PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/16, 9/50	A1	(11) International Publication Number: **WO 99/66904** (43) International Publication Date: 29 December 1999 (29.12.99)

(21) International Application Number: PCT/US98/17120

(22) International Filing Date: 18 August 1998 (18.08.98)

(30) Priority Data:
09/104,952 25 June 1998 (25.06.98) US

(71) Applicant: THERATECH, INC. [US/US]; Suite 100, 417 Wakara Way, Salt Lake City, UT 84108 (US).

(72) Inventors: PATEL, Phenil, J.; 740 University Village, Salt Lake City, UT 84108 (US). ACHARYA, Ramesh; 3176 Carrigan Canyon, Salt Lake City, UT 84109 (US). DAVE, Sirish, C.; 7611 South Toni Circle, Salt Lake City, UT 84121 (US).

(74) Agents: WESTERN, M., Wayne et al.; Thorpe, North & Western, L.L.P., P.O. Box 1219, Sandy, UT 84091–1219 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, 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, SL, TJ, TM, TR, TT, UA, UG, 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, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: INCORPORATION OF LATENT ACID SOLUBILIZING AGENTS IN COATED PELLET FORMULATIONS TO OBTAIN pH INDEPENDENT RELEASE

(57) Abstract

This invention is directed to a composition and method for the sustained delivery of an orally administered pharmaceutical agent where said agent has a pH dependent solubility profile. A pH independent release for drugs with pH dependent solubility is accomplished through the incorporation of a latent acid member with the pharmaceutical agent in the core of the tablet or pellet formulation which maintains the microenvironmental pH within and around the tablet or pellet in the solubility pH range of the pharmaceutical agent.

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		

INCORPORATION OF LATENT ACID SOLUBILIZING AGENTS IN COATED PELLET FORMULATIONS TO OBTAIN pH INDEPENDENT RELEASE

BACKGROUND OF THE INVENTION

The present invention relates to the controlled in vivo release of an active drug having pH dependent solubility from pellet formulations, comprised of a solid core containing the drug, a latent acid solubilizing agent, and an outer rate controlling polymeric membrane. Because the drug has a pH dependent solubility, the pellet formulation contains one or more latent acid solubilizing agents that hydrolyze and alter the microenvironmental pH such that the drug becomes soluble even where the surrounding pH would tend to limit or inhibit drug solubility.

Several illnesses, such as hypertension and angina pectoris, require continuous and constant controlled drug release at therapeutic levels. In such instances, medications must be administered at consistent intervals, e.g. every six to eight hours, so as to maintain a therapeutically effective blood concentration of the active agent. When using medications such as diltiazem, which has a short half-life in blood of approximately three to four hours, such administration becomes even more inconvenient. Such frequent administration times render the treatment annoying to the patient and impractical to administer, particularly during the night. Furthermore, after each administration of an immediate release form of such medications, the metabolic system undergoes a succession of rapidly increasing, followed by rapidly decreasing, plasma concentrations of the pharmaceutical agent or drug. Thus, the patient being treated and the targeted organ, e.g., the cardiac system, are successively subjected to plasma drug levels above and then below the desired therapeutic level. When plasma drug levels are higher than desired there are obvious disadvantages, i.e. waste of drug, possibility of toxicity, development of drug resistance, and the like. On the other hand, when plasma levels are lower than desired the drug may be ineffective or of marginal benefit. Obviously, it would be beneficial to maintain plasma drug levels as close to the optimal therapeutic level as possible.

A drug that has pH dependent solubility usually shows a pH dependent release rate relative to the formation of its corresponding salt species. Examples of such drugs include but are not limited to verapamil, diltiazem, albuterol, propranolol, bromocriptine, chlorphenaramine, prochlorperazine, dextromethorphan, enalapril, labetalol, nicardipine, pentazocine, phenylpropanolamine, promethazine, diphenhydramine, metoclopramide, selegiline, timolol, trimethobenzamide, and quinidine, etc. These drugs contain a basic side chain moiety such that, at basic pHs, the drug is charge neutral and therefore is less soluble in aqueous systems. Indeed, such drugs are soluble only if ionized, such as when an acidic salt is formed. Therefore, pH dependent drugs, such as enumerated herein, require the continued, consistent formation of a salt of the drug so as to ensure hydrophilic solubility and thus bioavailability. Unfortunately, the digestive tract does not favor the use of the acidic salts of these drugs. The digestive tract is known to vary in pH from about 1 to 2 in the stomach to a neutral or even a basic pH in the duodenum and small and large intestines. This wide variation of pH renders the acid soluble drugs less and less soluble, and hence less bioavailable, as they traverse the digestive tract.

It has been historically problematic to achieve a controlled, sustained release of a pharmaceutical agent throughout all portions of the digestive system because of this varying pH range. One approach to solving this problem is disclosed in U.S. Patent No. 5,202,128 to Angelo M. Morella, wherein is disclosed a pharmaceutical pellet composition having a core element including at least one highly soluble active ingredient and a core coating, which is partially soluble at a highly acidic pH. The pharmaceutical composition also includes a slow release of active ingredients at the acidic pH of the stomach and additionally provides a constant, relatively faster rate of release of a pharmaceutical agent at the more alkaline pH of the intestine. This patent discloses a method and composition whereby the pellet composition is altered such that the polymers selectively included in the pellet composition have increased or decreased solubility based on the changes in pH within the biological system. However, this invention does not take into account those pharmaceutical agents which are insoluble themselves at more basic pH levels. This patent appears to conclude that all pharmaceuticals are bioavailable even under basic conditions. The

disclosed invention therefore fails to solve the problem of affording solubility to those pharmaceutical agents which have pH dependent solubility.

Additional attempts at pH independent release rates of drugs having a pH dependent solubility profile have been disclosed by a variety of approaches such as the addition of an organic acid to a pellet formulation comprising a core made up of layers of the active agent and/or a salt thereof, and a polymeric material whereby the environment around the pellet becomes selectively acidic on a time release basis as disclosed in U.S. Patents 4,721,619; 4,826,688 and 4,863,742. Illustrative of organic acids that can be employed include acids such as adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and mixtures or combinations thereof. Disadvantages to this approach are stability of acid labile drugs while in the solid state in the pellet, stomach discomfort caused by the additional acid, and depletion of the added acid prior to complete dissolution and release of the drug.

An additional approach, which does not utilize organic acids, makes use of surfactants or wetting agents in the solid supports used for administration of these pharmaceutical agents, to increase solubility of the hydrophobic drug into the hydrophilic biological environment as disclosed in U.S. Patents 5,288,505 and 5,529,791. The surfactants or wetting agents include fatty acid esters of saccharose (commercialized under the trade names of SUCROESTERS and CRODESTERS), generically xylose esters or xylites, polyoxyethylenic glycerides, esters of fatty acids and polyoxyethylene sorbitan fatty acid esters, and polyglycides-glycerides as disclosed in U.S. Patent No. 5,288,505. However, the addition of such acids and/or surfactants may compromise the stability of certain drugs and/or may cause processing problems due to the corrosive nature of the acids used. It would therefore be useful to achieve the pH independent bioavailability of a drug having a pH dependent solubility profile. It would furthermore be useful to achieve these goals without alteration of the ambient pH, or through the addition of surfactants to facilitate the assimilation of the hydrophobic drug in a hydrophilic biological environment.

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.