PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/28, 9/50, 31/34, 31/485, 31/635, 31/13	A1	(11) International Publication Number: WO 98/27967
		(43) International Publication Date: 2 July 1998 (02.07.98)

(21) International Application Number: PCT/DK97/00582

(22) International Filing Date: 18 December 1997 (18.12.97)

(30) Priority Data:
1456/96 20 December 1996 (20.12.96) DK

(71) Applicant *(for all designated States except US)*: DUMEX–ALPHARMA A/S [DK/DK]; Dalslandsgade 11, DK–2300 Copenhagen S (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: RÖMMELMAYER LARSEN, Annette [DK/DK]; Espegårdsvej 26A, DK–2880 Bagsværd (DK). PEDERSEN, Steen [DK/DK]; Grønnevej 84, 2. tv., DK–2830 Virum (DK).

(74) Agent: HOFMAN–BANG & BOUTARD, LEHMANN & REE A/S; Hans Bekkevolds Allé 7, DK–2900 Hellerup (DK).

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

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: RELEASE–CONTROLLED COATED TABLETS

(57) Abstract

A tablet suitable for oral administration being formed from the following ingredients: a) an inner core containing a biologically active agent and conventional excipients (part B) and a pharmaceutically acceptable, water insoluble, non–swellable carrier (part A), wherein part A constitutes from 20 % to 70 % by weight of the core; b) an entering coating, which prevents gastric fluid to enter into the core thereby preventing drug release in the stomach, but being soluble in the intestinal fluid (pH > 5); and c) an outer coating consisting of one or more polymer(s), the permeability of which is independent of pH.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Release-controlled coated tablets.

The present invention is concerned with a novel delivery system for targeting a wide variety of therapeutically active medicaments to the intestine and/or the colon. The delivery system is a tablet suitable for oral administration and comprising three parts:

a) an inner core containing a biologically active ingredient and conventional excipients,

b) an enteric coating, which prevents gastric fluid to enter into the core thereby preventing drug release in the stomach, but being soluble in the intestinal fluid (pH > 5), and

c) an outer coating consisting of one or more polymer(s). The permeability of the outer coating is independent of the pH value, therefore the release of the drug is largely unaffected by individual variations in the gastrointestinal fluids.

Among the biologically active agents which can advantageously be formulated and orally administrated in form of the tablet of the present invention, there are considered in particular active agents for which a delayed effect and/or a local effect are desired.

In a first aspect of the present invention the tablet can be used to provide controlled/delayed effect over a desired period of time.

In a further aspect of the present invention the tablet is especially suitable for time-varying delivery of a drug, the s.c. chronobiologically mode of action. E.g. patients with elevated blood pressure experience that

their blood pressure has within-day rhytmicity and that high pressure values are often seen in the morning just after the patient has woken up. Treatment of the rise in blood pressure just after awakening requires a dosage form that is administrated at bed-time and delivers the drug after a predetermined drug free period. Examples of drugs which beneficially can be delivered in this way are calcium antagonists like e.g. verapamil.

Other Examples of drugs, which are advantageously delivered in a release-controlled manner, are organic nitrates like e.g. glyceryl trinitrate or isosorbide nitrates. Especially preferred is isosorbide-5-mononitrate, (1,4:3,6-dianhydro-D-glucitol-5-mononitrate).

Isosorbide-5-mononitrate (5-ISMN) is a vasodilator and an arterial dilator. 5-ISMN is an active metabolite of 2,5-isosorbide-dinitrate, which have been used in treatment of angina pectoris for many years. Unlike the parent compound, 5-ISMN does not undergo hepatic first-pass metabolism, thus providing for a greater systemic bioavailability of the mononitrate dose. 5-ISMN is also completely absorbed from the gastrointestinal tract after oral administration and has a much longer half-life than isosorbide dinitrate. These factors make 5-ISMN a more attractive form of nitrate therapy for the management of angina and also for the development of long-acting oral nitrate forms.

It is obvious, that once-a-day dosing of a drug has advantages over twice- or three times a day dosing regimens, both from a patient compliance point of view but also because it prevents unwanted side-effects like high peak/low through plasma profile. However, if a controlled release form of 5-ISMN gives a serum con-

centration more than 100 ng/ml constantly during 24 hours, development of tolerance is likely to occur.

Nitrate tolerance may be defined as that condition where the haemodynamic responsiveness of the target tissue is lost. Whilst the direct cause of nitrate tolerance is unknown, a possibility may be changes in pharmacokinetics or to alterations in the property of target tissues such as the arterial and venal smooth muscle, making them less sensitive to the nitrate effect.

Nitrate therapy is the oldest treatment regimen for angina pectoris and the phenomenon of nitrate tolerance has been observed in humans with all commonly known nitrates, regardless of route of administration. 5-ISMN is no exception, and a need exists to design a form that overcomes this tolerance effect.

Another well-known problem to those skilled in the art of treating angina is that many angina patients chronically experience discomfort during sleep, just before awakening and for the first hour or so upon awakening. A further need exists to a form which overcomes this problem.

In US 4.956.181 to Eastman Kodak, a nitrate drug for angina pectoris is disclosed, more specifically a method and a transdermal patch for treating angina pectoris and preventing tolerance to nitrate drugs which takes into account the frequent need to provide the patient with relief or prevention of pre-waking or early morning angina. The treatment comprises administrating a daily unit dose of the nitrate before bedtime in a transdermal dosage form that provides a washout period of 3-12 hours by sufficiently retarding delivery of the nitrate from the patch to the patient during the washout period so as to provide a rate of delivery of nitrate that is so low

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.