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(54) **Title**: EXTENDED RELEASE 'FORMULATION OF METOPROLOL

(57) **Abstract**: The present invention relates to a dry ready to use modified release dosage formulation for Metoprolol dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTAMODEL (A43D00051, A43 D00043) manufactured by Ideal Cures Private Limited Mumbai India thereof also use thereof as additive to animal feeds, foods and food supplements and also cosmetic and pharmaceutical compositions. Invention also relates to ready-to-use modified release compositions capable of regulating release of Metoprolol at various dosage strength, a process for production thereof and also use thereof as formulated pharmaceutical compositions.

Description

EXTENDED RELEASE FORMULATION OF METOPROLOL

Technical Field

[1] The present invention relates to a dry ready to use modified release dosage formulation for Metoprolol dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTAMODEL (A43D00051, A43D00043) manufactured by Ideal Cures Private Limited Mumbai India thereof also use thereof as additive to animal feeds, foods and food supplements and also cosmetic and pharmaceutical compositions. Invention also relates to ready-to-use modified release compositions capable of regulating release of Metoprolol at various dosage strength, a process for production thereof and also use thereof as formulated pharmaceutical compositions.

Background Art

[2] Metoprolol succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended release tablets. Metoprolol is a potent inhibitor of #-receptor mediated effects mainly involving #1-adrenoreceptors. Such effects include not only reduction of exercise-induced tachycardia but also antihypertensive and cardiac antianginal and antiarrhythmic effects. The in vivo absorption of metoprolol is rapid and complete. The plasma metoprolol levels following administration of extended release metoprolol succinate are characterized by lower peaks, longer time to peak and significantly lower peak to trough variations.

[3] The peak plasma levels following once daily administration of modified release metoprolol succinate average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of extended release metoprolol succinate, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol.

[4] In state of the art modified release compositions are developed to provide relatively constant drug plasma levels and sustained efficacy for longer period of time. In principle aim of extended and modified release composition is to get required therapeutic concentration of the active in the blood stream and maintain its therapeutic concentration without deviation from strength during specified period. US 7976871, US 5399358 and US 4927640 are prior arts which disclose compositions for sustained release of active ingredients.

[5] In state of art various grades of cellulosic polymers are used in the modified release compositions e.g. HPMC polymer. These polymers extend the release of drug by showing osmosis nature in aqueous conditions. Cellulosic matrix based system work by the swelling and gelling function i.e. these polymer swell through influx of liquids

and a gel like physical structure is formed which provides extended release effect facilitated by diffusion of the Metoprolol. Some patent documents disclosing matrix based systems for modified release of active ingredients include US 4252786, US 4351825 and WO 2008090569.

[6] In theory it is known that with high viscosity grade polymer after attaining gelling effect drug release is lower but as time progresses drug release is increased. On the contrary with low viscosity grade polymer after attaining gelling effect drug is released at faster speed due to larger pore sized and concentration of drug decrease as time progresses.

[7] In order to minimize difficulties associated in ratios of polymers, batch to batch variations, formulating, storing and preserving many loose components of differently textured and sized ingredients means have been desired in industry to make ready to use extended release or modified release composition which are convenient to handle.

[8] The object of the present invention is to provide a ready-to-use matrix system and method of preparation for Metoprolol extended release or modified release formulation.

Disclosure of Invention

Summary of Invention

[9] Accordingly, the present invention provides hydrophilic matrix system based ready to use technology for Modified or Extended Release Formulation of Metoprolol Hydrochloride using INSTAMODEL (A43D00051, A43D00043) manufactured by Ideal Cures Private Limited Mumbai India.

[10] Accordingly, the present invention also provides method for making ready to use Metoprolol modified or extended release formulation, involving steps of aqueous granulation, drying, lubrication and punching of tablets.

[11] In another aspect, present invention also provides once a day Metoprolol table dosage form.

[12] Extended release or modified release tablet formulation can be in the form of single or multilayer tablets, capsule shaped oral dosage form, caplet, granules, disc, pellets, granules in capsule, mini-tablets in oral dosage form and other possible oral dosage form mean thereof.

[13] In yet another embodiment, the solid oral dosage form can optionally include one or more pharmaceutically acceptable excipients.

[14] The details of one or more embodiments in the practice of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the appended examples and claims.

Detailed Discription

[15] Below description specify various scientific terms unless stated with context, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although

any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

[16] Unless stated to the contrary, The feature 'ready-to-use', in the context of the present invention, is taken to mean the property that the composition according to the invention can be used directly for its purposes by the user by simply dispersing it in required quantity of water.

[17] The term 'modified release' is in context of the invention as a way of active drug delivery where the rate of release of the active drug from the composition is not exclusively dependent on the concentration of active drug remaining in the dosage form and / or the solubility of the active drug in the liquid surrounding the composition, and where the time course with or without respective location of release of active drug from an oral dosage form are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. For the purpose of invention active drug is selected from Aceclofenac, its intermediates and derivatives thereof.

[18] The term 'Aceclofenac' is in context of the invention includes its polymorphic forms, the pharmaceutically acceptable salts, including salts esters and pother chemical derivatives or intermediates etc. The solid pharmaceutical composition comprises Aceclofenac from 1 to 80 w/w % of dosage form.

[19] The term 'dosage', 'solid pharmaceutical composition' may include one or more of tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitablets, minitablets in capsule, pellets in capsule, sachet and the like. The solid pharmaceutical composition also includes multilayer tablets. The solid pharmaceutical compositions are meant for oral administration.

[20] The term 'tablet' includes pharmaceutical compositions of all shapes and sizes, whether coated or uncoated.

[21] The term 'Lubricant' in the context of the present invention, is taken to mean that an ingredient added to prevent the adhesion of tablet materials to the punches and dies, reduce inter-particle friction and facilitate the ejection of oral dosage forms from the die cavity. Lubricant of present invention includes but not limited to talc, magnesium stearate, stearic acid, sodium stearyl fumarate and there derivatives thereof.

[22] The term 'Glidant' in the context of the present invention, is taken to mean that an ingredient which enhance product flow by reducing inter-particulate friction. Glidant can be used in present invention includes but not limited to silicon di-oxide, colloidal silicon dioxide and there derivatives thereof. It is available under several brand names like AEROSIL® and CAB-O-SIL®.

[23] The term 'Solvent' in the context of the present invention, is taken to mean ingredient that facilitate mixing of components in wet granulation process. Solvent can be used in present invention includes but not limited to Acetone, ethanol, methylene di chloride, isopropyl alcohol, water or their mixture thereof.

[24] The term 'Binder' or 'Binding agent' in the context of the present invention, is taken to mean ingredient that facilitate binding of components in wet granulation process. Solvent can be used in present invention includes but not limited to dextrin and their derivatives, maltodextrin, polyvinyl polymers, Polyvinyl pyrrolidone K30 (PVP K30) and there derivatives thereof.

[25] The ready to use polymeric composition Instamodel A43D00045 for extended and modified release formulation was supplied by Ideal Cures Private Limited, Mumbai, www.idealcures.co.in . This product was used to create inventive dosage form having ideal modified release profile for twice a day administration.

[26] According to inventors it was surprisingly found that extended release solid oral dosage form for Aceclofenac can be created with ready to use Instamodel (A43D00045) system and dosage form have advantageous modified release properties. The ready to use composition in accordance with present invention comprise INSTAMODEL (A43D00045). In one of the embodiment of present invention Aceclofenac is formulated with ready to use composition to prepare modified release dosage form. In accordance with present invention different salts, derivatives, polymorphs of Aceclofenac could be combined to achieve ready-to-use composition to achieve extended or modified release dosage form.

[27] In a dosage form according to the invention Aceclofenac is blended with the ready to use polymer and aqueous granulated further the granulated mixture is compressed to produce a solid formulation. The ingredients are blended to form a uniform powder and then compressed with means generally known to skilled in the art.

[28] In yet another embodiment of present invention Aceclofenac and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and finally coated.

[29] In yet another embodiment of present invention Aceclofenac and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and optionally coated.

[30] This system of formulation uses simple and economic polymers hence cost effective to the customer. Another advantage of the present formulation is its robust and reproducible results for extended release dose form without batch to batch variations. Further by using aqueous solvent system for granulation dosage form does not have any residual solvent or hazardous effect found in many organic solvent based formulations.

[31] Inventive dosage form may be prepared by blending Aceclofenac, their derivatives or combination thereof along with ready to use composition. Therefore inventive formulation preparation comprise steps as:

[32] Below description specify various scientific terms unless stated with context, all

technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

[33] Unless stated to the contrary, The feature 'ready-to-use', in the context of the present invention, is taken to mean the property that the composition according to the invention can be used directly for its purposes by the user by simply dispersing it in required quantity of water.

[34] The term 'modified release' is in context of the invention as a way of active drug delivery where the rate of release of the active drug from the composition is not exclusively dependent on the concentration of active drug remaining in the dosage form and / or the solubility of the active drug in the liquid surrounding the composition, and where the time course with or without respective location of release of active drug from an oral dosage form are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. For the purpose of invention active drug is selected from Metoprolol, its intermediates and derivatives thereof.

[35] The term 'Metoprolol' is in context of the invention includes its polymorphic forms, the pharmaceutically acceptable salts, including salts esters and pother chemical derivatives or intermediates etc. The solid pharmaceutical composition comprises Metoprolol from 1 to 50 w/w % of dosage form.

[36] The term 'dosage', 'solid pharmaceutical composition' may include one or more of tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitablets, minitablets in capsule, pellets in capsule, sachet and the like. The solid pharmaceutical composition also includes multilayer tablets. The solid pharmaceutical compositions are meant for oral administration.

[37] The term 'tablet' includes pharmaceutical compositions of all shapes and sizes, whether coated or uncoated.

[38] The term 'Lubricant' in the context of the present invention, is taken to mean that an ingredient added to prevent the adhesion of tablet materials to the punches and dies, reduce inter-particle friction and facilitate the ejection of oral dosage forms from the die cavity. Lubricant of present invention includes but not limited to talc, magnesium stearate, stearic acid, sodium stearyl fumarate and there derivatives thereof.

[39] The term 'Glidant' in the context of the present invention, is taken to mean that an ingredient which enhance product flow by reducing inter-particulate friction. Glidant can be used in present invention includes but not limited to silicon di-oxide, collioidal silicon dioxide and there derivatives thereof. It is available under several brand names like AEROSIL® and CAB-O-SIL®.

[40] The term 'Solvent' in the context of the present invention, is taken to mean ingredient that facilitate mixing of components in wet granulation process. Solvent can

be used in present invention includes but not limited to Acetone, ethanol, methylene di chloride, isopropyl alcohol, water or their mixture thereof.

[41] The term 'Binder' or 'Binding agent' in the context of the present invention, is taken to mean ingredient that facilitate binding of components in wet granulation process. Solvent can be used in present invention includes but not limited to polyvinyl polymers, Polyvinyl pyrrolidone K30 (PVP K30) and there derivatives thereof.

[42] The ready to use polymeric composition Instamodel A43D00051, A43D00043 for extended and modified release formulation was supplied by Ideal Cures Private Limited, Mumbai, www.idealcures.co.in . This product was used to create inventive dosage form having ideal modified release profile for twice a day administration.

[43] According to inventors it was surprisingly found that extended release solid oral dosage form for Metoprolol can be created with ready to use Instamodel (A43D00051, A43D00043) system and dosage form have advantageous modified release properties. The ready to use composition in accordance with present invention comprise IN-STAMODEL (A43D00051, A43D00043). In one of the embodiment of present invention Metoprolol is formulated with ready to use composition to prepare modified release dosage form. In accordance with present invention different salts, derivatives, polymorphs of Metoprolol could be combined to achieve ready-to-use composition to achieve extended or modified release dosage form.

[44] In a dosage form according to the invention Metoprolol is blended with the ready to use polymer and aqueous granulated further the granulated mixture is compressed to produce a solid formulation. The ingredients are blended to form a uniform powder and then compressed with means generally known to skilled in the art.

[45] In yet another embodiment of present invention Metoprolol and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and finally coated.

[46] In yet another embodiment of present invention Metoprolol and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and optionally coated.

[47] This system of formulation uses simple and economic polymers hence cost effective to the customer. Another advantage of the present formulation is its robust and reproducible results for extended release dose form without batch to batch variations. Further by using aqueous solvent system for granulation dosage form does not have any residual solvent or hazardous effect found in many organic solvent based formulations.

[48] Inventive dosage form may be prepared by blending Metoprolol, their derivatives or combination thereof along with ready to use composition. Therefore inventive formulation preparation comprise steps as

[49]

1. Blending of ready to use formulation Instamodel (A43D00051, A43D00043) with Metoprolol.
2. Thorough mixing to form dry powder
3. Optionally addition of lubricant
4. Slugging of blended powder
5. Deslugging of tablet
6. Milling and Sieving through appropriate size
7. Optionally adding Instamodel again
8. Optionally addition of lubricant
9. Final tablet compression
10. Optional film coating

[50] According to one of the embodiment inventive dosage form is prepared by blending ready to use composition (Instamodel A43D00051, A43D00043), process blending is performed by conventional dry blender or a food processor or 'V-blender' or a similar function device. In one of the alternative embodiment Metoprolol are processed using aqueous solvent with binder through wet granulation or a similar wet mixing method to generate dosage formulation. Dosage formulation is further dried, sieved and compressed optionally with addition of lubricant, binder, glidant to form modified release oral dosage form.

[51] In one of the embodiment of present invention, inventive dosage formulations are prepared by blending Metoprolol along with Instamodel. Initially all components are blended by conventional dry blending in a food processor or 'V-blender' or a similar function device. Other solid oral dosage formulation components like binders, lubricants, glidants, detackifier, excipients can be added to create inventive formulation Further mixture is then processed, granulated and sieved. Obtained sieved granulated formulation is then again uniformly mixed with Instamodel and premeasured amount of the lubricant to improve industrial acceptability and oral dosage compression quality. Subsequently uniform mixed inventive formulation is compressed in standard pharmacopoeial equipment to get a controlled release oral dosage formulation of the correct desired weight and strength.

[52] In one of the embodiment of present invention, inventive dosage formulations are prepared by blending Metoprolol along with Instamodel. Initially all components are blended by conventional dry blending in a food processor or 'V-blender' or a similar function device. Other solid oral dosage formulation components like binders, lubricants, glidants, detackifier, excipients can be added to create inventive formulation. Further mixture is then processed, granulated and sieved. Obtained sieved granulated formulation is then uniformly mixed with premeasured amount of the lubricant to improve industrial acceptability and oral dosage compression quality. Subsequently uniform mixed inventive formulation is compressed in standard pharmacopoeial

equipment to get a controlled release oral dosage formulation of the correct desired weight and strength.

[53] According to one of the main embodiment wherein hardness of tablets produced is in range of 5 Kg/cm² to 15 Kg/cm². In one of the embodiment oral dosage forms produced by inventive composition having human administrable active ingredient is suitable for human use. Alternatively drug suitable for veterinary purpose formulated in accordance with present composition will be suitable for veterinary use.

[54] According to the objective of present invention Metoprolol is formulated in oral dosage form for modified or extended release delivery. Inventive composition comprising 20, 25, 50, 100, 150 mg or 200 mg of Metoprolol in plurality of dosage formulations. Controlled release formulation can have combination of one or more additional drugs.

[55] Suitable APIs that can be used with the present invention include, but are not limited to: andrenergic blocking agent; acetyl-cholin-esterase inhibitor; analgesic or antipyretics; angiotensin modulator; anthelmintic agents; anti anxiety agent; antibacterial; antibiotic; anticoagulant; anticonvulsant; antidepressant; antifungal; antihistamine; antimalarial; antimicrobial agent; antipsychotic agent; Antiviral agents; blood glucose lowering drug; calcium channel modulator; diuretic; erectile dysfunction; gastric acid secretion inhibitor; histamine H2-receptor antagonist; inhibitor of steroid Type II 5[alpha]- reductase including; lipid regulating agents; selective H1-receptor antagonist; vasodilator; vitamins.

[56] Following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof.

Mode for Invention

[57] **Exampie 1 .**

[58] **Preparation of Metoprolol modified release tablets (25 mg)**

[59] The dosage formulation for 100,000 (17.00 kg) Tablets of Metoprolol is prepared using composition as stated in table:- 1 wherein Metoprolol is 2.37 kg and weighed accordingly, subsequently sieved to get uniformly granulated powder through 40 mesh screen. It is noted that other size screen could be used to get similar results. Sieved Metoprolol is blended with 12.12 kg of ready to use Instamodel (A43D00043) in blender for 20 minutes (e.g. RMG granulator). Further 0.12 kg of Colloidal silicon dioxide and 0.12 kg of magnesium stearate sieved through 40 mesh screen is added to above blended for subsequent 5 minutes. Resulting granules are then processed using slugging method and compressing it on 18 x 7.5 mm of capsule shaped punches at 700 mg of average weight and 7- 10 kg/cm2 of hardness. Mill the slug obtained and sift them using 1.0 mm screen. De-slugging is performed on milled formulation using vibratory sifter fitted with #30 mesh screen. Material generated by de-slugged process is further blended with 2.0 kg Instamodel (A43D00043) using vibratory sifter fitted with # 40 mesh sieve for 20 minutes in suitable blender or octagonal blender.

[60] **Table 1**

Formulation ingredients	Composition		Quantity for Batch size of 100,000 Tabs.
	% w/w	mg/ tablet	Kg
Metoprolol Succinate	13.97%	23.75	2.375
Instamodel (A43D00043) IH (Intragranular)	71.33%	121.25	12.125
Instamodel (A43D00043) IH (Extra granular)	11.76 %	20.00	2.000
Magnesium Stearate	1.47 %	2.50	0.250
Colloidal silicon dioxide (Aerosil 200)	1.47 %	2.50	0.250
	100.00	**170.0**	**17.000**
Coating ingredients			
Instacoat Universal (ICU 3849) white IH		4.0	0.51 kg(includes 25% extra to compensate process losses)
Purified water	**q.s.**	**q.s.**	**4.13 kg**
	Total	**174.0**	

[61] To promote efficient tablet punching further 0.12 kg of Colloidal silicon dioxide and 0.12 kg of magnesium stearate sieved through 40 mesh screen is added to above dried blended formulation in blender for subsequent 5 minutes. Final screened granules are compressed using 8.0 mm (for 25 mg strength at 170 mg average weight) circular, standard concave circular punches using Karnavati Tablet Compression M/C-17 Stn. GMP machine at hardness not less than 5-8 kg/cm^2. Generated dosage form tablets are then subjected to film coating using Instacoat Universal. Coating composition is weighed in accordance with table 1 and 11% coating suspenstion is prepared in water with stirrer and mixed for about 45 minutes subsequently it is passed through 80 mesh screen. Coating is preformed on dosage form using INSTACOAT Pharma RnD coater (6' pan) at 25 rpm with inlet temperature being 53 °C and bed temperature at 40 °C. coating was done using 1mm nozzle sprayer with peristaltic pump injecting coating suspension at the rate of 1ml/min. Coated tablets are then dried and packed as per pharmacopoieal guidelines.

[62] **Example 2**

[63] **Preparation of Metoprolol modified release tablets (50 mg)**

[64] The dosage formulation for 100,000 (27.50 kg) Tablets of Metoprolol is prepared using composition as stated in table:- 2 wherein Metoprolol is 4.75 kg and weighed accordingly, subsequently sieved to get uniformly granulated powder through 40 mesh screen. It is noted that other size screen could be used to get similar results. Sieved

Metoprolol is blended with 21.75 kg of ready to use Instamodel (A43D00051) in blender for 20 minutes (e.g. RMG granulator). Further 0.25 kg of Colloidal silicon dioxide and 0.25 kg of magnesium stearate sieved through 40 mesh screen is added to above blended for subsequent 5 minutes. Resulting granules are then processed using slugging method and compressing it on 18 x 7.5 mm of capsule shaped punches at 700 mg of average weight and 7- 10 kg/cm^2 of hardness. Mill the slug obtained and sift them using 1.0 mm screen. De-slugging is performed on milled formulation using vibratory sifter fitted with #30 mesh screen.

[65] **Table 2**

[66]

Formulation ingredients	Composition		Quantity for Batch size of 100,000 Tabs.
	% w/w	mg/ tablet	Kg.
Metoprolol Succinate	17.27%	47.5	4.750
Instamodel (A43D00051) IH	79.09%	217.5	21.750
Magnesium Stearate	1.82 %	5.0	0.50
Colloidal silicon dioxide (Aerosil 200)	1.82 %	5.0	0.50
	100.00	**275.0**	**27.5**
Coating ingredients			
Instacoat Universal (ICU-3849) white IH		**5.0**	0.80 kg(includes 20% extra to compensate process losses
Purified water	**q.s.**	**q.s.**	6.47 kg
	Total	**174.0**	

[67] To promote efficient tablet punching further 0.25 kg of Colloidal silicon dioxide and 0.25 kg of magnesium stearate sieved through 40 mesh screen is added to above dried blended formulation in blender for subsequent 5 minutes. Final screened granules are compressed using 9.0 mm (for 50 mg strength at 275 mg average weight) circular, standard concave circular punches Karnavati Tablet Compression M/C-17 Stn. GMP machine at hardness not less than 6-10 kg/cm^2. Generated dosage form tablets are then subjected to film coating using Instacoat Universal. Coating composition is weighed in accordance with table 2 coating suspenstion is prepared in water with stirrer and mixed for about 45 minutes subsequently it is passed through 80 mesh screen. Coating is preformed on dosage form using INSTACOAT Pharma RnD coater (6' pan) at 25 rpm with inlet temperature being 53 °C and bed temperature at 40 °C. coating was done using 1mm nozzle sprayer with peristaltic pump injecting coating suspension at the rate of 1ml/min. Coated tablets are then dried and packed as per pharmacopoieal

guidelines.

[68] **Example 3**

[69] Dissolution Profile Evaluation of Metoprolol tablet

[70] Metoprolol dose form dissolution study was performed. Drug dissolution profiles of tablet prepared are measured by USP 35 dissolution test of rotating basket method <711>. It is evident from standard state of the art that active ingredient may have its own dissolution testing parameters which can be found in their respective monographs. The active ingredient content for present invention is standardized for sustained release profile is as per table 2:-

[71] Medium: pH 6.8 phosphate buffer 500 ml

[72] Time interval: 1, 4, 8 and 20 hours

[73] **Table 2**

Time (Hour)	Accepted Limits (as per USP)
1	NMT 20 %
4	20 - 40 %
8	40 - 60 %
20	NLT 80 %

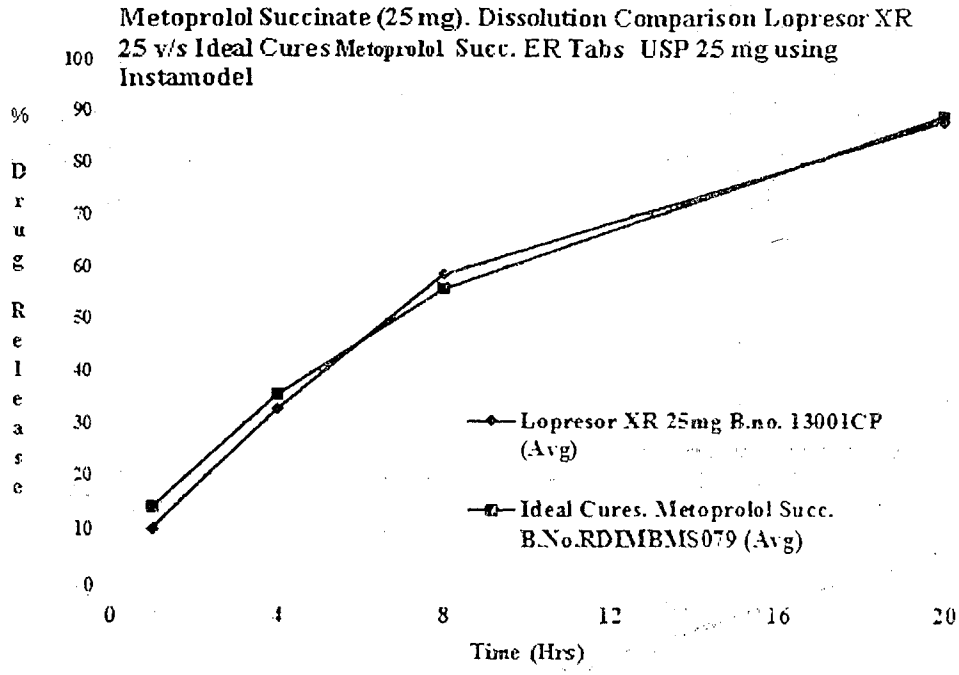
[74] It was observed that it shows maximum absorbance at 284 nm on Double Beam UV-VIS Spectrophotometer (UV 2700- Thermo Fisher Scientific).

[75] **METOPROLOL (25mg) IN VITRO % DRUG RELEASE USING IN-STAMODEL (A43D00043) DISSOLUTION COMPARISON**

[76]

Time Intervals (USP)	Dissolution Limits (USP)	% Drug release Reference Product: Lopresor – XR – 25 Tablets Mfg By : Novartis India Ltd			% Drug release Test Product : Metoprolol Succinate ER Tabs.		
		Min	Max	Average	Min	Max	Average
1	NMT 25%	9.10	10.78	10.11	13.85	14.14	14.11
4	20% - 40%	31.35	33.66	32.54	34.99	35.55	35.28
8	40% - 60%	54.80	62.42	58.30	54.55	56.82	55.50
20	NLT 80%	85.80	91.40	87.71	88.38	88.87	88.71

[77]

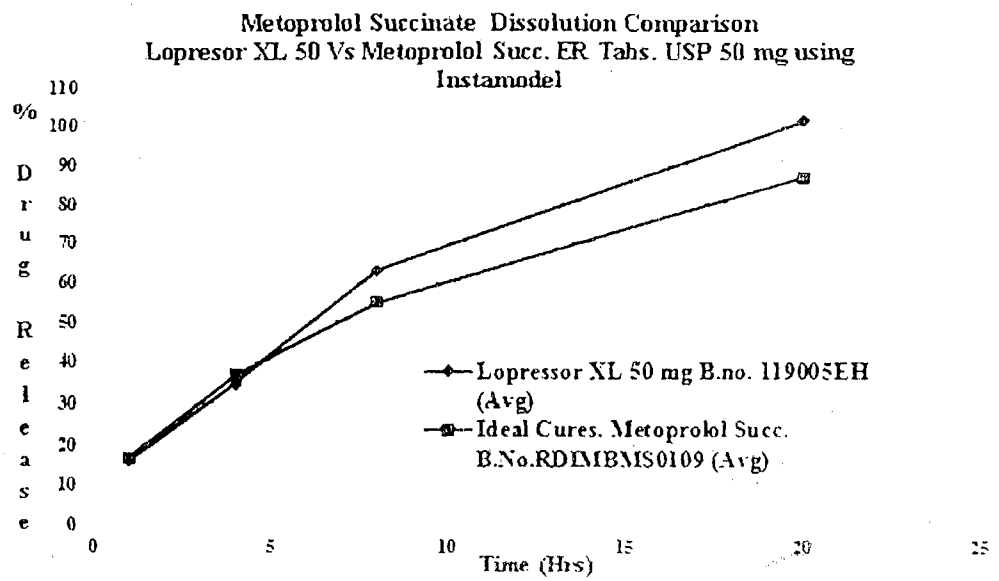


[78] IN VITRO COMPARISON OF DISSOLUTION PROFILE (% Drug Release) METOPROLOL SUCCINATE ER TABLETS 50 MG USING INSTAMODEL

[79]

Time Intervals	Dissolution Limits	Reference Product: Lopresor XL 50mg (mfg by: Novartis) B.No. 119005EH			Test Product: Metoprolol Succinate ER tabs. USP 50 mg Using Instamodel B.No.RDIMBMS0109 (Mfg by: Ideal Cures Pvt Ltd.)		
		Min	Max	Average	Min	Max	Average
1	NMT 25%	14.83	17.42	15.77	15.61	17.43	16.48
4	20% - 40%	31.56	35.48	34.47	36.18	36.88	36.57
8	40% - 60%	60.32	64.38	62.70	53.12	55.92	54.66
20	NLT 80%	100.68	102.1	101.39	85.22	87.5	86.66

[80]



[81] The drug dissolved profile of the Reference products and Metoprolol having dose strength of 25 and 50 mg using Instamodel (A43D00051, A43D00043) formulations are compared. The release exponents for the Reference and formulated Metoprolol is found to be having similar modified release profile indicating a predominantly diffusion based drug release mechanism.

Claims

[1] A modified release solid pharmaceutical composition comprising Metoprolol, Instamodel (A43D00051, A43D00043), binder, lubricant, glidant optionally opacifiers, colorants.

[2] The solid pharmaceutical composition of claim 1, wherein Metoprolol can be in form of salt, polymorphic form, its derivatives or mixture thereof.

[3] The solid pharmaceutical composition of claim 1, wherein binder is selected from polyvinyl polymers, Polyvinyl pyrrolidone K30 (PVP K30) and like.

[4] The solid pharmaceutical composition of claim 1, wherein lubricant is selected from talc, magnesium stearate, stearic acid, sodium stearyl fumarate and combination thereof.

[5] The solid pharmaceutical composition of claim 1, wherein glidant is selected from silicon di-oxide, colloidal silicon dioxide and there derivatives thereof.

[6] A process for preparing Metoprolol tablet according to claim 1 comprising

a. Blending of ready to use formulation Instamodel with Metoprolol
b. Thorough mixing to form dry powder
c. Optionally addition of lubricant
d. Slugging of blended powder
e. Deslugging of tablet
f. Milling and Sieving through appropriate size
g. Optionally adding Instamodel again.
h. Optionally addition of lubricant
i. Final tablet compression
j. Optional film coating

[7] The solid pharmaceutical composition prepare using process for preparing Metoprolol tablet according to claim 1 comprising

a. Blending of ready to use formulation Instamodel with Metoprolol
b. Thorough mixing to form dry powder
c. Optionally addition of lubricant
d. Slugging of blended powder
e. Deslugging of tablet
f. Milling and Sieving through appropriate size
g. Optionally adding Instamodel again.
h. Optionally addition of lubricant
i. Final tablet compression
j. Optional film coating

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2014/000600

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/553,A61K31/138,A61K9/20 Version=2014.01

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)

A61K31,A61K9

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)

Orbit database , IPO Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2011/0159094 A1,(30-06-2011) Para 0027,0031,0036,0057-0157	1-7
X	WO2007/036952 A2, (05-04- 2007) Examples 1-3	1-7
X	WO2006/102964 A2,(05-10-2006) Page 36,37 and Claims 1-5	1-7
X	WO2003/051340 A1 (26-06-2003) Claims 1-23	1-7
X	WO2007/011972 A2 (2007-01-25) Claims 1-72	1-7
X	http://news.cision.com/ideal-cures-pvt--ltd/r/extended-release-tablets formulationsimplified,c9285826THU,JUL19, 201209:20CET Whole Document	1-7
X	www.topnews.in/health/ideal-cures-unveil-newtechnology-prolong-drug-release-	1-7

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"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
15-01-2015	15-01-2015
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Dr. A. P. Singh Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2014/000600

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	new technology to prolong drug releaseSubmitted by Mohit Joshi on Mon, 07/23/2012 -08:5 Whole document	
Y	WO2005/079752 A2 (01-09-2005) Pages 12-16 , claims 1-32	1-7
Y	WO03/075896 A1(18-09-2003) Pages 15-19 , Examples 1-5	1-7
A	US2012/0045506 A1 (23-02-2012) Whole document	1-7

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2014/000600

Citation	Pub.Date	Family	Pub.Date
US 20110159094 A1	30-06-2011	EP 2361616 A1	31-08-2011
WO 2007/036952 A2	05-04-2007	IN 0168/MUMNP/2008 A	22-02-2008
		EP 1898886 A2	19-03-2008
		US 2009053310 A1	26-02-2009
WO 2006/102964 A2	05-10-2006	CA 2600282 A	05-10-2006
		IN 0324CHE2005 A	15-03-2007
		EP 1863453 A2	12-12-2007
		JP 2008220080 A1	11-09-2008
WO 2003/051340 A1	26-06-2003	CN 100341491 C	10-10-2007
		AT 287259 T	26-06-2003
		AU 2002361447 A1	30-06-2003
		EP 1355633 A1	29-10-2003
WO 2007011972 A2	25-01-2007	AU 2006269944 A1	25-01-2007
		US 2009214643 A1	27-08-2009
WO 2005/079752 A2	01-09-2005	EP 1750717 A2	14-02-2007
		US 2007196396 A1	23-08-2007
		US 2014371282 A1	18-12-2014
WO 03075896 A1	18-09-2003	AU 2003220782 A1	22-09-2003