving the IP injection of saline alone never reached a normoglycemic level (FIG.3, open circles). In contrast, the experimental animals, after administration of nasal drops of exendin-4/TDM, or IP injection of exendin-4/TDM, showed a rapid and immediate decrease in blood glucose levels.

[0140] Also exendin-4 administered about 15-30 minutes ahead of the glucose bolus (before time 0 in FIG. 3; data not shown) produced an even more pronounced lowering of blood glucose effect, because the absorption of the hormone takes a certain amount of time to be absorbed and to be active. Thus, exendin-4 (or Exenatide) which is currently in human clinical trials, when combined with alkyl glycosides of the invention, effectively treats a hyperglycemic condition by lowering the blood glucose levels of the hyperglycemic subject.

[0141] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference

into this application in order to more fully describe the state of the art to which this invention pertains.

Birkett et al., (1991) "Bioavailability and first pass clearance," *Austra Prescr* 14:14-16.

Birkett et al., (1990) "How drugs are cleared by the liver," *Austra Prescr* 3:88-89.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132:107-113.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides. B. Oral absorption *in vivo* in rats," *Int. J. Pharmaceutics* 132:115-121.

Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508.

Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213.

[0142] Although the present process has been described with reference to specific details of certain embodiments thereof in the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

What is claimed is:

1. A surfactant composition comprising of at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed with a drug, the surfactant stabilizes the biological activity and increases the bioavailability, of the drug.

2. The composition of claim 1, wherein the drug is a peptide or a protein.

3. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level.

4. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 10 times higher than the daily intake amount of the surfactant.

5. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 100 times higher than the daily intake amount of the surfactant.

6. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 1000 times higher than the daily intake amount of the surfactant.

7. The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. The composition of claim 1, wherein the surfactant has from about 10 to 16 carbon atoms.

9. The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system.

13. The composition of claim 1, wherein the surfactant is stable for at least six months from about 4°C to 25°C.

14. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 20%.

15. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 5%.

16. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 2%.

17. A therapeutic composition comprising of at least one biologically active compound(s) and at least one surfactant, wherein the surfactant is further comprised of at least one alkyl glycoside and/or saccharide alkyl ester and wherein said composition stabilizes the biological activity of the drug, for at least about 6 months from about 4°C to 25°C.

18. The composition of claim 17, wherein the pH of the composition is less than 8.0.

19. The composition of claim 17, wherein the composition is stable for at least six months from about 4°C to 25°C.

20. The composition of claim 17, wherein the composition concentration is from about 0.01% to 20%.

21. The composition of claim 17, wherein the composition concentration is from about 0.01% to 5%.

22. The composition of claim 17, wherein the composition concentration is from about 0.01% to 2%.

23. A stable therapeutic composition according to claim 17, wherein the composition is formulated for mucosal administration to a subject.

24. A stable therapeutic composition according to claim 17, wherein the administration to the subject yields enhanced mucosal delivery of said biologically active compound(s) comprising:

a) a peak concentration (C_{max}) of said biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of said subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;

b) an area under concentration curve (AUC) of the biologically active compound(s) in the central nervous system (CNS) tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to said subject; or

c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

25. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS tissue or fluid or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

26. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to the subject.

27. The therapeutic composition of claim 17, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active compound(s) in said CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater compared to an AUC of said biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to said subject.

28. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields an area under concentration curve (AUC) of said biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

30. The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.2 to 0.5 hours.

31. A method of administering a drug composition comprising of a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10 to 24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug.

32. The method of claim 31, wherein the surfactant has a high no observable adverse effect level.

33. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 10 times higher than the daily intake amount of the surfactant.

34. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 100 times higher than the daily intake amount of the surfactant.

35. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 1000 times higher than the daily intake amount of the surfactant.

36. The method of claim 31, wherein the surfactant reduces the bioavailability variance from patient to patient.

37. The method of claim 31, wherein the composition does not enter the hepatic portal blood system.

38. The method of claim 31, wherein the pH of the composition is less than 8.0.

39. The method of claim 31, wherein the composition is stable for at least six months from about 4°C to 25°C.

40. The method of claim 31, wherein the composition concentration is from about 0.01% to 20%.

41. The method of claim 31, wherein the composition concentration is from about 0.01% to 5%.

42. The method of claim 31, wherein the composition concentration is from about 0.01% to 2%.

43. The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. The method of claim 1, wherein the composition is further comprised of an enteric coating.

45. The method of claim 1, wherein the alkyl glycoside is tetradecylmaltoside (TDM).

46. The method of claim 45, wherein the TDM has anti-bacterial activity.

47. A method of increasing absorption of a low molecular weight compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route, the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, wherein the compound is selected from nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

48. The method of claim 47, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

49. The method of claim 47, wherein the alkyl has from 9 to 24 carbons.

50. The method of claim 49, wherein the alkyl has from 9 to 14 carbon atoms.

51. The method of claim 50, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

52. The method of claim 47, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

53. The method of claim 47, wherein the linkage is selected from the group consisting of a glycosidic linkage, a thioglycosidic linkage, an amide linkage, a ureide linkage and an ester linkage.

54. The method of claim 47, wherein the compound is a protein or a peptide.

55. The method of claim 54, and further comprising administering a protease or peptidase inhibitor.

56. The method of claim 47, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

57. The method of claim 47, wherein the composition is an intranasal spray.

58. The method of claim 47, wherein the administered dosage of the composition comprises a total volume of about 0.03 mL to about 0.3 mL per administered dose.

59. The method of claim 47, wherein the administered dosage of the composition comprises a total volume of about 0.1 mL per administered dose.

60. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 20 μg.

61. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per kg.

62. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 1% or greater than 1%.

63. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 0.5%.

64. The method of claim 47, wherein the composition is an intranasal spray.

65. The method of claim 47, wherein the composition comprises a total volume of about 0.03 mL to about 0.3 mL per administered dose.

66. The method of claim 47, wherein the composition comprises a total volume of about 0.1 mL per administered dose.

67. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per administered dose.

68. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per kg.

69. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 1% or greater than 1%.

70. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 0.5%.

71. A method of claim 47, wherein the composition is administered within 60 minutes before a meal.

72. A method of claim 47, wherein the composition is in the form of a single or unit dose and comprising no preservatives.

73. A method of claim 47, wherein the compound further comprises a polymeric coating selected from a group consisting of a hydrophilic, hydrophobic or enteric coating.

74. A method of claim 47, wherein the coating is an enteric coating.

75. A method of claim 47, wherein the enteric coating is selected from selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate

copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof.

76. A method of treating diabetes comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a blood glucose reducing amount of a composition comprising an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the effectiveness of incretin mimetic agent or insulin and lowering the level of blood glucose and treating the diabetes in the subject.

77. The method of claim 76, wherein the subject has Type-2 diabetes.

78. The method of claim 76, wherein the subject is a human.

79. The method of claim 76, wherein the incretin mimetic is Exenatide.

80. A method of treating congestive heart failure in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a therapeutically effective amount of a composition comprising a GLP-1 peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

81. A method of treating obesity or diabetes associated with obesity in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a therapeutically effective amount of a composition comprising a PYY peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

82. A method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation, pulmonary, oral cavity (sublingual, Buccal cell), or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the compound is not insulin, calcitonin, or glucagon.

83. The method of claim 82, wherein the compound has a molecular weight of less than about 15 kD.

84. The method of claim 82, wherein the compound is selected from vasopressin, a vasopressin polypeptide analog, desmopressin, glucagon, corticotropin, gonadotropin, C-peptide of insulin, parathyroid hormone, human growth hormone, growth hormone, growth hormone releasing hormone, oxytocin, corticotropin releasing hormone, somatostatin, a somatostatin polypeptide analog, gonadotropin agonist, a gonadotropin agonist polypeptide analog, atrial natriuretic peptide, thyroxine releasing hormone, follicle stimulating hormone, or prolactin.

85. The method of claim 82, wherein the compound is selected from a growth factor, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, or a polypeptide involved in the blood coagulation cascade.

86. A method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject comprising administering via the oral,

ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the subject does not have diabetes.

87. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of Exenatide in a pharmaceutically acceptable carrier.

88. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of GLP-1 in a pharmaceutically acceptable carrier.

89. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of nicotine in a pharmaceutically acceptable carrier.

90. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of interferon in a pharmaceutically acceptable carrier.

91. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of PYY in a pharmaceutically acceptable carrier.

92. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic

saccharide in combination with a therapeutically effective amount of parathyroid hormone in a pharmaceutically acceptable carrier.

93. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of a peptide having a molecular weight of about 1-75 kD in a pharmaceutically acceptable carrier, with the proviso that the peptide is not insulin, calcitonin, and glucagon.

94. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount erythropoietin in a pharmaceutically acceptable carrier.

95. A method as in claims 47-94 for ameliorating neurological disorder which comprises intranasal administration to the cerebrospinal fluid (CSF) of a subject with the disorder of a therapeutically effective amount of a therapeutic agent such that the therapeutic agent persists in the cerebro-ventricular space for a time sufficient to ameliorate the disorder.

96. A method for ameliorating neurological disorder which comprises intranasal administration to the cerebrospinal fluid (CSF) of a subject with the disorder of a therapeutically effective amount of a therapeutic agent as in claims 87-95 such that the therapeutic agent persists in the cerebro-ventricular space for a time sufficient to ameliorate the disorder.

97. A method of increasing absorption of a compound into the CSF of a subject comprising administering intranasally the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

98. The method of claim 97, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

99. The method of claim 97, wherein the alkyl has from 9 to 24 carbons.

100. The method of claim 97, wherein the alkyl has from 9 to 14 carbon atoms.

101. The method of claim 97, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

102. The method of claim 97, wherein the compound is a protein or a peptide.

103. The method of claim 102, wherein the protein or peptide drug is selected from the group consisting of insulin and glucagon.

104. The method of claim 97, and further comprising administering a protease or peptidase inhibitor.

105. The method of claim 97, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

106. A method of controlling caloric intake by administering a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of TDM alkyl saccharide.

107. A method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

108. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent wherein the mucosal delivery-enhancing agent is selected from:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, resulting in stabilization of the compound for enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

109. The pharmaceutical composition of claim 108, further comprising a plurality of intranasal delivery-enhancing agents.

110. The pharmaceutical composition of claim 108, wherein said mucosal delivery-enhancing agent(s) is/are selected from the group consisting of citric acid, sodium citrate,

propylene glycol, glycerin, L-ascorbic acid, sodium metabisulfite, EDTA disodium, benzalkonium chloride, sodium hydroxide and mixtures thereof.

111. The pharmaceutical composition of claim 108, wherein the alkyl has from 10 to 16 carbon atoms.

112. A method of increasing absorption of a low molecular weight compound into the circulatory system of a subject comprising administering, via the ocular, nasal, nasolacrimal, inhalation, or CSF delivery route (a) the compound; (b) an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide; and (c) a mucosal delivery-enhancing agent.

113. The method of claim 112, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

114. The method of claim 112, wherein the alkyl has from 9 to 24 carbons.

115. The method of claim 112, wherein the alkyl has from 9 to 14 carbon atoms.

116. The method of claim 112, wherein the alkyl has from 10 to 16 carbon atoms.

117. The method of claim 112, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

118. The method of claim 112, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

119. The method of claim 112, wherein the linkage is selected from the group consisting of a glycosidic linkage, a thioglycosidic linkage, an amide linkage, a ureide linkage and an ester linkage.

120. The method of claim 112, wherein the compound is a protein or a peptide.

121. The method of claim 112, wherein the method comprises a protease or peptidase inhibitor.

122. The method of claim 112, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

123. The method of claim 112, wherein the compound is selected from nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

124. A dosage dependent release composition comprising:

(a) a core comprising:

(i) at least one therapeutic agent or drug;

(ii) a surfactant comprising at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is impermeable, permeable, semi-permeable or porous and becomes more permeable upon sustained contact with contents of the gastrointestinal tract.

125. The membrane coating of claim 124 further comprising an alkalizing agent and/or a plasticizer.

126. The composition of claim 124 wherein the core is in the form of a tablet, hard capsule or gel capsule.

127. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 7.

128. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 6.

129. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 5.

130. The composition of claim 124, wherein the coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof.

131. The composition of claim 124, wherein the drug is selected from a group consisting of insulin like growth factor-I (IGF-I), somatomedin-C (SM-C), insulin, calcitonin, leptin, leptin derived short peptide (OB-3), hGH, human parathyroid hormone (PTH), melatonin, GLP-1 or Glucagon-like peptide-1, GiP, pituitary adenylate cyclase-activating polypeptide (PACAP), GM-1 ganglioside, nerve growth factor (NGF), nafarelin, Synarel®, (D-tryp6)-LHRH, FGF, VEGF antagonists, VEGF agonist, leuprolide, interferon-alpha, low molecular weight heparin, PYY, LHRH antagonists, LH, ghrelin antagonists, KGF, GDNF, G-CSF, Imitrex, Integrelin, Natrecor®, human B-type natriuretic peptide (hBNP), SYNAREL®, Sandostatin, Forteo, DDAVP® Nasal Spray, Cetrotide®, Antagon™, Angiomax, Accolate®, Exendin-4, SYMLIN®, desmopressin, glucagon, ACTH, C-peptide of insulin, GHRH and analogs (GnRHa), growth hormone

releasing hormone, oxytocin, corticotropin releasing hormone (CRH), atrial natriuretic peptide (ANP), thyroxine releasing hormone (TRHrh), follicle stimulating hormone (FSH), prolactin, or tobramycin ocular.

132. The composition of claim 124, wherein the coating is a porous coating.

133. The composition of claim 124, further comprising a protease inhibitor.

134. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 24 carbon atoms.

135. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 20 carbon atoms.

136. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 16 carbon atoms.

137. The composition of claim 124, wherein the alkyl group has from about 10 to 14 carbon atoms.

138. The composition of claim 124, wherein the alkyl glycoside is tetradecyl maltoside (TDM).

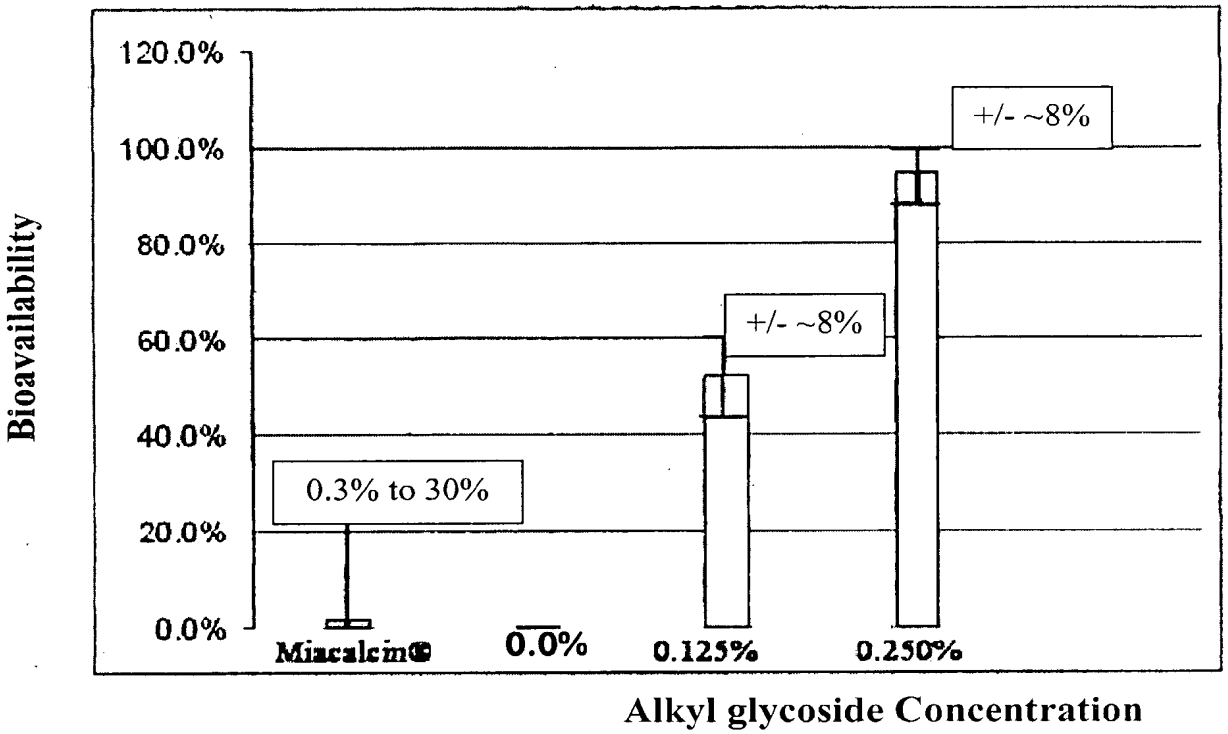

120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
Bioavailability
+/- ~8%
+/- ~8%
0.3% to 30%
Miacalcin®
0.0%
0.125%
0.250%
Alkyl glycoside Concentration

Figure 1

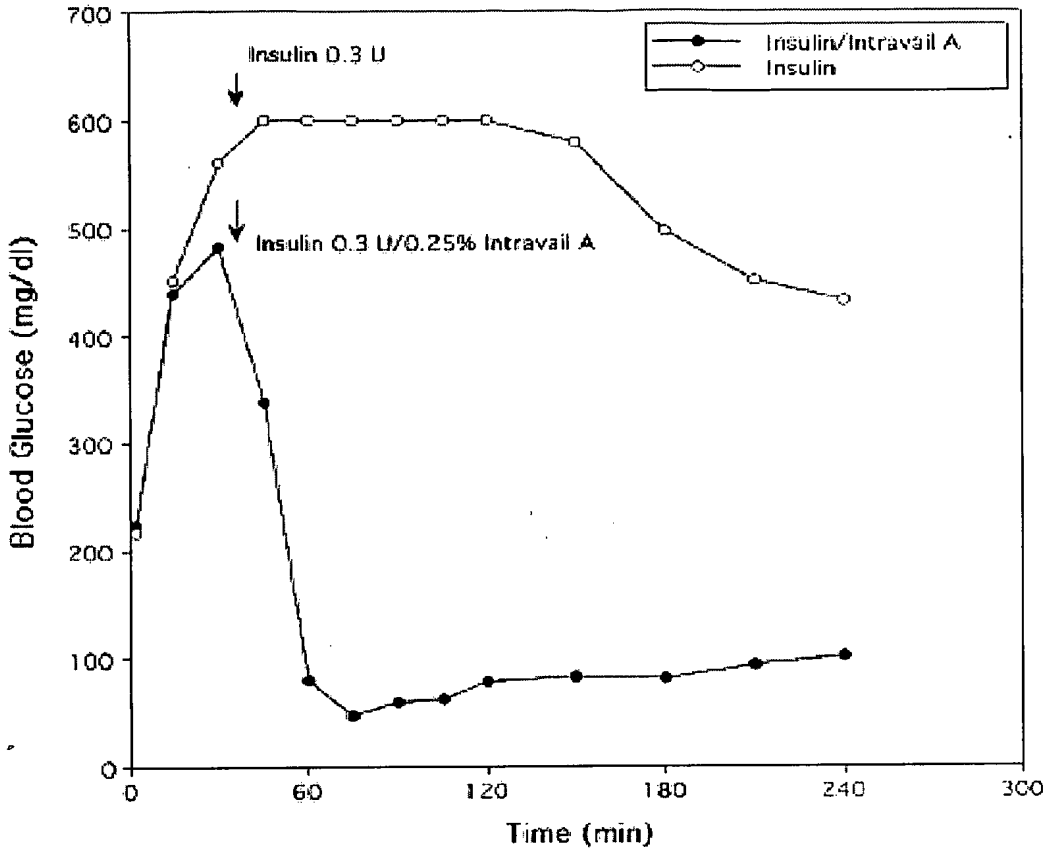

Insulin/Intravail A
Insulin
Insulin 0.3 U
Insulin 0.3 U/0.25% Intravail A
Blood Glucose (mg/dl)
Time (min)
0
100
200
300
400
500
600
700
0
60
120
180
240
300

Figure 2

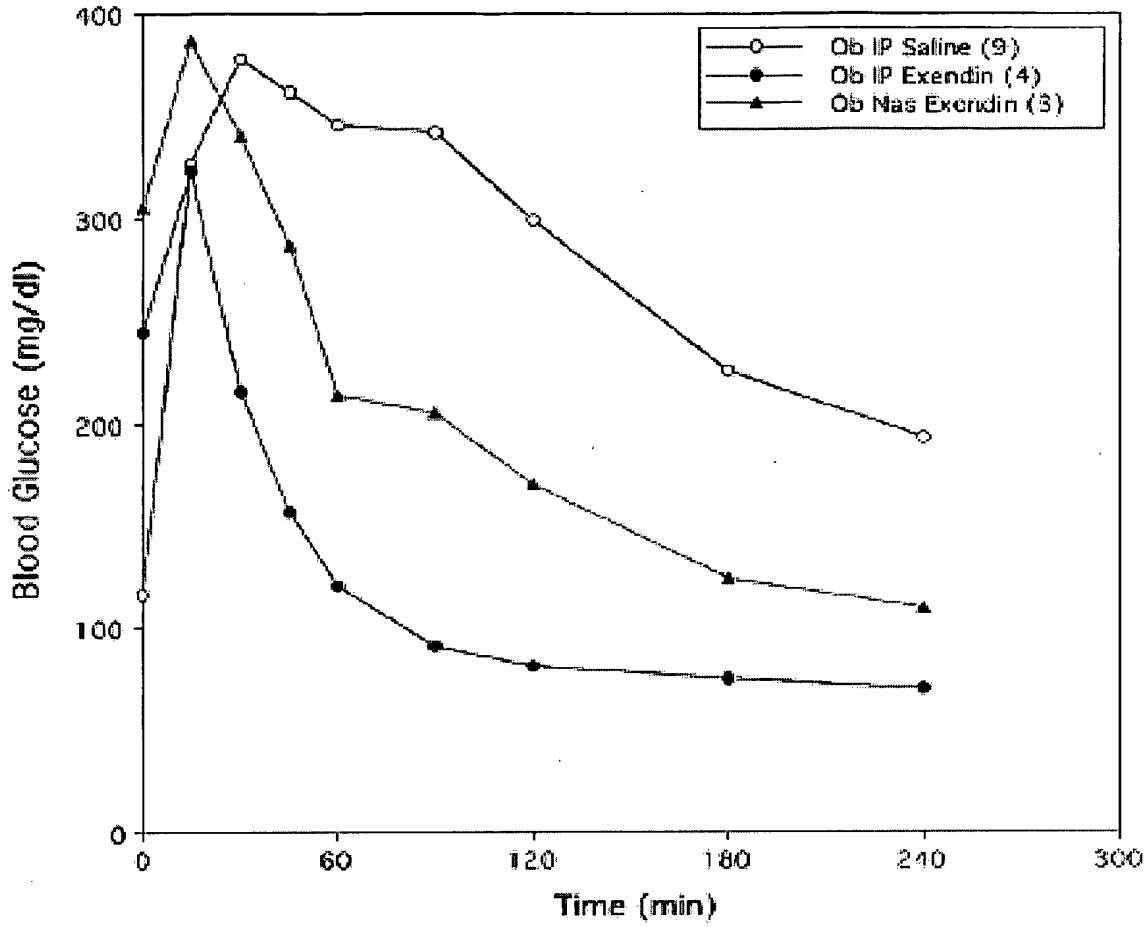

Ob IP Saline (9)
Ob IP Exendin (4)
Ob Nas Exendin (3)
Blood Glucose (mg/dl)
Time (min)
0
100
200
300
400
0
60
120
180
240
300

Figure 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt et al.	Group Art Unit: 1612
Serial Number: 13/495,942	Examiner: Adam C. Milligan
Filing Date: June 13, 2012	**CONFIRMATION NO: 7399**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: October 16, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Madam/Sir:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☐ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☐ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☐ a fee of $180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $90.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the

requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.35401-716.501).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: 10/16/2014

By: /Matthew V. Grumbling/
Matthew V. Grumbling, Reg. No. 44,427

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

STATEMENTS UNDER 37 C.F.R. § 1.97(E)

(Attachment to Information Disclosure Statement)

☐ *37 CFR §1.97(e)(1).* **THE UNDERSIGNED HEREBY STATES THAT** each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement:

☐ All references cited herein;

-- OR --

☐ The following subset of references: _____

--AND/OR--

☒ *37 CFR §1.97(e)(2).* **THE UNDERSIGNED HEREBY STATES THAT** no item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing of this Information Disclosure Statement:

☐ All references cited herein;

-- OR --

☒ The following subset of references: All except U.S. Serial No. 12/413,439 Office action mailed June 19, 2014

Respectfully submitted,

Dated: 10/16/2014 By: /Matthew V. Grumbling/

Matthew V. Grumbling
Registration No. 44,427

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 07/24/2014
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	06/13/2012	Steve Cartt	35401-716.501	7399

TITLE OF INVENTION: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	10/24/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLIGAN, ADAM C	1612	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Wilson Sonsini
2 Goodrich & Rosati
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Hale Biopharma Ventures, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Encinitas, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☑ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 23-2415 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Matthew V. Grumbling/ Date 10/16/2014

Typed or printed name Matthew V. Grumbling Registration No. 44,427

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	13495942
Filing Date:	13-Jun-2012
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/J C
Attorney Docket Number:	35401-716.501

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	2501	1	480	480
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	20438323
Application Number:	13495942
International Application Number:	
Confirmation Number:	7399
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/J C
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.501
Receipt Date:	16-OCT-2014
Filing Date:	13-JUN-2012
Time Stamp:	16:55:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$480
RAM confirmation Number	3546
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	35401-716-501-IFP-10-16-2014.pdf	426877 87fe3d2df6b69637f30361d58999b62c6921b416	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30597 d23fbfa5694e5ff0072de96896d6c8742d523c3e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	457474	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	06/13/2012	Steve Cartt	35401-716.501	7399

21971 7590 10/29/2014

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
MILLIGAN, ADAM C	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/29/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address : COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
13/495,942	13 June, 2012	CARTT ET AL.	35401-716.501

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
ADAM C. MILLIGAN	
ART UNIT	PAPER
1612	20141024

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Applicants IDS filed 10/16/2014 with the issue fee has been considered and attached hereto. - AM

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

PTO-90C (Rev.04-03)

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	June 13, 2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	1	of	1	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-6,165,484	12/26/2000	Raad et al.	
	2.	US-6,316,029	11/13/2001	Jain et al.	
	3.	US-7,008,920	3/7/2006	Kimura et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	4.	WO-2006-025882 A2	3/9/2006	The UAB Research Foundation et al.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	5.	Fix, "Oral controlled release technology for peptides: status and future prospects", Pharmaceutical Research 1996 Dec;13(12):1760-1764.	
	6.	Hussain et al, "Absorption enhancers in pulmonary protein delivery." J Control Release. 2004 Jan 8;94(1):15-24.	
	7.	Kissel et al., "Tolerability and absorption enhancement of intranasally administered octreotide by sodium taurodihydrofusidate in healthy subjects." Pharm Res. 1992 Jan;9(1):52-57.	
	8.	Kite et al., "Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro." J Clin Microbiol. 2004 Jul;42(7):3073-3076.	
	9.	Liu et al., "Interaction between chitosan and alkyl P-D-glucopyranoside and its effect on their antimicrobial activity", Carbohydrate Polymers. 2004; 56: 243-250.	
	10.	U.S. Serial No. 12/413,439 Office action mailed June 19, 2014	

Examiner Signature	/Adam Milligan/	Date Considered	10/23/2014

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	2	of	9	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	28.	US-3,547,828	12/15/1970	Mansfield et al.	
	29.	US-3,849,341	11/19/1974	Lambeiti	
	30.	US-4,397,951	8/9/1983	Taki et al.	
	31.	US-4,748,158	5/31/1988	Biermann et al.	
	32.	US-4,868,289	9/1/1989	Magnusson et al.	
	33.	US-4,921,838	5/1/1990	Catsimpoolas et al.	
	34.	US-5,182,258	1/1/1993	Chiou	
	35.	US-5,192,528	3/3/1993	Radhakrishnan et al.	
	36.	US-5,236,707	8/17/1993	Stewart	
	37.	US-5,268,461	12/7/1993	Shoji et al.	
	38.	US-5,308,531	5/3/1994	Urfer et al.	
	39.	US-5,317,010	5/31/1994	Pang et al.	
	40.	US-5,369,095	11/29/1994	Kee et al.	
	41.	US-5,550,220	8/27/1996	Meyer et al.	
	42.	US-5,639,733	6/17/1997	Koike et al.	
	43.	US-5,738,845	4/14/1998	Imakawa	
	44.	US-5,789,375	8/4/1998	Mukae et al.	
	45.	US-5,795,896	8/18/1998	Löfroth et al.	
	46.	US-5,814,607	9/29/1998	John S. Patton	
	47.	US-5,817,634	10/1/1998	Meezan et al.	
	48.	US-5,955,425	9/21/1999	Morley et al.	
	49.	US-6,004,574	12/21/1999	Backstrom et al.	
	50.	US-6,254,854	7/3/2001	Edwards, et al.	
	51.	US-6,316,410	11/13/2001	Barbier et al.	
	52.	US-6,395,300	5/28/2002	Straub et al.	
	53.	US-6,461,591	10/8/2002	Keller et al.	
	54.	US-6,482,834	~~9/20/2001~~	Spada, et al.	November 19, 2002
	55.	US-6,495,498	12/17/2002	Niemiec et al.	

Change(s) applied to document,
/D.D./
9/6/2014

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	06/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam Milligan
Sheet	2	of	6	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	28.	US-3,136,815	6/9/1964	Reeder et al.	
	29.	US-3,243,427	3/29/1966	Reeder et al.	
	30.	US-3,296,249	1/13/1967	Bell	
	31.	US-3,299,053	1/17/1967	Archer et al.	
	32.	US-3,371,085	2/27/1968	Reeder et al.	
	33.	US-3,374,225	3/19/1968	Reeder et al.	
	34.	US-3,567,710	3/2/1971	Fryer et al.	
	35.	US-3,609,145	~~9/28/1972~~	Moffett	September 28, 1971
Change(s) applied to document, /D.D./ 9/6/2014	36.	US-3,722,371	3/27/1973	Boyle	
	37.	US-3,987,052	10/19/1976	Hester, Jr.	
	38.	US-4,280,957	7/28/1981	Walser et al.	
	39.	US-4,608,278	8/26/1986	Frank et al.	
	40.	US-4,826,689	5/2/1989	Violanto et al.	
	41.	US-4,973,465	11/27/1990	Baurain et al.	
	42.	US-4,997,454	3/5/1991	Violanto et al.	
	43.	US-5,091,188	2/25/1992	Haynes	
	44.	US-5,100,591	3/31/1992	Leclef et al.	
	45.	US-5,118,528	6/2/1992	Fessi et al.	
	46.	US-5,145,684	9/8/1992	Liversidge et al.	
	47.	US-5,188,837	2/23/1993	Domb	
	48.	US-5,457,100	10/10/1995	Daniel	
	49.	US-5,560,932	10/1/1996	Bagchi et al.	
	50.	US-5,661,130	8/26/1997	Meezan et al.	
	51.	US-5,661,130	08/26/1997	Meezan et al.	
	52.	US-5,662,883	9/2/1997	Bagchi et al.	
	53.	US-5,665,331	9/9/1997	Bagchi et al.	
	54.	US-5,716,642	2/10/1998	Bagchi et al.	
	55.	US-5,780,062	7/14/1998	Frank et al.	

Examiner Signature	/Adam Milligan/	Date Considered	09/27/2013

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.D./ 9/6/2014 A.M./

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	06/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam Milligan
Sheet	1	of	6	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US,3,340,253	9/5/1967	Reeder et al.	
	2.	US-2001-0042932	11/22/2001	Mathiowitz et al.	
	3.	US-2001-0042932	11/22/2001	Mathiowitz et al.	
	4.	US-2002-0127278	~~09/12/2012~~	Kipp	September 12, 2002
	5.	US-2002-0168402	11/14/2002	Kipp	
	6.	US-2003-0031719	02/13/2003	Kipp	
	7.	US-2003-0181411	9/25/2003	Bosch et al.	
	8.	US-2006-0046962	3/2/2006	Meezan et al.	
	9.	US-2006-0198896	9/7/2006	Liversidge et al.	
	10.	US-2006-0198896	09/07/2006	Liversidge et al.	
	11.	US-2008-0200418	08/21/2008	Maggio	
	12.	US-2008-0248123	10/09/2008	Swanson et al.	
	13.	US-2008-0279784	11/13/2008	Cartt	
	14.	US-2008-0299079	12/04/2008	Meezan et al.	
	15.	US-2009-0047347	2/19/2009	Maggio	
	16.	US-2009-0130216	5/21/2009	Cartt	
	17.	US-2009-0163447	06/25/2009	Maggio	
	18.	US-2009-0297619	12/03/2009	Swanson et al.	
	19.	US-2009-0304801	12/10/2009	Liversidge et al.	
	20.	US-2009-258865	10/15/2009	Cartt	
	21.	US-2010-0068209	03/18/2010	Maggio	
	22.	US-2011-0172211	07/14/2011	Back et al.	
	23.	US-2011-0257096	10/20/2011	Maggio	
	24.	US-2012-0196941	08/02/2012	Maggio	
	25.	US-2013-0065886	03/14/2013	Cartt	
	26.	US-3,102,116	8/27/1963	Chase et al.	
	27.	US-3,109,843	11/5/1963	Reeder et al.	

Change(s) applied to document, /D.D./ 9/6/2014

Examiner Signature	/Adam Milligan/	Date Considered	09/27/2013

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.D./ 9/6/2014

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/495,942
				Filing Date	6/13/2012
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	1	of	9	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2002-0110524 Al	8/15/2002	Cowan et al.	
	2.	US-2002-0141971 Al	10/3/2002	Frey	
Change(s) applied to document, /D.D./ 9/6/2014	3.	US-2003-0017203 Al	~~6/23/2003~~	Crotts et al.	January 23, 2003
	4.	US-2003-0040497 Al	2/27/2003	Teng et al.	
	5.	US-2003-0087820 Al	5/1/2003	Young et al.	
	6.	US-2003-0100755 Al	5/29/2003	Sham et al.	
	7.	US-2003-0118547 Al	~~6/1/2303~~	Vandenberg	June 26, 2003
	8.	US-2003-0118594 Al	6/26/2003	Nag et al.	
Change(s) applied to document, /D.D./ 9/10/2014	9.	US-2003-0158206 Al	8/21/2003	Billotte et al.	
	10.	US-2003-0170206 Al	9/11/2003	Rasmussen et al.	
	11.	US-2004-0115135 Al	6/17/2004	Quay	
	12.	US-2004-0126358 Al	7/1/2004	Warne et al.	
	13.	US-2004-0147473 Al	7/29/2004	Warriell, Jr.	
	14.	US-2004-0258663 Al	12/23/2004	Quay & El-Shafy	
	15.	US-2005-0130260 Al	6/16/2005	Linden et al.	
	16.	US-2005-0234101 Al	10/20/2005	Stenkamp et al.	
	17.	US-2006-0045869 A1	03/02/2006	Meezan et al.	
	18.	US-2006-0046969 Al	3/2/2006	Maggio	
	19.	US-2006-0106227 Al	5/18/2006	Reddy et al.	
	20.	US-2006-0147386 Al	07-062006	Wermling	
	21.	US-2007-0298010 Al	12/27/2007	Maggio	
	22.	US-2007-0059254 Al	3/15/2007	Singh	
	23.	US-2007-0098805 Al	5/3/2007	Liversidge	
	24.	US-2008-0268032 Al	10/30/2008	Maggio	
	25.	US-2009/0258865 Al	10/15/2009	Cartt et al.	
	26.	US-2010-0203119 Al	8/12/2010	Leane et al.	
	27.	US-2010-0209485 Al	8/19/2010	Maggio	

Examiner Signature	/Adam Milligan/	Date Considered	07/14/2014

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	11/25/2014	8895546	35401-716.501	7399

21971 7590 11/05/2014

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Steve Cartt, San Carlos, CA;
David Medeiros, South San Francisco, CA;
Garry Thomas Gwozdz, Jim Thorpe, PA;
Andrew Loxley, Philadelphia, PA;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;