Attorney Docket No. : 72350/004

FORM PTO-1619A
Expires 06/30/99
OMB 0651-0027

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Name (line 2):

Second Party

Name (line 1): Suma G. MENON — Execution Date Month Day Year: 07232001

Name (line 2):

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Name (line 1): Sun Pharmaceutical Advanced Research Centre LImited

Name (line 2):

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Area Code and Telephone Number: 212.969.4021

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Name (line 2)		
Name (line 1)	Nitin B. DHARMADHIKARI	07162001
Name (line 2)		
Name (line 1)	Ratnesh H. SHRIVASTAVA	07142001
Name (line 2)		

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Execution Date
Month Day Year

Name (line 1) Pratibha S. PILGAONKAR — 07172001

Name (line 2)

Execution Date
Month Day Year

Name (line 1)

Name (line 2)

Execution Date
Month Day Year

Name (line 1)

Name (line 2)

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Patent Application Number(s)	Patent Number(s)

I hereby claim the benefit under 35 U.S.C. ∋ 120 of any United States application(s), or ∋ 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. ∋ 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR ∋ 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status--patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:
Charles Guttman, Reg. No. 29,161; Kenneth Rubenstein, Reg. No. 30,586; Evan L. Kahn, Reg. No. 35,912; Anthony C. Coles, Reg. No. 34,139; Gregg I. Goldman, Reg. No. 38,896; Mitul Desai, Reg. No. 46,661; Tzvi Hirshaut, Reg. No. 38,732; and Rachel Watt, Patent Agent, Reg. No. 46,186

Address all telephone calls to Charles Guttman at telephone number: (212) 969-3000
Address all correspondence to: Proskauer Rose LLP
Patent Dept.
1585 Broadway
New York, New York 10036

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of the first or sole inventor (given name, family name): Shivanand P. PUTHLI	
Inventor's signature: > S.P. Puthli	Date: > JULY 17, 2001
Residence: 3/49, Juhu Darshan New D.N. Nagar Andheri (West), Mumbai 400053, Maharashtra, India	Citizenship: India
Post Office Address: Same as above	

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4746/72350-003 NYWORD/29403 v1

Full name of the second inventor (given name, family name): Suma G. MENON	
Inventor's signature: > Suma	Date: > 23 July, 2001
Residence: A-8, Gurukripa, Opp. Canara Bank Kalina, Mumbai - 400098 Maharashtra, India	Citizenship: India
Post Office Address: Same as above	

Full name of the third inventor (given name, family name): Jayant S. KARAJGI	
Inventor's signature: > Jayant S.	Date: > 19th July 2001
Residence: c/o H.S. Modak 4, Gulmohar, Lt. Prakash Kotnis Marg, Mahim Mumbai -- 400016 Maharashtra, India	Citizenship: India
Post Office Address: Same as above	

Full name of the fourth inventor (given name, family name): Nitin B. DHARMADHIKARI	
Inventor's signature: > N.B. Dharmadhikari	Date: > JULY 16 2001
Residence: 70B, Ram Nagar Nagpur - 440010 Maharashtra, India	Citizenship: India
Post Office Address: Same as above	

Full name of the fifth inventor (given name, family name):

Ratnesh H. SHRIVASTAVA	
Inventor's signature: > Ratnesh Shrivastava	Date: > July 14, 2001
Residence: D-3/203, Lok Upvan, Phase II Off Pokhran Road No. 2 Majiwade, Thane (West) -- 400601 Maharashtra, India	Citizenship: India
Post Office Address: Same as above	

Full name of the sixth inventor (given name, family name): Pratibha S. PILGAONKAR	
Inventor's signature: > P S Pilgaonkar	Date: > July 17, 2001
Residence: 801/802, 'L', Neelam Nagar, Building No. 6 V.B. Phadke Road Mulund (East), Mumbai - 400081 Maharashtra, India	Citizenship: India
Post Office Address: Same as above	

ASSIGNMENT OF PATENT APPLICATION

For value received, the undersigned sell(s), assign(s) and transfer(s) to:

Sun Pharmaceutical Advanced Research Centre Limited

a corporation organized under the laws of: Federal Republic of Germany and having a place of business at:

Acme Plaza, Opp. Sangam Cinema
Andheri Kurla Road,
Andheri (East)
Mumbai 400059, India

and to Assignee's successors, assigns and legal representatives or nominees as it may designate (collectively, hereinafter, "Assignee"), the entire right, title and interest, for:

___ The United States of America and Its Territories and Commonwealth and Possessions

_X_ All countries throughout the world

in and to all inventions and improvements disclosed in an application for United States Patent entitled:

ORAL OSMOTIC CONTROLLED DRUG DELIVERY SYSTEM FOR A SPARINGLY SOLUBLE DRUG

The above-entitled United States Patent application was:

___ executed by the undersigned on:_____

_X_ filed in the United States Patent and Trademark Office on: June 26, 2001

and assigned serial number: 09/891,848

___ filed as PCT International Application No.:_____

on:_____

The undersigned assign(s) to Assignee the rights for all patents, divisions, reissues, reexamination certificates, continuing applications and extensions thereof, together with the right of priority of any earlier corresponding patent application filed by the undersigned in the United States or elsewhere.

The undersigned covenant(s) that the rights and property conveyed by this Assignment are free and clear of any encumbrance, and that the undersigned have (has) full right to convey the rights and property as expressed herein.

7/13/01 11:16:28 AM (00000)

The undersigned authorize(s) and request(s) that any and all patents on the aforesaid inventions be issued to Assignee.

The undersigned agree(s), when requested, without further charge to Assignee but at its expense, to communicate to Assignee or its representatives all facts known to the undersigned regarding the aforesaid inventions and improvements, testify in any legal proceeding, sign all papers, make all rightful oaths or declarations, execute all divisional, continuing, re-examination and reissue applications and generally perform all acts, which may be necessary, desirable or convenient, to aid Assignee in securing, maintaining and enforcing patents for the aforesaid inventions and improvements in the aforesaid countries, and for vesting title thereto in Assignee.

Date: July 17, 2001 — S.P. Puthli
Shivanand P. PUTHLI

Date: July 23, 2001 — Suma
Suma G. MENON

Date: July 19th 2001. — Jayant
Jayant S. KARAJGI

Date: July 16, 2001 — N.B. Dharmadhikari
Nitin B. DHARMADHIKARI

Date: July 14, 2001 — Ratnesh, Shrivastava
Ratnesh H. SHRIVASTAVA

Date: July 17, 2001 — P.S. Pilgaonkar
Pratibha S. PILGAONKAR

THE PATENTS ACT, 1970.

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Complete specification filed on 2.2.2001 in respect of Patent Application No 119/MUM/2001 of Sun Pharmaceutical Industries Ltd, Acme Plaza, Andheri-Kurla Road, Andheri(E) Mumbai- 400 059 , Maharashtra, India.

This certificate is issued under the powers vested on me under Section 147(1) of the Patents Act, 1970.....

.....Dated this 9th day of March 2001.

N Garg

(N.K.Garg)

Asst Controller of Patents & Designs

ORIGINAL

FORM 1
THE PATENTS ACT, 1970
(39 OF 1970)
APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, **SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.**

AN INDIAN COMPANY
hereby declare -

(i) that we are in possession of an invention titled **"ORAL OSMOTIC CONTROLLED DRUG DELIVERY SYSTEM FOR A SPARINGLY SOLUBLE DRUG"**
(ii) that the complete specification relating to this invention is filed with this application.
(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are
Dr. Puthli, Shivanand Premanand; Mrs. Menon, Suma Girish; Dr. Karajgi, Jayant Shrikant; Dr. Dharmadhikari, Nitin Bhalachandra; all of SUN PHARMACEUTICAL ADVANCED RESEARCH CENTRE LIMITED, Bombay College of Pharmacy Building, 2nd Floor, C.S.T. Road, Kalina, Mumbai 400098, Maharashtra, INDIA; Dr. Shrivastava, Ratnesh Harinarayan of SUN PHARMACEUTICAL INDUSTRIES LIMITED, Acme Plaza, Andheri-Kurla Road, Andheri (E), Mumbai-400059, Maharashtra, India; and Mrs. Pilgaonkar, Pratibha S., 801 / 802 'L' Neelam Nagar, Building No.6, V.B. Phadke Road, Mulund (East), Mumbai - 400 081, Maharashtra, INDIA;
all Indian nationals.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Mr. S. Majumdar,
S. Majumdar & Co.
5, Harish Mukherjee Road
Calcutta 700025, INDIA.
TELEPHONE NO-91 33 455 7484/85/86
FACSIMILE NO- 91 33 455 7487/88

119/mum/2001

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- 2 FEB 2001

Received Rs. 5200/- in Cash
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FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

COMPLETE SPECIFICATION

(See section 10)

ORAL OSMOTIC CONTROLLED DRUG DELIVERY SYSTEM FOR A SPARINGLY SOLUBLE DRUG

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

The present invention relates to a process for the preparation of an oral osmotic controlled drug delivery system for a sparingly soluble drug. More particularly the invention relates to a process for the preparation of an oral osmotic controlled delivery system for desired delivery of carbamazepine over a period of 24 hours.

BACKGROUND OF THE INVENTION.

Carbamazepine, 5H-dibenz-[b,f]azepine-5-carboxamide, is used as an anti-convulsant and is available commercially in the form of tablets, syrups, chewable tablets and extended-release formulations. It is used in patients who do not respond satisfactorily to other forms of treatment. The drug appears to act by reducing polysynaptic responses and by blocking post-tetanic potentiation.

The therapeutic range of carbamazepine is about 4-12 μg/ml. Blood levels of carbamazepine below 4μg/ml are ineffective in treating clinical disorders, while levels above 12 μg/ml are most likely to result in side-effects. The side-effects are seen to a greater extent in syrup formulations due to the presence of fine particles of the active ingredient, which dissolve rapidly leading to faster drug absorption and higher peak plasma levels. The tablet formulations are relatively free of this disadvantage.

The oral osmotic system (OROS®, Alza Corp.), described by F. Theeuwes in J. Pharm. Sci., Vol. 64, 12, 1987-1991 (1975), consists of a

therapeutic system in the form of a coated and/or a laminated monocompartment system, comprising a semi-permeable wall/coat covering a drug-containing core and a passageway through the wall for releasing the contents of the core. Water permeates from the surrounding body fluids through the semi-permeable wall/coat and the pressure that is built-up causes a solution or suspension of the drug in the core to be released from the passageway. When a suspension of the drug is released, the released drug crystals dissolve and the dissolved drug is available for absorption from the gastrointestinal fluids into the general circulation. Hereinafter, the term "release" is used while referring to release of a suspension of a drug from an osmotic system and the term "delivery" or "drug delivery" is used in reference to appearance of dissolved drug in dissolution fluids or gastrointestinal fluids.

The OROS® system is unsuitable for drugs like carbamazepine, which are sparingly soluble in water and thus the osmotic pressure generated by the drug on its own is too low to cause release of the drug formulation from the core at a constant rate. Incorporation of an osmotic agent other than the drug itself requires fabrication of a two-layered osmotic system, one layer containing the drug and a second layer containing the osmotic agent and a swelling agent or swellable polymer. Osmotic influx of water causes the swelling of swellable polymer(s) in the core and expels the contents of the drug compartment through the passageway. As compared to single compartment systems, the manufacture of two-compartment systems is more complicated. Another problem cited in the prior art is that anhydrous carbamazepine (amorphous or crystalline) gets converted to the dihydrate form in an aqueous environment. These dihydrate crystals are needle-shaped and grow to ca. 500μm in size in the longitudinal direction. They affect the release of the drug formulation by blocking the passageway of the dosage form. Still another problem is

that which known swelling agents such as polyhydroxy polyethylene oxide, polymethacrylate, etc, are used in single compartment systems as the swellable polymer, the swelling pressure is so great that in contact with water, the semi-permeable wall bursts and the whole system disintegrates in the stomach after a short time.

The above mentioned drawbacks were overcome by a single compartment osmotic system disclosed in United States Patent No. 4,857,336 ('336) reissued as RE 34990, assigned to Ciba-Geigy, and which are incorporated herein by reference. The foregoing describe an oral therapeutic system comprising a core containing finely particulate anhydrous carbamazepine as a drug, hydroxypropyl methylcellulose (HPMC) as a protective colloid, a swellable hydrophilic polymer selected from the group consisting of poly-N-vinyl-2-pyrrolidone, polyvinyl alcohol, alkylene oxide homopolymers, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, a copolymer of vinyl pyrrolidone and vinyl acetate, a mixture of a copolymer of vinyl pyrrolidone and vinyl acetate and a homopolymer of ethylene oxide, and a water-soluble compound for inducing osmosis. HPMC herein works as a protective colloid or a crystal habit modifier such that it inhibits the ability of carbamazepine to change from the anhydrous form to any other form. Thus, in the presence of HPMC, the anhydrous carbamazepine crystals within the system remain in their original fine state without converting to large crystals of the dihydrate, which were believed to block the drug formulation releasing orifice. It is explained in lines 35-39 of column 4 of the '336 patent that the therapeutic system is therefore able to release carbamazepine microcrystals having a size of up to about 20 μm.

The oral osmotic dosage delivery form disclosed in United States Patent No. 5,284,662 ('662) (incorporated herein by reference) is an

improvement over the system of the '336 patent and comprises a core comprising (i) carbamazepine, (ii) an effective amount of a crystal habit modifier for said carbamazepine selected from the group consisting of C_{1-4}alkyl cellulose, hydroxypropyl-C_{1-4}alkyl cellulose, sodium carboxymethyl cellulose, sodium carboxymethyl C_{1-4}alkyl cellulose, and gelatin, (iii) from about 2% to about 15% of the total core weight of a mixture of at least two different hydroxy-C_1-C_4-alkyl celluloses wherein the ratio of the higher viscosity to the lower viscosity hydroxy-C_1-C_4-alkyl cellulose is about 2:1, (iv) a C_6 sugar alcohol, (v) a mono-or di-saccharide, (vi) from 0 to an effective amount of a tabletting lubricant, and (vii) from 0 to an effective amount of a wetting agent, with the core surrounded by a semi-permeable wall with a hole that connects the core with the external environment. In comparison to the system of the '336 patent, the system disclosed in the '662 patent required the presence of additional specific excipients, particularly a mono- or di-saccharide, more particularly a dextrate, and also required the two different hydroxyalkyl celluloses to be present in a particular ratio of 2:1. These changes are said to result in a surprising and unexpectedly better product in that carbamazepine was released in a zero-order fashion over about 6 hours, whereas the system of the '336 patent having the two different hydroxyalkyl celluloses in a 1:1 ratio delivered only 33% of the carbamazepine in a zero-order fashion over a period of only about 4 hours. Although a broad group of cellulose-based polymers and gelatin were claimed as crystal habit modifiers in the '662 patent, only hydroxypropyl methylcellulose is exemplified.

United States Patent No. 4,992,278 ('278) (incorporated herein by reference) discloses a peroral therapeutic system in tablet form for continuous and controlled administration of active ingredients that are sparingly soluble in water, and consists of (a) a casing made of a semi-permeable material, (b) a compressed core containing the active ingredient, a hydrophilic swelling polymer consisting of a mixture of a

vinylpyrrolidone/vinyl acetate copolymer with an ethylene oxide homopolymer, optionally a water soluble substance for inducing osmosis, and optionally other pharmaceutically acceptable adjuvants, and (c) a passage through the casing for transport of the components of the core to the surrounding aqueous body fluid. The patent teaches that when known swelling agents such as polyvinylpyrrolidone, polyethylene oxide, polymethacrylate and the like, are used in single compartment systems the swelling pressure is so great that in contact with water the semi-permeable wall bursts and the whole system disintegrates in the stomach after a short time. The problem is said to be solved by the advantageous swelling polymer mixture of the '278 patent. However, the systems exemplified in the '278 patent use large quantities of polymer. It would be desirable to use swelling polymers having a high degree of swelling such that they are usable in small amounts and do not contribute to increase in size of the system. As such, a large tablet or capsule is difficult to swallow and is not often acceptable to the patient leading to non-compliance of prescribed dosage regimens.

United States Patent No. 5,122,543 ('543) (incorporated herein by reference) discloses an aqueous suspension in the form of syrup for the oral administration of carbamazepine. This suspension exhibits delayed drug delivery characteristics and improved stability, and comprises carbamazepine dihydrate crystals having cubic or cuboidal shape and a particle size of approximately 10μm to approximately 200μm, wherein said crystals are obtained by dispersing in water anhydrous carbamazepine and polyvinylpyrrolidone/vinyl acetate copolymer as crystal habit modifier. The patent teaches that the use of the larger cuboidal crystals of a size between 10 μm to 200 μm results in delayed drug delivery, in comparison to fine needle-shaped crystals of the dihydrate less than 10 μm in size. Syrups containing the finer needle-

shaped crystals of the dihydrate make available a larger specific surface area for dissolution and absorption of carbamazepine. The greater side effects with syrups as opposed to tablets are attributed to the higher peak plasma levels of carbamazepine resulting from its rapid absorption.

OBJECTS OF THE INVENTION :

It is the object of the present invention to provide an oral osmotic controlled drug delivery system, which provides the desired rate of delivery of carbamazepine preferably over a period of about 24 hours.

A further object of the present invention is to provide an oral osmotic controlled drug delivery system for carbamazepine which utilizes a novel polymeric swelling agent comprising one or more swellable hydrophilic polymers selected such that the polymeric swelling agent exhibits controlled swelling and the wall does not rupture or burst.

A still further object of the invention is to meet the above two objectives, particularly the latter objective, while using swelling polymers having a high degree of swelling such that they are usable in small amounts and do not contribute to an increase in size of the system. As such, a large tablet or capsule is difficult to swallow and is not often acceptable to the patient leading to non-compliance of prescribed dosage regimens.

A further object of the invention is to provide a zero order rate of delivery of carbamazepine for up to about 6 hours while meeting the above objectives.

We have found a novel osmotic controlled drug delivery system for oral administration of carbamazepine, which does not employ a protective colloid or crystal habit modifier of the type used in the prior art '336 and

)62 patents but employs a crystal habit modifier in whose presence, ıpon contact with water, the anhydrous carbamazepine converts to :uboidal and/or rod-shaped crystals. In comparative experiments where ve suspended anhydrous carbamazepine in water or aqueous solution (with pH adjusted in the range from 1 to 7) of a crystal habit modifier, we found that whereas in the absence of a crystal habit modifier the anhydrous carbamazepine immediately transformed to long discrete needles that clustered together forming larger agglomerates, and also whereas in the presence of hydroxypropyl methylcellulose the anhydrous carbamazepine microcrystals did not convert to the dihydrate crystals, in the presence of crystal habit modifiers of the present invention the anhydrous carbamazepine converted to cuboidal and/or rod-shaped crystals. It is surprisingly found that in the present invention, these cuboidal and/or rod-shaped carbamazepine dihydrate crystals do not by themselves or by agglomeration or clustering cause blockage of the drug-releasing passageway when the drug formulation is squeezed out of the passageway due to the pressure created by the osmotic influx of water and swelling of the polymers. We have further found a novel mixture of swelling polymers such that upon contact with water the swelling pressure generated is not so great that the semi-permeable wall bursts and at the same time the swelling polymers have a high degree of swelling such that they are usable in small amounts and do not contribute to an increase in size of the system. It was furthermore quite surprising that in spite of an inference that may be made from prior art United States Patent No. 5,122,543 that crystal size is an important factor in carbamazepine dissolution, the oral osmotic controlled delivery system of the present invention, while exhibiting the above desirable characteristics and in spite of a change in crystal form and size, provided the desired rate and manner (zero order) of drug delivery.

SUMMARY OF THE INVENTION:

Thus the present invention provides a process for the preparation of an oral osmotic controlled drug delivery system for a sparingly soluble drug comprising:

a. providing a core comprising (i) finely particulate anhydrous carbamazepine (ii) a polymeric swelling agent comprising one or more swellable hydrophilic polymers selected such that the polymeric swelling agent exhibits controlled swelling and the wall does not rupture or burst, (iii) a crystal habit modifier, in whose presence, upon contact with an aqueous medium, the anhydrous carbamazepine crystals are transformed to cuboidal and/or rod-shaped crystals of the dihydrate of carbamazepine, and (iv) water-soluble compounds for inducing osmosis,
b. providing a wall made of acylated cellulose, the wall being impermeable to the components of the core, but permeable to water,
c. forming a passageway through the wall for releasing the components present in the core to the surrounding environment.

DETAILED DESCRIPTION OF THE INVENTION.

The core of the drug delivery system prepared by the invention is surrounded by a semi-permeable wall, which is permeable to water but impermeable to the contents of the core, e.g. carbamazepine, swellable hydrophilic polymers, osmotic agents and the like, and has a passageway through the wall.

The active ingredient in the core is finely particulate anhydrous carbamazepine in amorphous or crystalline form. The average particle size of the anhydrous carbamazepine is generally less than about 100

swellable hydrophilic polymers. Often, a mixture of two hydrophilic polymers provides the desired controlled swelling.

The preferred cellulose derivatives that may be used as swellable hydrophilic polymers in the polymeric swelling agent of the present invention include hydroxy C_{1-4} alkyl celluloses such as hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and the like. For example, the polymeric swelling agent may be a mixture of two different types or two different grades of the hydroxy C_{1-4} alkyl celluloses. In one more preferred embodiment of the present invention, the polymeric swelling agent is a mixture of two different grades of hydroxyethyl celluloses, still more preferably a mixture of hydroxyethyl cellulose 250H and hydroxyethyl cellulose 250L, wherein the designation "250" indicates the degree of substitution and "H" and "L" denote high and low viscosity, respectively. A preferred weight ratio of 250H to 250L is about 1:4 to about 4:1, more preferably about 1:2 to about 2:1. The hydroxy C_{1-4} alkyl C_{1-4} alkyl celluloses that may be used as swellable hydrophilic polymers include hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose and the like. Carboxyalkyl celluloses like carboxymethyl cellulose and its alkali salts, and in more preferred embodiments of the present invention crosslinked carboxyalkyl celluloses like crosslinked carboxymethyl cellulose, commonly known as croscarmellose, and its alkali salts may also be used as the swellable hydrophilic polymers.

In another embodiment of the present invention, copolymers of vinyl pyrrolidone and vinyl acetate, in admixture with alkylene oxide homopolymers such as polypropylene oxide, preferably ethylene oxide homopolymers or in admixture with hydroxy C_{1-4} alkyl celluloses, preferably hydroxyethyl cellulose, may be used as the polymeric swelling agent. The ethylene oxide homopolymers are commercially available as

Polyox® (Union Carbide), having a degree of polymerization of ca. 2000 to 100,000, with the molecular weight ranging between 100,000 and 7,000,000 Daltons.

A still more preferred polymeric swelling agent that may be used in the present invention comprises a mixture of croscarmellose sodium and xanthan gum. Croscarmellose sodium is a crosslinked polymer of sodium carboxymethyl cellulose, also known as Ac-Di-Sol, and available commercially as Nymcel® ZSX, Pharmacel® XL, Primellose® or Solutab®. Xanthan gum is a high molecular weight microbial polysaccharide gum obtained by the aerobic fermentation of carbohydrates with *Xanthomonas campestris*. Xanthan gum is of several different grades that have varying particle sizes, and is available commercially as Rhodigel, Rhodigel EZ, Rhodigel 200, Keltrol T and Xanthan gum Type FF. A preferred embodiment of the present invention contains xanthan gum type FF, having a particle size such that 100% of the particles pass through ASTM 80#, and a minimum of 92% pass through ASTM 200#, where ASTM stands for American Society for Testing and Materials, and 80# indicates a sieve with 80 meshes, each of size 180μm, present in a length of 2.54cm in each transverse direction parallel to the wires, and 200# indicates a sieve with 200 meshes, each of size 75μm, present in a length of 2.54cm in each transverse direction parallel to the wires, the sieve being made of stainless steel, brass or other inert material. The croscarmellose sodium and xanthan gum are present in suitable amounts such that the polymeric swelling agent exhibits controlled swelling and the wall does not rupture or burst, the desired rate of drug delivery is obtained and the polymeric swelling agent does not contribute significantly to increasing the size of the osmotic system. Generally, the croscarmellose sodium may be present in an amount from about 1% to about 10%, preferably about 3% to about 4.5% by weight of the core; and

the xanthan gum may be present in an amount from about 2% to about 5%, preferably about 3.5% to about 4% by weight of the core.

The core contains an effective amount of a crystal habit modifier, in whose presence, upon contact with an aqueous medium, anhydrous carbamazepine crystals are transformed to cuboidal and/or rod-shaped crystals of the dihydrate of carbamazepine. In this context, an "effective amount of crystal habit modifier" generally means about 0.1% to about 10% by weight based on the weight of the core. The crystal habit modifier may be any compound in whose presence carbamazepine crystals are transformed to cuboidal and/or rod-shaped crystals of the dihydrate of carbamazepine. However, it is generally a water soluble polymer or water swellable polymer or a surfactant or mixture thereof. Experiments conducted by us showed that vinylpyrrolidone polymers, polyethylene oxide polymers, polyethylene glycols, polyoxyethylene-polyoxypropylene glycol copolymers and several surfactants worked successfully as crystal habit modifiers of the present invention. We found that within a range of pH of gastrointestinal fluid, in aqueous medium, the anhydrous carbamazepine was transformed to cuboidal and/or rod-shaped crystals. Further specific examples of the crystal habit modifiers include polyvinylpyrrolidone having an average molecular weight of 1,000,000 Daltons, polyoxyethylene having an average molecular weight of 100,000 Daltons, polyethylene glycol 400, polyethylene glycol 8000, polyoxyethylene-polyoxypropylene having an average molecular weight of 7680 to 9510, polyoxyl 60 hydrogenated castor oil and long chain C_{12}-C_{18} fatty acid glycerides. Particularly preferred crystal habit modifiers of the present invention include vinylpyrrolidone polymers, more particularly, vinylpyrrolidone/vinyl acetate copolymers.

Vinylpyrrolidone polymers or polyvinylpyrrolidone (PVP), also referred to as Povidone, are synthetic polymers consisting essentially of linear 1-

vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights, the molecular weight ranging between 2500 and 3,000,000 Daltons. PVP is commercially available as Kollidon® (BASF), Plasdone® and Peristone® (General Aniline). PVP is classified into different grades on the basis of its viscosity in aqueous solution. Different grades of PVP available are PVP K-12, PVP K-15, PVP K-17, PVP K-25, PVP K-30, PVP K-60, PVP K-90 and PVP K-120. The K-value referred to in the above nomenclature is calculated from the viscosity of the PVP in aqueous solution, relative to that of water. The preferred vinylpyrrolidone polymer for use as a crystal habit modifier is PVP K-90, having an approximate molecular weight of 1,000,000 Daltons. It is more preferably used in the present invention when the hydroxyalkyl celluloses are used as the swellable hydrophilic polymers.

The most preferred crystal habit modifier is a vinylpyrrolidone/vinyl acetate copolymer having a monomer ratio of vinylpyrrolidone to vinyl acetate of approximately 60:40 (% by weight) and a molecular weight of 60,000 ± 15,000 Daltons. The preferred 60:40 copolymer is commercially available, for example, under the commercial name Kollidon® VA 64 (BASF). In preferred embodiment of the present invention, Kollidon® VA 64 is present in an amount ranging from about 0.1% to about 5%, more preferably about 2% to about 3% by weight of the core.

Water-soluble compounds suitable for inducing osmosis, i.e. osmotic agents or osmogents, include all pharmaceutically acceptable and pharmacologically inert water-soluble compounds referred to in the pharmacopoeias such as United States Pharmacopoeia, as well as in Remington: The Science and Practice of Pharmacy; edition 19; Mack Publishing Company, Easton, Pennsylvania (1995). Pharmaceutically acceptable water-soluble salts of inorganic or organic acids, or non-ionic

organic compounds with high water solubility, e.g. carbohydrates such as sugar, or amino acids, are generally preferred. The examples of agents used for inducing osmosis include inorganic salts such as magnesium chloride or magnesium sulfate, lithium, sodium or potassium chloride, lithium, sodium or potassium hydrogen phosphate, lithium, sodium or potassium dihydrogen phosphate, salts of organic acids such as sodium or potassium acetate, magnesium succinate, sodium benzoate, sodium citrate or sodium ascorbate; carbohydrates such as mannitol, sorbitol, arabinose, ribose, xylose, glucose, fructose, mannose, galactose, sucrose, maltose, lactose, raffinose; water-soluble amino acids such as glycine, leucine, alanine, or methionine; urea and the like, and mixtures thereof. The amount of osmogents that may be used depends on the particular osmogent that is used and may range from about 1% to about 60% by weight of the core.

Further, additional pharmaceutical excipients may be present in the core. Examples of other additional excipients include those excipients which are used in tabletting, during the preparation of granules, e.g. binders, lubricants, glidants, dispersants, colorants and the like. Thus, it is possible to use conventional adjuvants like lactose, saccharose, sorbitol, mannitol, cellulose, microcrystalline cellulose, or magnesium stearate, in addition to those mentioned above. The lubricants are typically present in an amount ranging from about 0.5% to about 5% by weight of the core, preferably up to about 4%, more preferably up to about 3.5%, most preferably about 0.75% to about 2% by weight of the core. Preferred additional excipients are surface-active compounds as exemplified in United States Patent No. 5,284,662. A preferred embodiment of the present invention includes sodium lauryl sulfate as the surfactant, in an amount ranging between about 0.1% and about 5% by weight of the core, more preferably about 0.5% to about 0.75% by weight of the core.

The suitable materials that may be used in the present invention for forming the semi-permeable wall include polymeric microporous materials that are well known to those skilled in the art and have been described in prior arts, for example in United States Patent No. 4,857,336 (RE 34990) and United States Patent No. 5,284,662. The cellulose acetates are preferred materials for wall formation. A combination of cellulose acetates with different degrees of acetylation may be employed to form the semi-permeable wall. As the degree of acetylation of the cellulose acetate increases, the material becomes more impermeable to aqueous fluids. Hence, a suitable combination of the cellulose acetates should be used to impart impermeability to the wall. A hydroxy C_1-C_4 alkyl C_1-C_4 alkyl cellulose and a plasticiser may also be present as components of the semi-permeable wall.

A preferred combination for forming the wall is cellulose acetate, of two different types, with different degrees of acetylation, in an amount ranging from about 78% to about 82%, more preferably about 80% of the wall weight, a hydroxy C_1-C_4alkyl-C_1-C_4alkyl cellulose, preferably hydroxypropyl methylcellulose, present in an amount ranging between about 5% to about 10%, more preferably from about 7% to about 8% of the wall weight, a poly C_2-C_4 alkylene glycol, preferably polyethyleneglycol, more preferably, polyethyleneglycol 8000, in an amount ranging from about 10% to about 14%, more preferably from about 11.5% to about 12.5% of the wall weight, and a suitable solvent system to form the coating solution. A preferred embodiment of the invention contains cellulose acetate 320S and cellulose acetate 398-10 NF, with the weight ratio of 320 S : 398-10 NF being about 5:1 to about 8:1, more preferably about 6:1 to about 7:1, still more preferably about 6.2:1 to about 6.6:1.

The expression "a passageway through the wall for releasing the components present in the core to the surrounding environment" covers a suitable means for releasing the drug formulation from the therapeutic system. This passageway comprises orifices, bores or apertures and the like, through the semi-permeable wall prepared by various methods such as those mentioned in United States Patent No. 3,916,899 (incorporated herein by reference). The passageway acts as the connection between the drug-containing core and the aqueous fluid in the environment. The minimum diameter of this passageway should be greater than the maximum length of the cuboidal and/or rod-shaped dihydrate crystals of carbamazepine. However, the diameter of the passageway is restricted to a maximum value, in order to prevent movement of aqueous fluid into the drug-containing core by convection. The most suitable form of passageway is an orifice formed by mechanical or laser drilling of the semi-permeable wall.

The oral osmotic controlled drug delivery system of the present invention is prepared by known methods, e.g. by mixing, granulation, compression, coating, etc. The mixture can be dry granulated, wet granulated or can be directly compressed. In the wet granulation process, the crystal habit modifier and the surfactant are dissolved in the granulating solvent and this solution is added to the dry mixture of osmogents, swellable hydrophilic polymers, colorants and the like. Water is the preferred granulating agent. The drug is then added to this solution in a finely particulate form. The entire mix is then granulated and the granulates, after lubrication, are eventually compressed on a rotary compression machine using standard concave beveled edge punches. In case of dry granulation, the dry mixture of carbamazepine, crystal habit modifier, osmogents, swellable hydrophilic polymers, colorants and the like is passed through a chilsonator to obtain slugs of the material, which are then passed through suitable sieves to obtain granules. These granules

are lubricated with a suitable lubricant and compressed on a rotary compression machine. In case of direct compression, the components of the system are mixed thoroughly and directly compressed on a rotary compression machine. The compressed cores, obtained by any one of the above methods, are subjected to coating, moulding, spraying, or immersion in a solution of a suitable material, to form the semi-permeable wall. An orifice is finally drilled into the semi-permeable wall using mechanical or laser drilling.

The examples that follow do not limit the scope of the invention and are presented as illustrations.

Example 1

Tablet cores were prepared according to the formula given in Table 1 below.

Table 1

No.	Ingredient	Quantity (mg)	Percent (%) by weight of the core
1.	Carbamazepine	200	36.37
2.	PVP K90	20	3.63
3.	Hydroxyethyl cellulose 250 L	10	1.82
4.	Hydroxyethyl cellulose 250 H	20	3.64
5.	Sodium chloride	142.45	25.90
6.	Lactose monohydrate	150	27.28
7.	Iron oxide red	0.05	0.009
8.	Sodium lauryl sulfate	2.5	0.45
9.	Magnesium stearate	5	0.9
	Total	550	100

The hydroxyethyl cellulose 250L, hydroxyethyl cellulose 250H, sodium chloride, lactose and iron oxide red were sifted and mixed to obtain a solid mixture. PVP K90 and sodium lauryl sulfate (SLS) were dissolved in water. The solid mixture, carbamazepine and a part of the aqueous solution of PVP K90 and SLS were mixed at a slow speed for 15 minutes.

The rest of the aqueous solution of PVP K90 and SLS was then added till granulation end-point was reached. The granules thus obtained were dried at 60°C to a moisture content of 2%. These granules were then passed through a #20 sieve and compressed to obtain the drug core. A layer of the coating solution, equivalent to 13-14 % by weight of the drug-containing core, was then applied to the core in a perforated coating pan to form the semi-permeable wall, using dichloromethane and methanol as the solvents. The composition of the coating solution is given in Table 2.

Table 2

No	Ingredient	Quantity (mg)	Percent by weight of the wall
1.	Cellulose acetate 320 S	53.25	71.72
2.	Cellulose acetate 398 10NF	8.01	10.8
3.	Hydroxypropyl methylcellulose, 15 cps	5.72	7.71
4.	Polyethylene glycol 8000	7.25	9.77

The coated tablets were dried for 48 hrs. Finally, an orifice of suitable size was drilled into the coated tablet by mechanical or laser-drilling the coat. The dissolution profile of the tablets was tested in a USP type I apparatus at 100rpm in 900ml of degassed water at 37±0.5°C. The drug delivery characteristics of the tablets are recorded in Table 3 below.

Table 3

Time	% drug delivery (± S.D.)
3 hours	24 (±4.92)
6 hours	57 (±6.23)
12 hours	81 (±5.31)
24 hours	91 (±4.55)

Example 2

Tablet cores were prepared according to the formula given in Table 4 below.

Table 4

No.	Ingredient	Quantity (mg)	Percent by weight of the core
1.	Carbamazepine	200	50.0
2.	Kollidon® VA 64	10	2.5
3.	Ac-Di-Sol	15	3.75
4.	Xanthan Gum	15	3.75
5.	Sodium chloride	76.22	19.06
6.	Lactose monohydrate	76.22	19.06
7.	Iron oxide red	0.05	0.013
8.	Sodium lauryl sulfate	2.5	0.625
9.	Magnesium stearate	5	1.25
	Total	400	100

The process of preparation of the therapeutic system involves sifting of lactose, Ac-Di-Sol, xanthan gum, sodium chloride and iron oxide red, and mixing with carbamazepine and a solution of sodium lauryl sulfate and Kollidon VA 64® in water. The rest of the procedure is essentially similar to that given in Example 1. The composition of the coating solution used for coating the system is given in Table 5 below.

Table 5.

No	Ingredient	Quantity (mg)	Percent by weight of the wall
1.	Cellulose acetate 320 S	54.53	69.92
2.	Cellulose acetate 398 10NF	8.21	10.53
3.	Hydroxypropyl methylcellulose, 15 cps	5.86	7.52
4.	Polyethylene glycol 8000	9.38	12.03

A layer of the coating solution, equivalent to 19-20% by weight of the core was applied using dichloromethane and methanol as the solvents. An orifice was drilled into the wall using a laser-drilling equipment, after drying the tablets.

The tablets so obtained were subjected to dissolution studies using the method given in Example 1. The drug delivery profile of the tablets is recorded in Table 6.

Table 6.

Time	% drug delivery (± S.D.)
3 hours	25 (±2.65)
6 hours	51 (±5.14)
12 hours	70 (±3.32)
24 hours	79 (±3.19)

We claim :

1. A process for the preparation of an oral osmotic controlled drug delivery system for a sparingly soluble drug comprising :

    a. providing a core comprising, (i) finely particulate anhydrous carbamazepine (ii) a polymeric swelling agent comprising one or more swellable hydrophilic polymers selected such that the polymeric swelling agent exhibits controlled swelling and the wall does not rupture or burst, (iii) a crystal habit modifier, in whose presence, upon contact with an aqueous medium, the anhydrous carbamazepine crystals are transformed to cuboidal and/or rod-shaped crystals of the dihydrate of carbamazepine, and (iv) water-soluble compounds for inducing osmosis,

    b. forming a wall made of acylated cellulose, the wall being impermeable to the components of the drug-containing core, but permeable to water, and

    c. forming a passageway through the wall, for releasing the components present in the core to the surrounding environment.

2. A process as claimed in Claim 1, wherein the core is formed by mixing and granulating the components of the core.

3. A process as claimed in claim 1, wherein granulation is effected by the route of wet or dry granulation.

4. A process as claimed in claim 2 or 3, wherein the step of granulation is followed by compression of the granulated mass.

5. A process as claimed in claim 1, wherein the wall is formed by following known techniques selected from coating, moulding, spraying or immersion in suitable material.

6. A process as claimed in claim 1, wherein the passageway is formed by drilling the said wall using mechanical or laser drilling.

7. A process as claimed in claim 1, wherein the polymeric swelling agent comprises a mixture of xanthan gum and croscarmellose sodium.

8. A process as claimed in claim 7, wherein the xanthan gum and the croscarmellose sodium are added in a 1:1 weight ratio.

9. A process as claimed in claim 7 or 8, wherein the xanthan gum has a particle size such that about 100% of the particles pass through a sieve of ASTM 80# and a minimum of about 92% of the particles pass through a sieve of ASTM 200#.

10. A process as claimed in claim 9, wherein the xanthan gum is added in amounts in the range from about 3.5% to about 4% by weight of the core.

11. A process as claimed in claim 7 or 8, wherein croscarmellose sodium is added in amounts in the range from about 3% to about 4.5% by weight of the core.

12. A process as claimed in claim 1 wherein the crystal habit modifier is selected from a vinylpyrrolidone polymer, a vinylpyrrolidone/vinyl acetate polymer, a polyethylene oxide polymer, a polyoxyethylene-polyoxypropylene glycol copolymer, a polyoxyethylene castor oil derivative, a long chain C_{12}-C_{18} fatty acid glyceride and mixtures thereof.

13. A process as claimed in claim 12, wherein the crystal habit modifier comprises vinylpyrrolidone/vinyl acetate copolymer having a monomer ratio of vinylpyrrolidone to vinyl acetate of approximately 60:40 in % by weight.

14. A process as claimed in claim 12, wherein the crystal habit modifier comprises vinylpyrrolidone/vinyl acetate copolymer, mixed in an amount from about 2% to about 3% by weight of the core.

15. A process as claimed in claim 12, wherein the crystal habit modifier comprises polyvinylpyrrolidone K90.

16. A process as claimed in claim 1, wherein the wall is formed from one or more cellulose acetates, hydroxypropyl methylcellulose and polyethylene glycol 8000.

17. A process as claimed in claim 16, wherein one or more of the cellulose acetates are added in amounts of from about 78% to about 82% by weight of the wall, the hydroxypropyl methylcellulose is added

in an amount from about 5% to about 10% by weight of the wall, and the polyethylene glycol 8000 is added in an amount from about 10% to about 14% by weight of the wall.

Dated this the 31st day of January, 2001.

S. MAJUMDAR
of S. MAJUMDAR & CO.,
Applicant's Agent

ABSTRACT

The present invention relates to an oral osmotic controlled drug delivery system for a sparingly soluble drug comprising of –

a. a core comprising of the sparingly soluble drug, a polymeric swelling agent, a crystal habit modifier and osmogent(s),

b. a semi-permeable wall covering the core, and

c. a passageway through the wall for the delivery of the components of the core,

wherein the semi-permeable wall is impermeable to the components of the core and permeable to water and gastrointestinal fluids. The dosage form is designed to achieve a zero order release of the drug over a period of at least 6 hours.

To

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