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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2014 (16.10.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/167440 A1

(51) International Patent Classification:
A61K 31/135 (2006.01) *A61P 21/02* (2006.01)

(21) International Application Number:
PCT/IB2014/060055

(22) International Filing Date:
22 March 2014 (22.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1154/MUM/2013 26 March 2013 (26.03.2013) IN
1155/MUM/2013 26 March 2013 (26.03.2013) IN

(71) Applicant: **WOCKHARDT LIMITED** [IN/IN]; D-4, MIDC Area, Chikalthana, Aurangabad 431 006 (IN).

(72) Inventors: **JAIN, Girish Kumar**; 4, Sharada Niketan, Teacher's Colony, Pitam Pura, Delhi 110 034 (IN). **DABRE, Rahul Sudhakar**; 15 A, Ujjwal Society, Narendranagar, Nagpur 440 015 (IN). **DUBEY, Vivek**; Kaji Muhal, Near Kaji Kwan, Sagar 470 002, Madhya Pradesh (IN). **DAGA, Vishal Omprakash**; B-5, Shraddha Towers No: 3, Dharangaon Road, Dist: Ahmednagar, M.S., Kopargaon 423 601 (IN).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2014/167440 A1

(54) Title: MODIFIED RELEASE PHARMACEUTICAL COMPOSITIONS OF CYCLOBENZAPRINE OR SALTS THEREOF

(57) Abstract: The present invention relates to modified release pharmaceutical compositions of cyclobenzaprine or salts thereof. In particular, the present invention relates to modified release pharmaceutical compositions comprising unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units. The composition may provide extended and specific release of cyclobenzaprine or salts thereof to achieve therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions when administered to a patient in need thereof. The invention also includes process of preparing such composition.

MODIFIED RELEASE PHARMACEUTICAL COMPOSITIONS OF CYCLOBENZAPRINE OR SALTS THEREOF

Field of the Invention

The present invention relates to modified release pharmaceutical compositions of cyclobenzaprine or salts thereof. In particular, the present invention relates to modified release pharmaceutical compositions comprising unit dosage forms of cyclobenzaprine or salts thereof in the form of uncoated units. The composition may provide extended and specific release of cyclobenzaprine or salts thereof to achieve therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions when administered to a patient in need thereof. The invention also includes process of preparing such composition.

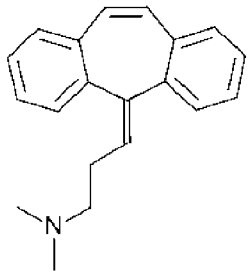
Background of the Invention

A spasm is a sudden, involuntary contraction of a muscle, a group of muscles. It most commonly refers to a muscle cramp which is often accompanied by a sudden burst of pain, but is usually harmless and ceases after a few minutes. There is a variety of other causes of involuntary muscle contractions, which may be more serious, depending on the cause. The spasm may also refer to a temporary burst of energy, activity, emotion, eustress, stress, or anxiety unrelated to, or as a consequence of, involuntary muscle activity.

Amongst causes of spasms are insufficient hydration, muscle overload, and absence of electrolytes. Spasmodic muscle contraction may be due to a large number of medical conditions, including the dystonias. A hypertonic muscle spasm is the state of chronic, excessive muscle tone, or tension in a resting muscle (the amount of contraction that remains when a muscle is not actively working).

A muscle relaxant is a drug which affects skeletal muscle function and decreases the muscle tone. It may be used to alleviate symptoms such as muscle spasms, pain, and hyper-reflexia. Cyclobenzaprine functions as a muscle relaxant by blocking nerve impulses (or pain sensations) that are sent to your brain. Cyclobenzaprine is used together with rest and physical therapy to treat skeletal muscle conditions such as pain or injury.

Cyclobenzaprine is a tricyclic class of antidepressant, skeletal muscle relaxant designated chemically as 3-(5H-dibenzo [a, d] cycloheptен-5-ylidene)-N, N-dimethyl-1-propanamine and has the following structural formula:



Cyclobenzaprine is one of the routinely prescribed muscle relaxant approved and marketed in United States under the proprietary name Amrix® as extended release capsule by Teva.

Amrix® is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Many active pharmaceutical agents have been formulated as orally administrable extended release (over a period of time) dosage form to permit once daily administration. The extended release of drug can be achieved either by coating the composition with release modifying substance or by dispersing drug in a matrix comprising one or more release modifying substance. In case of matrix-type dosage form, the drug is released over a period of time in the gastrointestinal tract upon dissolution or erosion of the matrix.

Extended-release dosage forms comprising a matrix system are conveniently prepared as compressed tablets. But drugs having relatively high solubility in water, for example a solubility of about 10 mg/ml or greater, present challenges to the formulator wishing to provide an extended-release dosage form and the higher the solubility the greater are the challenges.

U.S. Patent No. 4,590,062 discloses a compressed product containing an active produced by dry blending with a matrix combination of a hydrophobic polymer (e.g. ethylcellulose) and a wax, fatty acid, neutral lipid or combination thereof.

PCT Publication No. WO 2004/016249 discloses extended release matrix tablets for oral administration that include a cationic polymer, a water-swellable polymer, and an alginic acid derivative to cause the release rate of the active ingredient of the tablets to be independent of pH and gastric residence time.

PCT Publication No. WO 2010/133961 discloses extended release pharmaceutical compositions comprising cyclobenzaprine or salts thereof in the form of an inert core coated with matrix type extended release layer. The drug may be coated onto inert core or may be present in matrix type extended release layer.

PCT Publication No. WO 98/18610 discloses controlled release particles containing an active agent without substantial destruction of the matrix material. A release-rate controlling component is incorporated in a matrix to control the release rate of the encapsulant from the particles. A hydrophobic component or a high water binding capacity component may be used for extending the release time.

PCT Publication No. WO 98/06439 discloses a composition comprising dug encapsulated in a matrix comprising a polyether ester copolymer, such as polyethylene glycol terephthalate/polybutylene-terephthalate copolymer. The

polyether ester copolymer protects the active agent from degradation and thereby facilitates the drug delivery.

U.S. Patent No. 7,387,793 discloses modified release dosage forms wherein cyclobenzaprine extended release beads comprise active-containing core particle and an extended release coating of a water insoluble polymer membrane surrounding said core.

Several prior art references disclose different dosage forms wherein the active ingredient containing core/pellets/beads/matrix tablets were coated with release modifying polymer.

Pellets provide desired release profile based on the amount and type of coating of release modifying substances. But the pelletization is a sophisticated technique which requires high end manufacturing facilities and consume much of the time and resources and add complexity during production.

Coating the active containing tablet with release modifying substances can achieve sustained release of the drug. It is important to note that the additional handling operations involved in a coating step require a sufficient degree of tablet hardness to avoid tablet breakage and/or attrition during these operations, particularly in a high-speed manufacturing situation. But a tablet having a suitable sustained-release and with the good handling properties is difficult to formulate, particularly where the drug is having relatively high solubility, as in the case of cyclobenzaprine.

Thus, there exists an enduring need to develop an improved modified release simple pharmaceutical composition of cyclobenzaprine which will provide an alternative to existing formulations to provide relief of muscle spasm associated with painful musculoskeletal conditions over a 24 hour period.

Also there exists a need to develop modified release pharmaceutical composition of cyclobenzaprine by using simple and economical process, particularly without involving any coating procedure.

The inventors of the present invention have surprisingly found that it is possible to devise unit dosage form comprising uncoated units of cyclobenzaprine or salts thereof which may provide therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions when administered to a patient in need thereof.

Summary of the Invention

In one general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and optionally one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units filled in a capsule, wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and optionally one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units filled in a capsule, wherein the uncoated units are prepared by compression, extrusion or combination thereof.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and optionally one or more pharmaceutically acceptable excipients and the dimension of units is more than 0.5 mm, preferably more than 1.0 mm and more preferably more than 1.5 mm.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients and the ratio of amount of cyclobenzaprine or salts thereof and release modifying substances is in the range of about 1:1 to about 1:5.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein the capsule comprises about 0.1% to about 95% w/w, preferably of about 5% to about 85% w/w of cyclobenzaprine or salt thereof.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein the amount of release modifying substances in the dosage form ranges from about 5% to about 95% w/w, preferably about 15% to about 85% w/w of the composition.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein the dosage form comprises one or more pharmaceutically acceptable excipients selected from, but not limited to, diluent, binder, disintegrant, stabilizing agent, glidant, lubricant, and flavoring agents.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein cyclobenzaprine or salts thereof is dispersed in a matrix of one or more release modifying substances and optionally one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients and the dosage form exhibits a release profile such that not more than about 40% of cyclobenzaprine or salts thereof is released in 2 hours, not less than 40% of cyclobenzaprine or salts thereof is released in 4 hours and not less than 60% of cyclobenzaprine or salts thereof is released in 8 hours when measured in 900 ml of 0.1N HCl using USP Type II dissolution apparatus (Japanese sinker) and 50 rpm speed.

The modified release unit dosage form of cyclobenzaprine or salts may provide therapeutically effective plasma concentration of cyclobenzaprine over a period of 24 hours.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients, characterized in that the dosage form is bioequivalent to the formulation of cyclobenzaprine marketed under the trade name Amrix®.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:

(a) mixing cyclobenzaprine or salt thereof, ethyl cellulose, hypromellose, methacrylic acid copolymer, lactose, microcrystalline cellulose and povidone to form a dry blend;
(b) granulating the dry blend with water to form granules;
(c) drying and milling the granules;
(d) lubricating the dry milled granules with magnesium stearate;
(e) compressing the lubricated granules to form compressed units, and
(f) filling the compressed units in capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing cyclobenzaprine or salt thereof with one or more release modifying substances and optionally one or more pharmaceutically acceptable excipients to obtain a uniform mixture in form of dry powder to which a suitable amount of liquid is added to obtain a moistened plastically deformable mass;
(b) the extrusion of the mixture obtained from the step (a) through a perforated mesh in order to obtain cylindrical extrudates having desired length and diameter;
(c) the spheronization of the extrudates in order to obtain a product in the form of spherical pellets;
(d) the drying of the pellets and filling the extruded units in capsule.

In another general aspect, there is provided a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein the cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients, and characterized in that the dosage form retains at least 90% w/w of the potency of cyclobenzaprine or salt thereof when stored at 25°C and 40% relative humidity or at 40°C and 25% relative humidity for 3 months.

In another general aspect, there is provided a method of treating muscle spasm associated with acute, painful musculoskeletal conditions by administering a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a method of substantially minimizing the intersubject variability and improving the quality of life, especially in the elderly population, which method comprises administering the unit dosage form for delivering modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units filled in capsule, wherein cyclobenzaprine or salts thereof is dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutically acceptable excipients may include diluents, disintegrants, binders, bulking agents, anti-adherents, anti-oxidants, buffering agents, colorants, flavoring agents, coating agents, plasticizers, stabilizers, preservatives, lubricants, glidants, chelating agents, and the like known to the art used either alone or in combination thereof.

Detailed Description of the Invention

The present invention relates to a novel unit dosage form for delivering modified release of cyclobenzaprine or salts thereof in the form of uncoated units. Preferably, cyclobenzaprine is dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients. Such compositions may provide an extended release profile of cyclobenzaprine under in vitro conditions and may provide effective plasma concentration over a period of 24 hours. Such compositions can be used for treating muscle spasm

associated with painful musculoskeletal conditions when administered to a patient in need thereof.

The release modifying substances used for preparing uncoated units for extending the release of cyclobenzaprine or salts thereof include, but not limited to, water soluble or water insoluble release modifying substances.

The release modifying substances which can be used may be selected from the group consisting of hydrophilic agents (e.g. water-soluble polymers), lipophilic agents (water-insoluble polymers) and inert matrix agents, wherein the hydrophilic agents are selected from the group of pharmaceutical excipients which generate a gel in contact with water, including cellulose derivatives such as hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and the like; noncellulose polysaccharides such as galactomannanes, guar gum, carob gum, gum arabicum, alginates, pectins, and the like; polyvinylpyrrolidone; polyvinylacetate polymers and copolymers; acrylic acid polymers and copolymers, polyethylene oxide and mixtures thereof; the lipophilic agents are selected from the group consisting of waxes such as white wax, bees wax, carnauba wax and the like; fatty acids and alcohols such as stearic acid, palmitic acid, lauric acid and the like, and cetyl alcohol, cetostearyl alcohol, stearyl alcohol and the like; fatty acids esters such as monostearates of propylene glycol and fatty acid esters of sucrose, sucrose distearate and the like; and glycerides such as mono-, di- or triglycerides, e.g. palmitin, stearin, behenic, laurin, myristin, hydrogenated vegetable, castor, cottonseed oils, glyceril behenate and the like; ethyl cellulose; acrylic acid polymers and copolymers (available commercially under Eudragit® brand); and mixtures thereof; and the inert agents are selected from the group consisting of thermoplastic polymers, which are insoluble and indigestible in the gastrointestinal fluids, such as polyvinyl chloride, polyethylene, vinyl acetate/vinyl chloride copolymers, polymethylmethacrylates, polyamides, silicones, ethyl cellulose, polystyrene, and mixtures thereof.

In an embodiment, the amount of release modifying substances used in the composition may be in the range from about 5% to about 95% w/w of the composition, preferably of about 15% to about 85% w/w of the composition.

The term “cyclobenzaprine” used throughout the specification refers to not only cyclobenzaprine per se, but also its other pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof.

The term "modified release" used throughout the specification shall apply to dosage forms, matrices, particles, coatings, portions thereof, or compositions that alter the release of an active ingredient in any manner. Types of modified release include controlled, prolonged, sustained, extended, delayed, and the likes.

The term “matrix” used throughout the specification refers to the dispersion of drug within one or more release modifying substances and optionally one or more pharmaceutical excipients, or mixture thereof.

The term “uncoated units” used throughout the specification refers, but not limited to mini-tablets, tablet, pellets and granules prepared by standard either compression or extrusion methods known to the person skilled in the art.

The term "pharmaceutically acceptable excipients" includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering an active pharmaceutical ingredient. Each excipient should be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Excipients include diluents, binders, disintegrants, glidants, lubricants, flavoring, and others.

Diluents increase the bulk of a solid pharmaceutical composition. Exemplary diluents for solid compositions include, but are not limited to, microcrystalline cellulose, microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates, potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compressed may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Exemplary binders for solid pharmaceutical compositions include, but are not limited to, acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate and starch.

Disintegrants increase the dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach, for example. Exemplary disintegrants include, but are not limited to, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Exemplary excipients that may function as glidants include, but not limited to, colloidal silicon dioxide,

magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Exemplary lubricants include, but are not limited to, magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

In one embodiment, the composition of the present invention is a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units wherein the dimension of the uncoated units is more than 1.5 mm.

In another embodiment, the composition in accordance of the present invention is a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units, wherein the drug is dispersed in the matrix of one or more release modifying substances.

In another embodiment, the composition in accordance of the present invention is a modified release unit dosage form of cyclobenzaprine or salts thereof in the form of uncoated units filled in a capsule, wherein the uncoated units may be prepared by compression, extrusion or combination thereof.

In an embodiment, the ratio of amount of cyclobenzaprine or salts thereof and release modifying substances is in the range of about 1:1 to about 1:5.

In another embodiment, the amount of cyclobenzaprine or salt thereof in the compositions may present in the range from about 0.1% to about 95% w/w, and preferably from about 5% to about 85% w/w of the composition.

In another embodiment, the modified release unit dosage form of the present invention exhibits a release profile of cyclobenzaprine such that not more than about 40% of cyclobenzaprine or salts thereof is released in 2 hours, not less than 40% of cyclobenzaprine or salts thereof is released in 4 hours and not less than 60% of cyclobenzaprine or salts thereof is released in 8 hours when measured in 900 ml of 0.1N HCl using USP Type II dissolution apparatus (Japanese sinker) and 50 rpm speed, wherein said composition provides therapeutically effective plasma concentration over a period of 24 hours.

In another embodiment, the modified release unit dosage form of the present invention is bioequivalent to formulation of cyclobenzaprine marketed under the trade name Amrix®.

In another embodiment, the modified release unit dosage form of the present invention retains at least 90% w/w of the potency of cyclobenzaprine or salt thereof when stored at 25°C and 40% relative humidity or at 40°C and 25% relative humidity for 3 months.

In another embodiment, the modified release unit dosage form of the present invention is characterized in that it provides therapeutically effective plasma concentration of cyclobenzaprine or salt thereof over a period of 24 hours.

The modified release unit dosage form of the present invention can be prepared by methods known to the person skilled in the art. Preferably, the unit dosage form comprises plurality of uncoated units. The uncoated units can be prepared by various methods known to the person skilled in the art, such as extrusion, wet granulation, dry granulation, followed by compression or slugging.

In an embodiment, a process for preparation of a modified release capsule, which process comprises steps of:

(a) mixing cyclobenzaprine hydrochloride, ethyl cellulose, hypromellose, methacrylic acid copolymer, lactose microcrystalline cellulose and povidone to form a dry blend;
(b) granulating the dry blend with water to form granules;
(c) drying and milling the granules;
(d) lubricating the dry milled granules with magnesium stearate;
(e) compressing the lubricated granules to form compressed units, and
(f) filling the compressed units in capsule.

In an embodiment, a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing cyclobenzaprine or salt thereof with one or more release modifying substances and optionally one or more pharmaceutically acceptable excipients to obtain a uniform mixture in form of dry powder to which a suitable amount of liquid is added to obtain a moistened plastically deformable mass;
(b) the extrusion of the mixture obtained from the step (a) through a perforated mesh in order to obtain cylindrical extrudates having desired length and diameter;
(c) the spheronization of the extrudates in order to obtain a product in the form of spherical pellets;
(d) the drying of the pellets and filling the extruded units in capsule.

The modified release unit dosage form of cyclobenzaprine or salts thereof may be developed in the form a capsule, a tablet, a caplet and a mini-tablet. Preferably the dosage form is in the form of a capsule.

In an embodiment, the modified release unit dosage form in accordance of the present invention is in the form of a hard gelatin capsule filled with uncoated units comprising cyclobenzaprine or salt thereof, wherein cyclobenzaprine or salt thereof is dispersed in the matrix of one or more release modifying substances selected from group consisting of ethyl cellulose, methacrylic acid copolymer,

hydroxypropyl cellulose or hydroxypropyl methylcellulose or combination thereof, and lactose.

The composition of the present invention may comprise one or more pharmaceutically acceptable excipients selected from, but not limited to, diluent, binder, disintegrant, glidant, lubricant, stabilizing agent, and flavoring agents.

The present invention further provides a method of treating muscle spasm associated with acute, painful musculoskeletal conditions by administering the modified release unit dosage form of cyclobenzaprine or salts thereof as substantially described throughout the specification.

The present invention further provides a method of substantially minimizing the intersubject variability and improving the quality of life, especially in the elderly population, which method comprises administering a modified release unit dosage form of cyclobenzaprine or salts thereof as substantially described throughout the specification.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

The examples given below serve to illustrate embodiments of the present invention. However they do not intend to limit the scope of present invention.

Example 1: Cyclobenzaprine Capsule

Table 1

Sr. No.	Ingredients	15 mg strength	30 mg strength
		mg/ Capsule	mg/ Capsule
Intragranular			
1	Cyclobenzaprine Hydrochloride	15.000	30.000
2	Ethylcellulose	25.075	50.150
3	Methacrylic acid copolymer	18.054	36.108
4	Lactose	38.562	77.123
5	Hydroxypropyl cellulose	3.010	6.02
6	Purified Water	q. s.	q. s.
Extragranular			
7	Magnesium Stearate	0.300	0.600
	Capsule fill weight	100 mg / 10 Tablets	200 mg / 20 Tablets
8	Empty Hard gelatin Capsules Size “2”	--	1 no.
9	Empty Hard gelatin Capsules Size “4”	1 no.	--

Procedure:

Cyclobenzaprine hydrochloride, ethyl cellulose, methacrylic acid copolymer, lactose and hydroxypropyl cellulose were sifted. To this water was added to form the granules. These obtained granules were dried and milled. Magnesium stearate was sifted and added to the obtained granules. These granules were compressed and finally filled into capsules.

Example 2: Cyclobenzaprine Capsule

Table 2

Sr. No.	Ingredients	15 mg strength	30 mg strength
		mg/ Capsule	mg/ Capsule
Intragranular			
1	Cyclobenzaprine Hydrochloride	15.000	30.000
2	Hypromellose K 100 MCR	35.000	70.000
3	Ethyl cellulose	15.000	30.000
4	Lactose	16.690	33.380
5	Microcrystalline cellulose	15.000	30.000
6	Povidone K 30	3.010	6.020
7	Purified Water	q. s.	q. s.
Extragranular			
8	Magnesium Stearate	0.300	0.600
	Capsule fill weight	100 mg / 10 Tablets	200 mg / 20 Tablets
9	Empty Hard gelatin Capsules Size “2”	--	1 no.
10	Empty Hard gelatin Capsules Size “4”	1 no.	--

Procedure:

Cyclobenzaprine hydrochloride, ethyl cellulose, hypromellose, methacrylic acid copolymer, lactose, microcrystalline cellulose and povidone were sifted. To this water was added to form the granules. These obtained granules were dried and milled. Magnesium stearate was sifted and added to the obtained granules. These granules were compressed and finally filled into capsules.

Example 3: Dissolution and Stability Study (Related Substance Data) of Cyclobenzaprine HCl Capsule of Example 1

Table 3

Related Substance Data	Initial	1M 40/75	3M 40/75	1M 40/75	3M 40/75	1M 40/75	3M 40/75	1M 40/75	3M 40/75
		30 Counts		30 Counts		60 Counts		60 Counts	
		60cc HDPE TW + with 1 gm SG	60cc HDPE TW + with 1 gm SG	60cc HDPE TW + with 1 gm MS	60cc HDPE TW + with 1 gm MS	85cc HDPE TW + with 1 gm SG	85cc HDPE TW + with 1 gm SG	85cc HDPE TW + with 1 gm MS	85cc HDPE TW + with 1 gm MS
Impurity B	NA	0	0.01	0	0.01	0.01	0.01	0.01	0.01
Amitriptyline	NA	0.01	0.04	0.01	0.04	0	0.04	0	0.03
Impurity A	NA	0	0.02	0.010	0.02	0.01	0.02	0.01	0.02
@ RRT 0.28	NA	0	0.01	0	0.01	0	0.01	0	0.02
@ RRT 0.34	NA	0.01	0	0.02	0	0.020	0	0.04	NA
@ RRT 0.60	NA	0.06	NA	0.07	0.09	0.07	NA	0.07	NA
@ RRT 1.15	NA	NA	0.15	NA	0.18	NA	0.19	NA	0.2
@ RRT 1.16	NA	0.090	NA	0.14	NA	0.14	NA	0.18	NA
@ RRT 1.31	NA	NA	0.01	NA	0.02	NA	0.02	NA	0.03
Highest Unknown	0.04	0.090	0.15	0.14	0.49	0.14	0.19	0.18	0.2
Total Unknown	0.05	0.22	0.45	0.32	0.18	0.32	0.55	0.42	0.56
Total Related Substance	0.05	0.23	0.52	0.35	0.56	0.33	0.62	0.44	0.63

Result of the stability study conducted on the capsule of Example 1 filled in different size (i.e. 60cc or 85cc) HDPE bottles with 1gm of dessicant (Silica Gel

or Molecular Sieve) indicated that Cyclobenzaprine HCl composition in accordance with the present invention exhibits excellent storage stability over the 3 months at 40°C/75% relative humidity.

Table 4 provides dissolution profile of the capsule of Example 1 stored in different size (i.e. 60cc or 85cc) HDPE bottles with 1gm of dessicant (Silica Gel or Molecular Sieve). The dissolution study was performed in 900 mL of 0.1N HCl using USP Type II dissolution apparatus (Japanese sinker) and 50 rpm speed at initial, after 1 month at 40°C/75% relative humidity and 3 months storage at 40°C/75% relative humidity.

Table 4

Dissolution in 0.1N HCl Time (hrs.)	Initial	1M 40/75	3M 40/75	1M 40/75	3M 40/75	1M 40/75	3M 40/75	1M 40/75	3M 40/75
		30 Counts		30 Counts		60 Counts		60 Counts	
		60cc HDPE TW + with 1 gm SG	60cc HDPE TW + with 1 gm SG	60cc HDPE TW + with 1 gm MS	60cc HDPE TW + with 1 gm MS	85cc HDPE TW + with 1 gm SG	85cc HDPE TW + with 1 gm SG	85cc HDPE TW + with 1 gm MS	85cc HDPE TW + with 1 gm MS
0.5	13	9	9	9	9	8	7	10	8
1	22	17	18	18	16	17	14	17	16
2	27	30	30	27	27	28	24	29	27
3	41	40	41	39	38	40	34	39	36
4	52	50	51	49	48	51	43	49	46
6	70	64	68	71	60	65	56	66	64
8	85	81	78	81	70	79	72	84	77
10	92	88	86	91	83	88	79	89	85
12	95	90	90	94	88	93	87	95	92
14	96	92	92	96	93	96	91	97	95

16	97	94	93	98	95	98	94	99	97
20	99	95	94	99	96	100	98	99	98
24	NA	96	96	101	99	102	98	101	100

Claims:

1. A modified release unit dosage form in the form of uncoated units comprising cyclobenzaprine or salts thereof, one or more release modifying substances, and optionally one or more pharmaceutically acceptable excipients.

2. The modified release unit dosage form of claim 1, wherein the uncoated units comprises of cyclobenzaprine or salts thereof dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients.

3. The modified release unit dosage form of claim 1, wherein the uncoated units are prepared by compression, extrusion or combination thereof.

4. The modified release unit dosage form of claim 1, wherein the dimension of uncoated units is more than 1.0 mm.

5. The modified release unit dosage form of claim 1, wherein the ratio of amount of cyclobenzaprine or salts thereof and release modifying substances in the dosage form is in the range of about 1:1 to about 1:5.

6. The modified release unit dosage form of claim 1, wherein the composition exhibits a release profile such that not more than about 40% of cyclobenzaprine or salts thereof is released in 2 hours, not less than 40% of cyclobenzaprine or salts thereof is released in 4 hours and not less than 60% of cyclobenzaprine or salts thereof is released in 8 hours when measured in 900 ml of 0.1N HCl using USP Type II dissolution apparatus (Japanese sinker) and 50 rpm speed.

7. The modified release unit dosage form of claim 1, wherein the uncoated units are filled in capsule.

8. The modified release unit dosage form of claim 1, wherein the dosage form retains at least 90% w/w of the potency of cyclobenzaprine or salt thereof when stored at 25°C and 40% relative humidity or at 40°C and 25% relative humidity for 3 months.

9. A process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing cyclobenzaprine hydrochloride, ethyl cellulose, hypromellose, methacrylic acid copolymer, lactose microcrystalline cellulose and povidone to form a dry blend;
(b) granulating the dry blend with water to form granules;
(c) drying and milling the granules;
(d) lubricating the dry milled granules with magnesium stearate;
(e) compressing the lubricated granules to form compressed units, and
(f) filling the compressed units in capsule.

10. A process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing cyclobenzaprine or salt thereof with one or more release modifying substances and optionally one or more pharmaceutically acceptable excipients to obtain a uniform mixture in form of dry powder to which a suitable amount of liquid is added to obtain a moistened plastically deformable mass;
(b) the extrusion of the mixture obtained from the step (a) through a perforated mesh in order to obtain cylindrical extrudates having desired length and diameter;
(c) the spheronization of the extrudates in order to obtain a product in the form of spherical pellets;

(d) the drying of the pellets and filling the extruded units in capsule.

11. The process for preparation of a modified release capsule of claim 10 or 11, wherein the uncoated units comprises of cyclobenzaprine or salts thereof dispersed in the matrix of one or more release modifying substances and one or more pharmaceutically acceptable excipients.

12. A hard gelatin capsule filled with uncoated units comprising cyclobenzaprine or salt thereof, wherein cyclobenzaprine or salt thereof is dispersed in the matrix of one or more release modifying substances selected from group consisting of ethyl cellulose, methacrylic acid copolymer, hydroxypropyl cellulose or hydroxypropyl methylcellulose, bees wax, carnauba wax or combination thereof.

13. The modified release unit dosage form of claim 1, wherein the uncoated units comprises of mini-tablets, tablet, pellets and granules.

14. The modified release unit dosage form of claim 12, wherein the uncoated unit is in the form of one single tablet.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060055

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/135 A61P21/02
ADD.

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 A61P

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/133961 A1 (INVENTIA HEALTHCARE PRIVATE LTD [IN]; JAISWAL SUNIL BEHARILAL [IN]; SH) 25 November 2010 (2010-11-25) cited in the application page 13; claims 2,13; figure 1a; examples 1,2,3	1-13
X	EP 0 368 682 A1 (EURO CELTIQUE SA [LU]) 16 May 1990 (1990-05-16) page 2, line 19; claims 1,9	1,2,4
X	WO 2007/048219 A2 (LABOPHARM INC [CA]; LABOPHARM EUROPE LTD [IE]; LABOPHARM BARBADOS LTD) 3 May 2007 (2007-05-03) page 19, line 1; claims 9,17	1,2

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2014	28/07/2014

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, Fax: (+31-70) 340-3016	Pacreu Largo, Marta

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060055

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PARESH R. MAHAPARALE AND BHANUDAS S. KUCHEKAR: "Development and evaluation of sustained release wax matrix tablet of Cyclobenzaprine Hydrochloride", PHARMA UTILITY, [Online] 2012, XP002727208, ISSN: 2319-5894 Retrieved from the Internet: URL:http://www.pharmautility.com/index.php /PharmaUtility/article/view/30> abstract --- JAMUNADHEVI V ET AL: "Formulation and in vitro evaluation of bi-layer tablet of cyclobenzaprine hy-drochloride ER and diclofenac potassium IR - A novel fixed dose combination", INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES,, vol. 2, no. 2, 1 January 2011 (2011-01-01) , pages 170-178, XP009178726, ISSN: 0975-7538 page 171; tables 6,12	1,2
Y	--- US 2005/106247 A1 (VENKATESH GOPI [US] ET AL) 19 May 2005 (2005-05-19) cited in the application claims; examples	1,2
A	--- ----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/060055

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010133961 A1	25-11-2010	US 2012064164 A1	15-03-2012
		WO 2010133961 A1	25-11-2010
EP 0368682 A1	16-05-1990	AT 123218 T	15-06-1995
		AU 621949 B2	26-03-1992
		AU 4453089 A	17-05-1990
		CA 2002492 A1	11-05-1990
		DE 68922894 D1	06-07-1995
		DE 68922894 T2	11-01-1996
		DK 564589 A	12-05-1990
		EP 0368682 A1	16-05-1990
		ES 2075061 T3	01-10-1995
		GB 2225941 A	20-06-1990
		IE 893625 L	11-05-1990
		JP 2825202 B2	18-11-1998
		JP H02243618 A	27-09-1990
		US 5071646 A	10-12-1991
WO 2007048219 A2	03-05-2007	AU 2006308448 A1	03-05-2007
		AU 2006308449 A1	03-05-2007
		BR PI0615577 A2	11-12-2012
		BR PI0615860 A2	18-12-2012
		CA 2616204 A1	03-05-2007
		CA 2616416 A1	03-05-2007
		CN 101242856 A	13-08-2008
		CN 101252932 A	27-08-2008
		DK 1931346 T3	22-10-2012
		EA 200800783 A1	29-08-2008
		EC SP088239 A	28-04-2008
		EC SP088240 A	28-04-2008
		EP 1931346 A2	18-06-2008
		EP 1940467 A2	09-07-2008
		ES 2389666 T3	30-10-2012
		HK 1124237 A1	05-04-2013
		JP 5269595 B2	21-08-2013
		JP 2009507047 A	19-02-2009
		JP 2009507048 A	19-02-2009
		JP 2013116917 A	13-06-2013
		KR 20080047538 A	29-05-2008
		KR 20080047539 A	29-05-2008
		NZ 565591 A	29-07-2011
		PT 1931346 E	14-08-2012
		UA 94916 C2	25-06-2011
		US 2007128269 A1	07-06-2007
		US 2007128275 A1	07-06-2007
		US 2011015205 A1	20-01-2011
		US 2011021535 A1	27-01-2011
		US 2011027370 A1	03-02-2011
		US 2011033537 A1	10-02-2011
		WO 2007048219 A2	03-05-2007
		WO 2007048220 A2	03-05-2007
		ZA 200801158 A	26-08-2009
		ZA 200801162 A	29-04-2009
US 2005106247 A1	19-05-2005	US 2005106247 A1	19-05-2005
		US 2008124398 A1	29-05-2008
		US 2008124399 A1	29-05-2008
		US 2009017126 A1	15-01-2009

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/060055

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2009017127 A1	15-01-2009
		US 2011217384 A1	08-09-2011
		US 2013209567 A1	15-08-2013
		WO 2005048996 A2	02-06-2005