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(54) **Title:** LACTOSE FREE FORMULATION OF EMPAGLIFLOZIN USING DIRECT COMPRESSION PROCESS

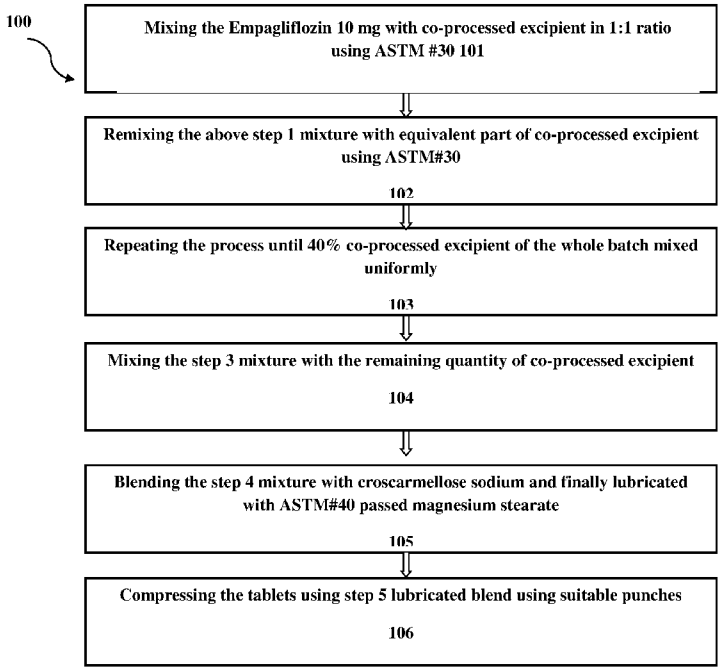

Fig. 1

(57) **Abstract:** A formulation of Empagliflozin prepared by a lactose-free co-processed pharmaceutical excipient using direct compression process, wherein the process comprising the steps of: mixing 101 the Empagliflozin 10 mg with co-processed excipient in 1:1 ratio using ASTM #30; remixing 102 the above step 1 mixture with equivalent part of co-processed excipient using ASTM#30; repeating 103 the process until 40% co-processed excipient of the whole batch mixed uniformly; mixing 104 the step 3 mixture with the remaining quantity of co-processed excipient; blending 105 the step 4 mixture with croscarmellose sodium and finally lubricated with ASTM#40 passed magnesium stearate; and compressing 106 the tablets using step 5 lubricated blend using suitable punches.

[Continued on next page]

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LACTOSE FREE FORMULATION OF EMPAGLIFLOZIN USING DIRECT COMPRESSION PROCESS

FIELD OF INVENTION

[0001] The embodiment herein generally relates to preparing a lactose free formulation. More specifically, the invention provides lactose free formulation of empagliflozin tablets using direct compression process.

BACKGROUND AND PRIOR ART

[0002] Excipient is an inactive substance that serves as the vehicle or medium for a drug or other active substance. These can be things like diluent, glidant, disintegrant, binders, coloring agents, preservatives and fillers.

[0003] An excipient is formulated alongside the active ingredient of a medication, included for the purpose of long term stabilization, bulking up solid formulation that contain potent active ingredients in small amounts or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug adsorption, reducing viscosity or enhancing solubility.

[0004] Pharmaceutical excipients are the vital components of drug formulations and play a significant role in any dosage form.

[0005] Lactose is a disaccharide. It is a sugar composed of galactose and glucose subunits and has the molecular formula $C_{12}H_{22}O_{11}$. Lactose makes up around 2–8% of milk (by weight). The name comes from *lac* (*gen. lactis*), the Latin word for milk, plus the suffix *-ose* used to name sugars. The compound is a white, water-soluble, non-hygroscopic solid with a mildly sweet taste.

[0006] Lactose is widely used as filler and diluent in the oral dosage form. Lactose is widely used as a filler or filler-binder in the manufacture of pharmaceutical tablets and capsules.

[0007] Lactose is used to help form tablets because it has excellent compressibility properties. It is also used to form a diluent powder for dry-powder inhalations.

[0008] The extremely tiny amount of actual working ingredient in a medication needs to be surrounded with fillers that bulk it out to be large enough to handle. A substance that is mostly tasteless but with just enough sweetness to balance out the bitter taste of many medications is great. Lactose can be formulated to break down in the stomach to release the medication making it nearly ideal.

[0009] Various lactose grades are commercially available with different physical properties such as particle size distribution and flow characteristics. These lactose properties permit selecting the most suitable material for a particular application; for example, the particle size range helps determine processes like direct compression or dry granulation.

[00010] Usually, fine lactose grades are used for the wet-granulation method or milling process. The fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently.

[00011] Lactose, is well known for producing tablets with high mechanical strength. However, its usage has been eroded by some relatively recent concerns, such as Bovine Spongiform Encephalopathy BSE, Variant Creutzfeldt-Jacob Disease (vCJD), and lactose intolerance.

[00012] These concerns have led researchers to evaluate other excipients in their formulations.

[00013] Lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase leads results in lactose being undigested and may cause cramps, diarrhea, distension, and flatulence.

[00014] Lactose intolerance is a digestive disorder caused by the inability to digest lactose. It can cause various symptoms, including bloating, diarrhea and abdominal cramps. People with lactose intolerance don't make enough of the enzyme lactase, which is needed to digest lactose.

[00015] Malabsorption of lactose (hypolactasia) may occur at an early age (4–8 years) and varies among different ethnic groups. The symptoms of lactose intolerance caused by the osmotic effect of the unabsorbed lactose, which increases water and sodium levels in the lumen.

[00016] Unabsorbed lactose, upon reaching the colon, can be fermented by colonic flora, which produces gas, causing abdominal distension and discomfort.

[00017] In addition, the abrasiveness of lactose can cause a decrease in tooling life due to excess wear on tableting or capsule-filling equipment. To overcome abrasiveness, lubricants must be used, but high lubricant levels can cause a decrease in tablet mechanical strength and can affect disintegration and dissolution.

[00018] Today, there is a need to develop an excipient that must be lactose-free but shows similar lactose properties and replaces the lactose to some extent.

[00019] Therefore, there is a need to develop an excipient that must be lactose-free but shows similar lactose properties and replaces the lactose to some extent. A single excipient cannot cater to the required properties; hence, there is a need to develop multifunctional co-processed excipients.

[00020] The co-processed excipient combines two or more compendial or non-compendial excipients designed to physically modify their properties, which cannot be achieved by simple physical mixing and without significant chemical changes.

OBJECTS OF THE INVENTION

[00021] Some of the objects of the present disclosure are described herein below:

[00022] A main object of the present invention is to provide a co-processed excipient which is ready to be used excipient.

[00023] Another object of the present invention is to provide a lactose free co-processed excipient which is ready to be used excipient.

[00024] Still another object of the present invention is to provide a lactose free co-processed excipient which is ready to be used excipient that shows similar lactose properties and replaces the lactose to some extent.

[00025] Yet another object of the present invention is to provide a lactose free co-processed excipient that provides high functionality compare to the individual excipients.

[00026] Another object of the present invention is to provide a lactose free co-processed excipient that has improved flow properties.

[00027] Another object of the present invention is to provide a lactose free co-processed excipient that has improved compressibility.

[00028] Another object of the present invention is to provide a lactose free co-processed excipient that depicts better dilution potential.

[00029] Another object of the present invention is to provide a lactose free co-processed excipient that shows lesser weight variation during direct compression.

[00030] Another object of the present invention is to provide a lactose free co-processed excipient that possesses reduced lubricant sensitivity.

[00031] Another object of the present invention is to provide lactose free formulation of Empagliflozin tablets.

[00032] Another object of the present invention is to provide lactose free formulation of Empagliflozin tablets using direct compression process.

[00033] The other objects and advantages of the present invention will be apparent from the following description when read in conjunction with the accompanying drawings, which are incorporated for illustration of preferred embodiments of the present invention and are not intended to limit the scope thereof.

SUMMARY OF THE INVENTION

[00034] In view of the foregoing, an embodiment herein provides a formulation of Empagliflozin prepared by a lactose-free co-processed pharmaceutical excipient using direct compression process, wherein the process comprising the steps of: mixing 101 the Empagliflozin 10 mg with co-processed excipient in 1:1 ratio using ASTM #30; remixing 102 the above step 1 mixture with equivalent part of co-processed excipient using ASTM#30; repeating 103 the process until 40% co-processed excipient of the whole batch mixed uniformly.

[00035] According to an embodiment, the step 3 mixture is mixed 104 with the remaining quantity of co-processed excipient; later blending 105 the step 4 mixture with croscarmellose sodium is done and finally lubricated with ASTM#40 passed magnesium stearate.

[00036] According to an embodiment, the tablets are further compressed 106 using step 5 lubricated blend using suitable punches.

[00037] These and other aspects of the embodiments herein will be better appreciated and understood when considered in conjunction with the following description and the accompanying drawings. It should be understood, however, that the following descriptions, while indicating preferred embodiments and

numerous specific details thereof, are given by way of illustration and not of limitation. Many changes and modifications may be made within the scope of the embodiments herein without departing from the spirit thereof, and the embodiments herein include all such modifications.

BRIEF DESCRIPTION OF DRAWINGS

[00038] The detailed description is set forth with reference to the accompanying figures. In the figures, the left-most digit(s) of a reference number identifies the figure in which the reference number first appears. The use of the same reference numbers in different figures indicates similar or identical items.

[00039] Fig.1 illustrates a flow chart showing the steps in Lactose free formulation of Empagliflozin tablets using direct compression method, according to an embodiment herein; and

[00040] Fig.2 illustrates a comparative analysis of *in vitro* dissolution of tablet with the reference product Jardiance 10 mg, according to an embodiment herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00041] The embodiments herein and the various features and advantageous details thereof are explained more fully with reference to the non-limiting embodiments and detailed in the following description. Descriptions of well-known components and processing techniques are omitted so as to not unnecessarily obscure the embodiments herein. The examples used herein are intended merely to facilitate an understanding of ways in which the embodiments herein may be practiced and to further enable those of skill in the art to practice

the embodiments herein. Accordingly, the examples should not be construed as limiting the scope of the embodiments herein.

[00042] As mentioned above, there is a need to develop lactose free formulation of Empagliflozin tablets using direct compression process. The embodiments herein achieve this by providing a multi functional co-processed excipient that is lactose free but shows lactose like properties and replaces lactose to some extent.

[00043] According to an embodiment, the present invention discloses a lactose-free tablet formulation of Empagliflozin tablets, 10 mg using a direct compression process.

[00044] According to an embodiment, the active substance is a crystalline solid, routinely manufactured as a single polymorphic form. It is very slightly soluble in aqueous media between pH 1-7.5 but has low intestinal permeability. The innovator, Jardiance (Mfg. by- Boehringer Ingelheim Pharmaceuticals, Inc., USA), used a wet granulation process throughout the development.

[00045] According to an embodiment, Empagliflozin, is a medication used together with diet and exercise to treat type 2 diabetes. It can be prescribed instead of metformin and has benefits over sulfonylureas. It may be used together with other medications such as metformin or insulin.

[00046] According to an embodiment, Empagliflozin is a non-reactive and robust material, and based on this physicochemical property of Empagliflozin, direct compression process adopted as proof of concept using co-processed excipient.

[00047] According to an embodiment, the process should provide adequate physical and mechanical stability, appearance suitable to the patient, and comparable in-vitro dissolution with the reference product.

[00048] According to an embodiment, for the direct compression, lactose-free co-processed excipient of sucrose was used. The co-processed excipient was prepared by using the process as mentioned in the Patent Application no. 202111005409.

[00049] According to an embodiment, direct compression method has many advantages over the wet granulation method. Wet granulation is a process of dry mixing, wet mixing, and particle size enlargement, and is a process of particle attachment (agglomeration).

[00050] According to an embodiment, direct compression is a popular choice because it provides the shortest, most effective and least complex way to produce tablets. During manufacturing API is blended with the excipient and the lubricant, followed by compression, which makes the product easy to process. No additional processing steps are required.

[00051] According to an embodiment, another benefit of using direct compression method is its cost effectiveness in contrast to the wet granulation method. In the direct compression method, the continuous manufacturing can be done with minimum optimization.

[00052] According to an embodiment, the Empagliflozin tablet, 10 mg prepared by direct compression process using geometric dilution technique. The geometric dilution technique is a pharmaceutical process that thoroughly mixes a small amount of a drug with an appropriate amount of a diluent, an inert substance that thins or binds the drug. It ensures equal distribution of the drug throughout the resulting compound.

[00053] Referring now to the drawings, and more particularly to FIGS. 1 through 2, where similar reference characters denote corresponding features consistently throughout the figures, there are shown preferred embodiments.

[00054] According to an embodiment, the Empagliflozin tablet, 10 mg prepared by direct compression process using geometric dilution technique is a detailed procedure as depicted in Fig. 1, in which mixing 101 of the Empagliflozin 10 mg with co-processed excipient in 1:1 ratio is done using ASTM #30 in the first step.

[00055] According to an embodiment, in the next step remixing 102 the step 1 mixture with equivalent part of co-processed excipient using ASTM #30 is done.

[00056] According to an embodiment, the process is repeated 103 until 40% co-processed excipient of the whole batch uniformly mixed. The mixture is further mixed 104 with the remaining quantity of co-processed excipient.

[00057] According to an embodiment, further this mixture is blended 105 with croscarmellose sodium and finally lubricated with ASTM # 40 passed magnesium stearate.

[00058] According to an embodiment, the tablets are compressed 106 using the lubricated blend of previous step using suitable punches.

[00059] According to an embodiment, the tablet composition and physical parameters are mentioned in Table 1 and Table 2.

Ingredients	Quantity % w/w	mg/tablet
Empagliflozin	4.0%	10.0
Co-processed excipient	90.5%	226.3
Croscarmellose Sodium	5.0%	12.5
Mg stearate	0.5%	1.3
Total	**100.0%**	**250.0**

Table 1: Tablet Composition

Parameters	Test Product	Jardiance 10 mg (Lot # 904699)
Excipient details	co-processed excipient of sucrose	**lactose monohydrate**, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating contains; hypromellose, titanium dioxide, talc, polyethylene glycol, and yellow ferric oxide.
Appearance	White, round-shaped, uncoated tablet, plain on both side	Pale yellow, round, biconvex, and bevel-edged, film-coated tablets debossed with "S 10" on one side and the Boehringer Ingelheim company symbol on the other side.
Weight (mg)	248.2±1.5	260.0±0.6
Hardness (kp)	8.4±1.1	9.5±0.3
Thickness (mm)	4.7±0.3	3.8±0.0
Disintegration time (seconds)	68±23.7	113±13.3

Table 2 Tablet Parameters

[00060] According to an embodiment, Tablet dissolution performed in release media, pH 6.8 phosphate buffer, paddle, 75 rpm, 900 m Land compared with the reference product, Jardiance 10 mg (Mfg. by- Boehringer Ingelheim Pharmaceuticals, Inc., USA) as shown in Fig. 2.

[00061] A main advantage of the present invention is that the excipient developed is lactose free but shows lactose similar properties and replaces the lactose to some extent.

[00062] Another advantage of the present invention is that the manufacturing process is simple and cost effective.

[00063] Still another advantage of the present invention is that the direct compression process can be performed with minimum optimization.

[00064] Yet another advantage of the present invention is that the final product possesses qualities like improved flow properties, better dilution potential, improved compressibility and reduced lubricant sensitivity.

[00065] The foregoing description of the specific embodiments will so fully reveal the general nature of the embodiments herein that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. Therefore, while the embodiments herein have been described in terms of preferred embodiments, those skilled in the art will recognize that the embodiments herein can be practiced with modification within the spirit and scope of the embodiments as described herein.

I claim:

1. A formulation of Empagliflozin prepared by a lactose-free co-processed pharmaceutical excipient using direct compression process, wherein the process comprising the steps of:

mixing 101 the Empagliflozin 10 mg with co-processed excipient in 1:1 ratio using ASTM #30;

remixing 102 the above step 1 mixture with equivalent part of co-processed excipient using ASTM#30;

repeating 103 the process until 40% co-processed excipient of the whole batch mixed uniformly;

mixing 104 the step 3 mixture with the remaining quantity of co-processed excipient;

blending 105 the step 4 mixture with croscarmellose sodium and finally lubricated with ASTM#40 passed magnesium stearate; and

compressing 106 the tablets using step 5 lubricated blend using suitable punches; characterized in that

the ratio of Empagliflozin to co-processed excipient is in the range of 1:99 to 10:90% w/w; and

the pharmaceutical composition with optimal mechanical strength comprises at least one active pharmaceutical ingredient, a co-processed pharmaceutical excipient comprising Dicalcium phosphate, Corn starch, Sucrose, Calcium silicate, Povidone, Croscarmellose Sodium, and Microcrystalline cellulose and one or more pharmaceutically acceptable excipients.

2. The process as claimed in claim 1 wherein, the Empagliflozin composition, 10 mg prepared by direct compression process using geometric dilution technique.

3. The process as claimed in claim 2, wherein the geometric dilution technique used for the uniform and homogenous mixing.

4. The lactose free co-processed pharmaceutical excipient as claimed in claim 1, wherein the co-processed excipient comprises a co-processed mixture of Dicalcium phosphate, Corn starch, Sucrose, Calcium silicate, Povidone, Croscarmellose Sodium, and Microcrystalline cellulose.

5. The process as claimed in claim 1, wherein co-processing involves wet granulation and microwave-assisted drying followed by blending.

6. The process as claimed in claim 5, wherein the granules produced by the granulation and microwave-assisted drying has not less than 50% of the particles passed through ASTM #60.

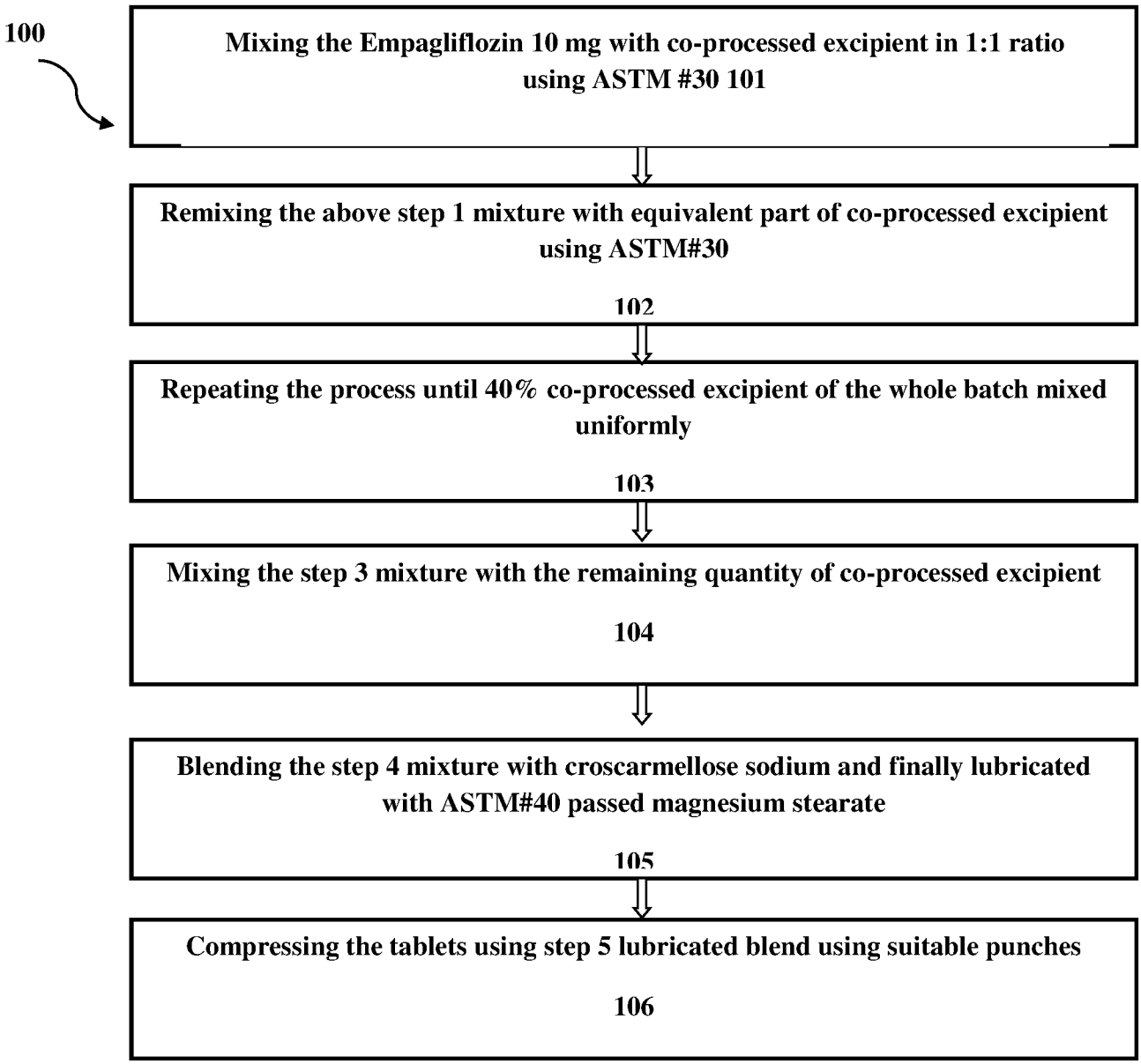
100
Mixing the Empagliflozin 10 mg with co-processed excipient in 1:1 ratio using ASTM #30 101
Remixing the above step 1 mixture with equivalent part of co-processed excipient using ASTM#30
102
Repeating the process until 40% co-processed excipient of the whole batch mixed uniformly
103
Mixing the step 3 mixture with the remaining quantity of co-processed excipient
104
Blending the step 4 mixture with croscarmellose sodium and finally lubricated with ASTM#40 passed magnesium stearate
105
Compressing the tablets using step 5 lubricated blend using suitable punches
106

Fig. 1

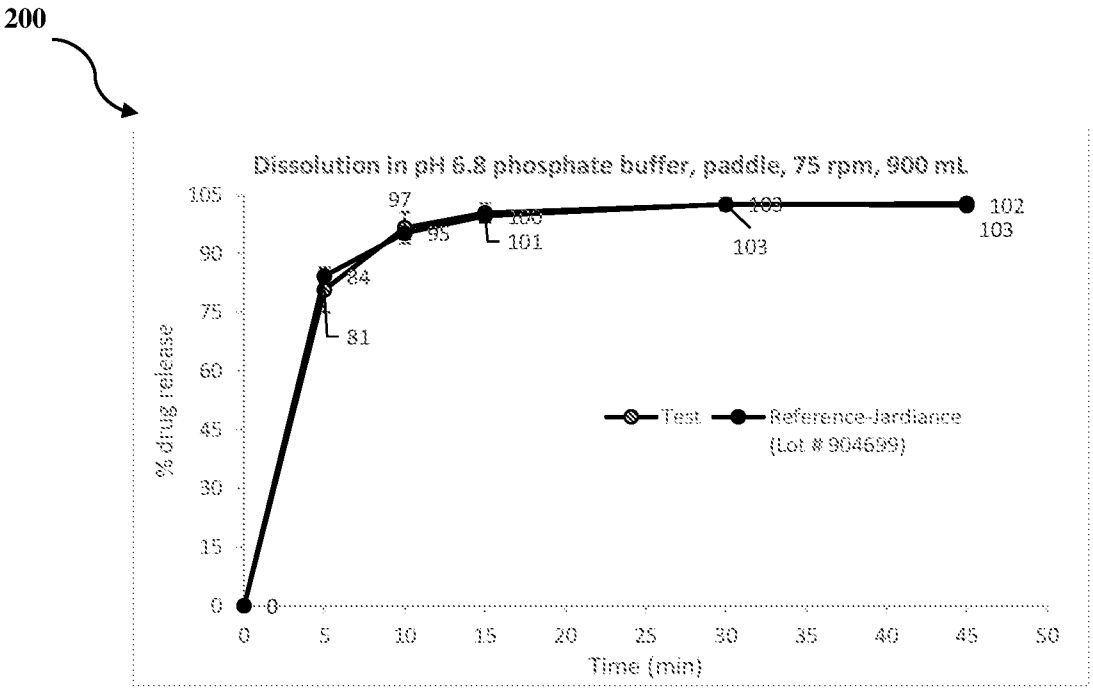
200
Dissolution in pH 6.8 phosphate buffer, paddle, 75 rpm, 900 mL
% drug release
Time (min)
Test
Reference-Jardiance
(Lot # 904699)
0
81
84
97
95
101
103
102
103

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/060821

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00,A61K9/14,A61K9/28,A61K9/20,A61K38/26 Version=2022.01

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)

A61K

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)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2010092126A1 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH, 19 AUGUST, 2010) the whole document, particularly claims 1-15, example 8	1-6
Y	WO2020058095A1 (GALENICUM HEALTH S.L.U., 26 MARCH, 2020) the whole document, particularly examples 1-2, 4-5	1-6
Y	Anna Viscasillas Clerch et.al. "Pharmaceutical design of a new lactose-free coprocessed excipient: application of hydrochlorothiazide as a low solubility drug model", Drug Development and Industrial Pharmacy, 2012; Early Online: 1-9, DOI: 10.3109/03639045.2012.686507. the whole document, particularly abstract, page 2 second column, results, and discussion section	1-6
Y	Gerad K. Bolhuis, "Excipients for Direct Compaction—an Update", Pharmaceutical Development and Technology, 11:111-124, 2006, DOI: 10.1080/10837450500464255. the whole document, particularly table 1, sections 4, 5,	1-6

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

* Special categories of cited documents:
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"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
11-03-2022	11-03-2022
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Ravi S Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/060821

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	11.5.	
Y	B. Mamatha et.al. "Co-processed excipient: an overview", World Journal of Pharmaceutical Research, 2017, Vol 6(15), 224-237. the whole document, particularly page 226	1-6
A	Akanksha Dwivedi et.al. "Design, optimization and evaluation of empagliflozin orodispersible tablets using different superdisintegrants", Int J Pharm Pharm Sci, Vol 11, Issue 7, 32-41, DOI: http://dx.doi.org/10.22159/ijpps.2019v11i7.33213. abstract	1-6

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/060821

Citation	Pub.Date	Family	Pub.Date
WO 2010092126 A1	19-08-2010	CN 105147662 A	16-12-2015
		AU 2010212868 B2	25-07-2013
		EP 2395968 A1	21-12-2011
		CA 2752435 C	17-01-2017
		JP 5600328 B2	01-10-2014
		KR 20170005156 A	11-01-2017
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