Abstract of the Invention

The present invention relates to sustained release pharmaceutical compositions of oxybutynin or its pharmaceutically acceptable salts for oral administration. The compositions of the present invention comprise oxybutynin or its pharmaceutically acceptable salts along with at least one pH independent sustained release agent and at least one pH dependent agent in matrix based system. The compositions of the present invention exhibit minimized pH-dependent dissolution profiles or pH-independent dissolution profiles. The invention also includes processes for preparation of such compositions. The compositions of the present invention are bioequivalent with marketed Ditropan XL tablets.

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We claim:

1. A pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, wherein said composition comprises oxybutynin or pharmaceutically acceptable salts thereof along with at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient.
2. The pharmaceutical composition of claim 1, wherein said at least one pH independent sustained release agent is selected from the group consisting of ethylcellulose, cellulose acetate, vinyl acetate/vinyl chloride copolymers, acrylate/methacrylate copolymers, polyethylene oxide, hydroxypropyl methylcellulose, carrageenan, alginic acid and salts thereof, hydroxyethyl cellulose, hydroxypropyl cellulose, karaya gum, acacia gum, tragacanth gum, locust bean gum, guar gum, sodium carboxymethyl cellulose, methyl cellulose, beeswax, carnauba wax, cetyl alcohol, hydrogenated vegetable oils, stearyl alcohol and the like.
3. The pharmaceutical composition of claim 1, wherein said at least one pH dependent agent is at least one polymers that swell at a pH above 5.5.
4. The pharmaceutical composition of claim 1, wherein said at least one pH dependent agent is at least one enteric agent.
5. The pharmaceutical composition of claim 1, wherein said at least one pH dependent agent is at least one agent that increases the solubility of oxybutynin at a pH above 5.5 by maintaining an acidic microenvironment in the tablet.
6. The pharmaceutical composition of claim 1 is enteric coated tablet.
7. A pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof along with at least one

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pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient, wherein said composition exhibits no significant difference in rate or extent of absorption of oxybutynin or salts thereof as compared to osmotic formulation commercially marketed under the trade name Ditropan XL.

8. A method for treating urinary incontinence in a patient, wherein the said method comprises administering to said patient a pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient,
9. A process for preparation of pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, wherein said process comprises steps of mixing, granulating oxybutynin or pharmaceutically acceptable salts thereof along with at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient and converting into a suitable dosage form.

Dated 05th day of June, 2010

Signature:

Dr. Aman Trehan
Deputy General Manager, IPR
Cadila Healthcare Limited

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SUSTAINED RELEASE PHARMACEUTICAL COMPOSITIONS OF OXYBUTYNIN OR ITS SALTS

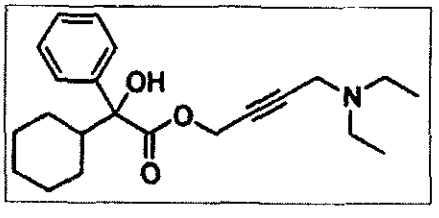
Field of the Invention

The present invention relates to sustained release pharmaceutical compositions of oxybutynin or its pharmaceutically acceptable salts for oral administration. The compositions of the present invention comprise oxybutynin or its pharmaceutically acceptable salts along with at least one pH independent sustained release agent and at least one pH dependent agent in matrix based system. The compositions of the present invention exhibit minimized pH-dependent dissolution profiles or pH-independent dissolution profiles. The invention also includes processes for preparation of such compositions.

Back ground of the Invention

Oxybutynin is an anticholinergic medication used to relieve urinary and bladder difficulties, including frequent urination and inability to control urination (urge incontinence), by decreasing muscle spasms of the bladder.

Chemically, it is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate, having a structure of Formula I.



[Formula I]

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U. S. Patent No. 5,912,268 discloses an osmotic drug delivery device comprising oxybutynin which deliver oxybutnin at a controlled rate for a period of about 24 hours.

U. S. Patent No. 6,248,359 discloses a simple multi-tablet system containing a first tablet that releases oxybutynin over a short period of time, e.g. less than six hours, and a second tablet that releases oxybutynin over an extended period of time, e.g., eighteen to twenty-four hours.

Oxybutynin is available as its hydrochloride salt in the form of immediate release tablets, extended release tablets, syrups and transdermal gel. It is marketed by Ortho McNeil Janssen Pharmaceutical under the trade name Ditropan XL® as extended release oral tablets containing 5 mg, 10 mg or 15 mg of oxybutynin chloride for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Ditropan XL® tablets are based on the osmotic drug delivery system.

Osmotic drug delivery system involves complicated processes. These are costly, since it requires special techniques for the manufacturing. Also, If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.

Oxybutynin is highly metabolised and exhibits pH-dependent solubility. The pH-dependent solubility leads to pH-dependent dissolution profile. In general, pH-dependent dissolution is an undesirable product characteristic.

It is well known that eating habits have an effect upon the observed plasma oxybutynin concentration in humans. Specifically, eating breakfast was shown to reduce the mean retention time of oxybutynin in the plasma.

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Moreover, patient age and health also have an effect upon the observed plasma oxybutynin concentration in humans. Specifically, a trend of increasing peak plasma levels and bioavailability was observed with increasing patient age and frailty, with the differences being more apparent between the active elderly and frail elderly groups than between the active elderly and the young volunteers. Currently available controlled release oxybutynin formulations are not able to compensate for the observed patient to patient variability in oxybutynin therapy.

Thus, a need remains for simple and economical pharmaceutical compositions treating urinary incontinence which provides a controlled delivery of oxybutynin and maintains safe and therapeutically effective levels of oxybutynin in patients while accounting for their age or health. The compositions of the invention overcome all the encountered problems exemplified above.

Summary of the Invention

In one general aspect, there is provided a pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, wherein the said composition exhibit minimized pH-dependent dissolution profiles or pH-independent dissolution profiles.

In another general aspect, there is provided a pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, wherein said composition comprises oxybutynin or pharmaceutically acceptable salts thereof along with at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient.

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In yet another aspect, there is provided a pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof along with at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient, wherein said composition exhibits no significant difference in rate or extent of absorption of oxybutynin or salts thereof as compared to osmotic formulation commercially marketed under the trade name Ditropan XL.

In another aspect, there is provided a method for treating urinary incontinence in a patient, wherein the said method comprises administering to said patient a pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient,

In another general aspect, there is provided a process for preparation of pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, wherein said process comprises steps of mixing, granulating oxybutynin or pharmaceutically acceptable salts thereof along with at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient, and converting into a suitable dosage form.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may further include one or more pharmaceutically acceptable excipients.

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The pharmaceutically acceptable excipients may include diluents, disintegrants, binders, glidants and lubricants.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description.

Detailed Description of the Invention

The inventors of the invention have discovered that oxybutynin or pharmaceutically acceptable salts thereof can be formulated into matrix compositions which are simple, economical and are bioequivalent to the Ditropan XL® tablets.

It is possible to use any salts and free base form of oxybutynin, including polymorphs, hydrates, solvents or amorphous form.

Suitable "pH independent sustained release agents" may include one or more of ethylcellulose, cellulose acetate, vinyl acetate/vinyl chloride copolymers, acrylate/methacrylate copolymers, polyethylene oxide, hydroxypropyl methylcellulose, carrageenan, alginic acid and salts thereof, hydroxyethyl cellulose, hydroxypropyl cellulose, karaya gum, acacia gum, tragacanth gum, locust bean gum, guar gum, sodium carboxymethyl cellulose, methyl cellulose, beeswax, carnauba wax, cetyl alcohol, hydrogenated vegetable oils, stearyl alcohol and the like. In general, the at least one pH independent sustained release agent is present in the composition in an amount of from about 5 wt. % to about 50 wt. %.

Suitable "pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5" may include one or more of polymers that swell at a pH above 5.5, enteric agents, agents that increase the solubility

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of oxybutynin at a pH above 5.5 by maintaining an acidic microenvironment in the tablet. The at least one pH-dependent agent is present in the composition in an amount of from about 0.5 wt. % to about 40 wt. %.

Suitable "Polymers that swell at a pH in excess of 5.5" may include one or more of acrylic acid copolymers, sodium alginate, carrageenan, alginic acid, pectin, sodium carboxymethyl cellulose and the like.

Suitable "Enteric agents" may include one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid coplymers, cellulose acetate trimellitate, hydroxypropyl methylcellulose acetate, succinate, shellac, zein and the like.

Suitable "Agents that increase the solubility of oxybutynin at a pH above 5.5" may include one or more of alginic acid, citric acid, fumaric acid, tartaric acid, adipic acid, glucono delta-lactone, malic acid, sodium lauryl sulfate, polysorbate 80 and the like.

Suitable "diluents" may include one or more of lactose, microcrystalline cellulose, calcium phosphate, dextrin, dextrose, dextrates, mannitol, sorbitol, xyliotol, starches and sucrose and the like. The diluent may be present in an amount from about 20% to about 80% by weight.

Suitable "disintegrants" may include one or more of low substituted hydroxypropyl cellulose, carmellose, sodium carboxystarch, calcium carmellose, corn starch, partially-alphatized starch, sodium croscarmellose, crospovidone, sodium starch glycolate, microcrystalline

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cellulose and the like. The disintegrant may be present in an amount from about 2% to about 7% by weight.

Suitable "binders" may include one or more of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, partial saponificates of these, starch and the like. The binder may be present in an amount from about 1% to about 7% by weight.

Suitable "glidants" includes one or more of talc, corn starch, silicon dioxide, sodium lauryl sulphate, metallic stearates and the like. The glidant may be present in an amount from about 0.1% to about 5 % by weight.

Suitable "lubricants" includes one or more of magnesium stearate, stearic acid, palmitic acid, calcium stearate, zinc stearate, sodium stearyl fumarate, glyceryl behenate, hydrogenated castor oil, waxes, talc and the like. The lubricant may be present in an amount from about 0.1% to about 5 % by weight.

In one embodiment, the compositions of the present invention are in the form of tablets.

In another embodiment, the compositions of the present invention are in the form of tablets which are enteric coated with an enteric coating composition.

Enteric coating composition comprises enteric substance, plasticizer and anti-taking agent.

Suitable "enteric substances" includes one or more of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, polyvinyl acetate

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phthalate, methyl cellulose phthalate, copolymerized methacrylic acid/methacrylic acid methyl esters and the like.

Suitable "plasticizers" may include one or more of polyethylene glycol, diethyl citrate, triethyl citrate, triacetylpropylene glycol and the like.

Suitable "anti-taking agent" may include one or more of talc, glyceryl monostearate and the like.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments, 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.

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Examples 1 to 3

Table 1

Sr. No.	Ingredient	Weight (mg)		
		Example 1	Example 2	Example 3
Tablet core				
1	Oxybutynin Chloride	15.000	15.000	15.000
2	Lactose Monohydrate	52.500	52.500	45.000
3	Methocel K100M	57.000	57.000	57.000
4	MCC (Avicel pH 101)	52.250	52.250	63.500
5	Alginic Acid	3.750	--	--
6	Succinic acid	--	3.750	--
7	Polysorbate 80	--	--	2.85
8	Povidone K 30	5.700	5.700	5.700
9	Hydrogenated castor oil	3.800	3.800	3.800
10	Magnesium stearate	2.000	2.000	2.000
11	Isopropyl alcohol	q.s.	q.s.	q.s.
Coating				
12	Eudragit L 30D55	6.000	6.000	6.0875
13	Talc	2.400	2.400	3.0437
14	Triethyl citrate	1.200	1.200	0.6087
15	Purified water	qs	qs	qs
	Tablet wt.	**201.600**	**201.600**	**204.59**

Procedure: Oxybutynin chloride, lactose, MCC, methocel K100M and *alginic acid (alginic acid is replaced by succinic acid in case of Example 2)* were mixed for 10 min in RMG. The resulting blend was granulated with a binder solution prepared by dissolving povidone in IPA. The granules were dried in a suitable fluidized bed dryer to achieve granules having LOD of

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less than 3.0% w/w. The dried granules were milled using 1.0 mm screen in an oscillating granulator to get granules of desired particle size. The resulting granules were lubricated using hydrogenated castor oil and magnesium stearate in a suitable blender for 5.0 min and compressed into tablets of desired thickness and hardness. The compressed tablets were coated with suitable enteric coating dispersion comprising of Eudragit L30D55, talc, triethyl citrate up to desired weight gain of around 5% w/w in a suitable coating pan.

Same procedure was employed for Example 3 except that alginic acid was replaced with polysorbate 80 and is added in the binder solution.

Example 4

Dissolution studies:

Dissolution of tablets in 2hr SGF without enzyme followed by pH 6.8 phosphate buffer, at dpm 25, in USP type III Apparatus.

Dissolution data of compositions of Examples 1 to 3 is given in Table 2.

Table 2

Example	Example 1	Example 2	Example 3
Time in hr			
0	*0*	*0*	*0*
2	2	0	13
4	19	23	25
6	35	39	ND
8	49	50	47
10	62	60	61
12	75	69	71
14	86	77	79

Example 5

Stability studies:

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The accelerated stability was carried out using 40cc heavy weight HDPE bottle at 40°C / 75%RH.

Stability data of compositions of examples 1 to 3 is given in Table 3.

Table 3

Example		Initial	3 month
1	Imp A (NMT 1%)	0.10	0.32
	Total (NMT 2%)	0.29	0.69
2	Imp A (NMT 1%)	0.10	0.22
	Total (NMT 2%)	0.10	1.00
3	Imp A (NMT 1%)	0.14	0.36
	Total (NMT 2%)	0.37	0.74

Example 6

In vivo studies:

Bioavailability study of the oxybutynin tablet (15 mg) prepared according to example 1 was carried out on healthy volunteers taking Ditropan XL 15mg as reference, the results of which are represented in Table 4.

Table 4

Parameter	Fasting	Fed
Cmax	100.92	95.91
AUC (last)	110.88	94.74

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We claim:

1. A pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, wherein said composition comprises oxybutynin or pharmaceutically acceptable salts thereof along with at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient.
2. The pharmaceutical composition of claim 1, wherein said at least one pH independent sustained release agent is selected from the group consisting of ethylcellulose, cellulose acetate, vinyl acetate/vinyl chloride copolymers, acrylate/methacrylate copolymers, polyethylene oxide, hydroxypropyl methylcellulose, carrageenan, alginic acid and salts thereof, hydroxyethyl cellulose, hydroxypropyl cellulose, karaya gum, acacia gum, tragacanth gum, locust bean gum, guar gum, sodium carboxymethyl cellulose, methyl cellulose, beeswax, carnauba wax, cetyl alcohol, hydrogenated vegetable oils, stearyl alcohol and the like.
3. The pharmaceutical composition of claim 1, wherein said at least one pH dependent agent is at least one polymers that swell at a pH above 5.5.
4. The pharmaceutical composition of claim 1, wherein said at least one pH dependent agent is at least one enteric agent.
5. The pharmaceutical composition of claim 1, wherein said at least one pH dependent agent is at least one agent that increases the solubility of oxybutynin at a pH above 5.5 by maintaining an acidic microenvironment in the tablet.
6. The pharmaceutical composition of claim 1 is enteric coated tablet.
7. A pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof along with at least one

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pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient, wherein said composition exhibits no significant difference in rate or extent of absorption of oxybutynin or salts thereof as compared to osmotic formulation commercially marketed under the trade name Ditropan XL.

8. A method for treating urinary incontinence in a patient, wherein the said method comprises administering to said patient a pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient,
9. A process for preparation of pharmaceutical composition comprising oxybutynin or pharmaceutically acceptable salts thereof, wherein said process comprises steps of mixing, granulating oxybutynin or pharmaceutically acceptable salts thereof along with at least one pH independent sustained release agent, at least one pH dependent agent that increases the dissolution rate of oxybutynin at a pH above 5.5 and one or more pharmaceutically acceptable excipient and converting into a suitable dosage form.

Dated 05th day of June, 2010

Signature:

Dr. Aman Trehan
Deputy General Manager, IPR
Cadila Healthcare Limited

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