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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 December 2023 (07.12.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/234899 A1

(51) International Patent Classification:
A61K 31/155 (2006.01) *A61K 9/24* (2006.01)
A61K 31/7048 (2006.01)

(21) International Application Number:
PCT/TR2023/050469

(22) International Filing Date:
25 May 2023 (25.05.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2022/008870 31 May 2022 (31.05.2022) TR

(71) Applicant: **SANOVEL ILAC SANAYI VE TICARET ANONIM SIRKETI** [TR/TR]; Istinye Mahallesi Balabandere Caddesi No:14, 34460 Sariyer/Istanbul (TR).

(72) Inventors: **SUNEL, Fatih**; Istinye Mahallesi Balabandere Caddesi No:14, 34460 Sariyer/Istanbul (TR). **PEHLIVAN AKALIN, Nur**; Istinye Mahallesi Balabandere Caddesi No:14, 34460 Sariyer/Istanbul (TR). **ARMUT, Merve**; Istinye Mahallesi Balabandere Caddesi No:14, 34460 Sariyer/Istanbul (TR). **GULER, Tolga**; Istinye Mahallesi Balabandere Caddesi No:14, 34460 Sariyer/Istanbul (TR).

(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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, 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, ME, 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))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

WO 2023/234899 A1

(54) Title: A BILAYER TABLET FORMULATION COMPRISING EMPAGLIFLOZIN AND METFORMIN

(57) Abstract: The present invention relates to a bilayer tablet comprising empagliflozin and metformin, the tablet provides the desired stability and pharmacotechnical properties and the desired dissolution profile. The present invention also relates to a simple, rapid, cost effective, time-saving and industrially convenient method of preparing the bilayer tablet.

A BILAYER TABLET FORMULATION COMPRISING EMPAGLIFLOZIN AND METFORMIN

Field of the Invention

The present invention relates to a bilayer tablet comprising empagliflozin and metformin, the tablet provides the desired stability and pharmacotechnical properties and the desired dissolution profile. The present invention also relates to a simple, rapid, cost effective, time-saving and industrially convenient method of preparing the bilayer tablet.

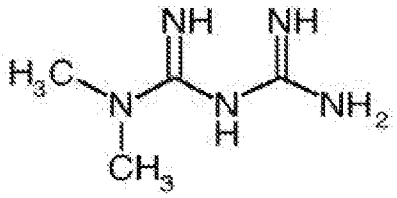
Background of the Invention

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity or a combination of both factors. There are two main types of diabetes; Type 1 and Type 2:

Type 1 diabetes occurs because the insulin-producing cells of the pancreas (beta cells) are damaged. In Type 1 diabetes, the pancreas makes little or no insulin, so sugar cannot get into the body's cells for use as energy. People with Type 1 diabetes must use insulin injections to control their blood glucose. In Type 2 diabetes, the pancreas makes insulin, but it either doesn't produce enough, or the insulin does not work properly. This diabetes occurs most often in people who are over 40 years old and overweighed. Type 2 diabetes may sometimes be controlled with a combination of diet, weight management, and exercise. However, treatment also may include oral glucose-lowering medications or insulin injections.

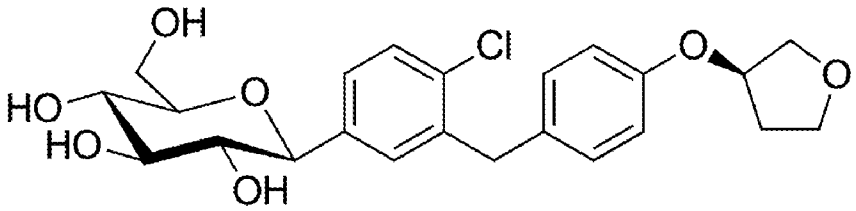
Metformin is antidiabetics having an orally-administrated biguanide structure. Metformin hydrochloride is a white to off-white crystalline compound and it is freely soluble in water and practically insoluble in acetone, ether and chloroform. Oral doses of metformin are generally recommended in the range of 500 to 2500 mg a day and a single dose may vary from 500 to 850 mg. It is used singly or in combination with sulfonylureas, alpha-glucosidase inhibitors, or insulin.

The chemical name of metformin hydrochloride is 1,1-dimethylbiguanide hydrochloride, has the following chemical structure of Formula I.



Formula I

Empagliflozin is a known SGLT2 inhibitor that is described for the treatment or improvement in glycemic control in patients with type 2 diabetes mellitus. The chemical name of empagliflozin is 1 -chloro-4-(3-D-glucopyranos-1 -yl)- 2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and its chemical structure is shown in the Formula II.



Formula II

Combination product of empagliflozin and metformin hydrochloride is marketed under the trademark Synjardy®. The combination is to help control blood glucose in people with T2D. Empagliflozin, a sodium glucose co-transporter-2 (SGLT2) inhibitor, removes excess glucose through the urine by blocking glucose re-absorption in the kidney.

Active ingredients have some disadvantages in the formulation and process. The main problem encountered when preparing formulations comprising empagliflozin is low solubility, leading to difficulties with disintegration and dissolution times. Furthermore, metformin is a very poorly compressible active substance and metformin presents in high amounts in a composition. This causes some problems for examples; homogeneity, flowability and dissolution profile.

WO2011039337 (A1) application discloses pharmaceutical compositions comprising fixed dose combinations of a SGLT-2 inhibitor drug and a partner drug, processes for the preparation thereof, and their use to treat certain diseases.

CN104586834 (A) application discloses a pharmaceutical composition of empagliflozin and metformin, a preparation method and application thereof. The composition comprises the following components: i.) empagliflozin; ii.) metformin hydrochloride; and one or more fillers; one or more adhesives; one or more flow aids and one or more lubricants.

In the prior art, there are also several patents which disclose empagliflozin and metformin hydrochloride in oral pharmaceutical dosage forms. However, because of the dissolution problem of empagliflozin, and the poorly compressible of metformin, an effective formulation and method has not been disclosed.

There still remains a need in the art to provide an improved a bilayer tablet comprising empagliflozin and metformin hydrochloride having high solubility, excellent pharmacomechanic properties and accordingly a high bioavailability and a long-term stability which is also obtained by using an effective process.

Detailed Description of the Invention

The main object of the present invention is to provide a bilayer tablet comprising empagliflozin and metformin hydrochloride with having the desired level of dissolution rate and excellent physicochemical properties, such as flowability, compressibility, homogeneity, and content uniformity which overcomes the above-described problems in the prior art and have additive advantages over them.

Another object of the present invention is to provide a bilayer tablet comprising empagliflozin and metformin hydrochloride with having high stability.

Another object of the present invention is to provide a process for preparing a bilayer tablet comprising empagliflozin and metformin hydrochloride. The process is a simple, rapid, cost effective, time-saving, and industrially convenient method.

The term “bilayer tablet” refers to a layered tablet consisting of two layers of granulate compressed together to form a single tablet. This dosage form has the advantage of separating two incompatible substances. Each layer is fed from distinct feed frame with individual weight control. For the purposes of the invention the expressions “layer” and “layer composition” have the same meaning.

In the invention, the bilayer tablet comprising empagliflozin and metformin hydrochloride offers advantages like: increased efficacy of the active components due to their additive or synergistic effect, improved adherence to treatment regimens by patients, convenience of use, and also the desired dissolution profile.

According to an embodiment of the present invention, a pharmaceutical bilayer tablet comprises;

a. first layer comprising metformin hydrochloride
b. second layer comprising empagliflozin

wherein each layer comprising at least one disintegrant. The bilayer tablet is obtained which shows good efficacy and an appropriate dissolution profile, and physicochemical properties, such as flowability, compressibility, homogeneity, and content uniformity.

Empagliflozin is low solubility, leading to difficulties with disintegration and dissolution times. Using at least one disintegrant at the second layer provides the desired dissolution profile.

Since metformin presents in high amounts in the composition, using the disintegrant at first layer helps to provide the desired dissolution profile and disintegration rate.

Suitable disintegrants are selected from the group comprising croscarmellose sodium, crospovidone, sodium starch glycollate, sodium alginate, gums, starch, magnesium aluminum silicate or a mixture thereof.

According to an embodiment of the present invention, the disintegrant is croscarmellose sodium. The disintegrant is used both the first layer and the second layer.

According to an embodiment of the present invention, the amount of disintegrants is 0.1% to 15.0% by weight, preferably 0.1% to 10.0% by weight in the first layer composition.

According to an embodiment of the present invention, the amount of disintegrants is 3.0% to 10.0% by weight, preferably 3.0% to 5.0% in the second layer composition.

According to an embodiment of the present invention, the bilayer tablet further comprises at least one pharmaceutically acceptable excipient which is selected from fillers, glidants/lubricants or mixtures thereof.

Another problem, at the first layer, encountered while developing formulations is the flowability-problem and compressibility of metformin HCl, which makes the production difficult. It has been observed that this problem is overcome by using at least one filler.

Suitable fillers are selected from the group comprising microcrystalline cellulose, lactose, anhydrous lactose, starch, mannitol, calcium hydrogen phosphate dihydrate, dicalcium hydrogen phosphate anhydrate, calcium phosphate trihydrate, neutral pellets, magnesium carbonate, magnesium oxide, maltodextrin, maltose, medium chain triglycerides or mixtures thereof.

According to an embodiment of the present invention, the filler is microcrystalline cellulose or lactose or mixtures thereof. The fillers provide flowability and compressibility of metformin HCl.

According to an embodiment of the present invention, the filler is microcrystalline cellulose in the first layer, the filler is lactose in the second layer.

According to an embodiment of the present invention, the amount of fillers is 5.0% to 50.0% by weight in the first layer composition.

According to an embodiment of the present invention, the amount of fillers is 70.0% to 85.0% by weight in the second layer composition.

Suitable glidants/lubricants are selected from the group comprising colloidal silicon dioxide, magnesium stearate, sodium stearyl fumarate, magnesium oxide, starch, silica colloidal anhydrous, talc, polyethylene glycol, stearic acid, aluminum silicate, magnesium silicate, colloidal silica or mixtures thereof.

According to an embodiment of the present invention, the glidant/lubricant is colloidal silicon dioxide or magnesium stearate or mixtures thereof.

According to an embodiment of the present invention, the amount of glidants/lubricants is 0.2% to 10.0% by weight in each layer composition. The amount of glidants/lubricants used helps to provide the desired flowability and compressibility of tablet. Especially, the amount of colloidal silicon dioxide used helps to provide the desired flowability and compressibility of tablet, the amount of colloidal silicon dioxide is 0.1% to 5.0% by weight in each layer composition.

According to an embodiment of the present invention, the bilayer tablet is coated with at least one film coating agent.

Suitable film coating agents are selected from the group comprising polymethacrylates, hydroxypropyl methylcellulose, lactose monohydrate, talc, hydroxypropyl cellulose, polyvinyl alcohol (PVA), polyethylene glycol (PEG), glycerin, polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat® IR), ethylcellulose dispersions (Surelease®), polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), iron oxide yellow, iron oxides, all kinds of Opadry®, pigments, dyes, titanium dioxide, coloring agent or mixtures thereof.

According to an embodiment of the present invention, the bilayer tablet comprises;

a) First layer comprising metformin HCl and microcrystalline cellulose,
b) Second layer comprising empagliflozin and lactose.

According to an embodiment of the present invention, the bilayer tablet comprises;

a) Metformin HCl
b) Empagliflozin
c) Microcrystalline cellulose

d) Croscarmellose sodium
e) Colloidal silicon dioxide
f) Magnesium stearate
g) Lactose

In general terms, excipients provided in a formulation may positively or negatively influence the physicochemical and pharmacokinetic properties, e.g. the solubility, absorption, bioavailability, stability of an active agent. For this reason, the excipients which accompany an active agents have to be selected in a careful and conscious manner while a formulation (especially the mixture) is developed. The described formulation should have no physicochemical incompatibility between the active agents and the excipients.

The bilayer tablet of the present invention may be prepared, using standard techniques and manufacturing processes well known in the art, such as direct compression or dry granulation.

According to one embodiment of the present invention, the first layer is obtained by using dry granulation, the second layer is obtained by using wet granulation. These methods are simple and low-cost production methods was employed.

According to this embodiment of the present invention, a solvent is used at wet granulation.

So, at first layer, using dry granulation helps to provide the desired uniformity of the content and therefore it provides the desired dissolution profile. The process provides the desired stability of tablet.

Suitable solvents are selected from the group comprising pure water, dichloromethane, 0.1N HCl, methanol, ethanol, isopropyl alcohol, benzyl alcohol, propylene glycol, polyethylene glycol, cyclomethicone or mixtures thereof. Preferably, the solvent is water.

According to one embodiment of the present invention, a process for the preparation of the bilayer tablet comprises the following steps:

First layer

a) Sieving metformin HCl through 2 mm,
b) Mixing Metformin HCl, microcrystalline cellulose and croscarmellose sodium,
c) Sieving the mixture through 630 µ and then mixing,
d) Adding colloidal silicon dioxide and magnesium stearate and then mixing, and obtained a mixture for the first layer.

Second layer

e) Mixing empagliflozin, lactose and croscarmellose sodium and sieving,

f) Granulating the mixture at step (e) with a solvent (for example; pure water),

g) Drying at fluid bed dryer and sieving,

h) Adding colloidal silicon dioxide and magnesium stearate and then mixing, and obtained a mixture for the second layer.

Tablet compression: The first layer and second layer are compressed to form a bilayer tablet.

Film coating: Film coating with moisture-barrier coating.

In this present invention, a desired compressibility and a desired content uniformity of the bilayer tablet is obtained and it has a simple and low-cost preparation process, in favor of industrial production.

Example 1: The bilayer tablet formulation

	Ingredients	**% by weight**
FIRST LAYER	Metformin HCl	80.0 – 90.0
	Microcrystalline cellulose	5.0 – 50.0
	Croscarmellose sodium	0.1 – 10.0
	Colloidal silicon dioxide	0.1 – 5.0
	Magnesium stearate	0.1 – 5.0
	The first layer total	**100**
SECOND LAYER	Empagliflozin	10.0 -20.0
	Lactose	70.0 -85.0
	Croscarmellose sodium	3.0 – 5.0
	Colloidal silicon dioxide	0.1 – 5.0
	Magnesium stearate	0.1 – 5.0
	The second layer total	**100**

A process for example 1

First layer

a) Sieving metformin HCl through 2 mm,

b) Mixing Metformin HCl, microcrystalline cellulose and croscarmellose sodium,

c) Sieving the mixture through 630 µ and then mixing,

d) Adding colloidal silicon dioxide and magnesium stearate and then mixing, and obtained a mixture for the first layer.

Second layer

e) Mixing empagliflozin, lactose and croscarmellose sodium and sieving,
f) Granulating the mixture at step (e) with a solvent (for example; pure water),
g) Drying at fluid bed dryer and sieving,
h) Adding colloidal silicon dioxide and magnesium stearate and then mixing, and obtained a mixture for the second layer.

Tablet compression: The first layer and second layer are compressed to form a bilayer tablet.

Film coating: Film coating with moisture-barrier coating.

CLAIMS

1) A pharmaceutical bilayer tablet comprises;
   a. first layer comprising metformin hydrochloride
   b. second layer comprising empagliflozin

wherein each layer comprising at least one disintegrant.

2) The pharmaceutical bilayer tablet according to claim 1, wherein disintegrants are selected from the group comprising croscarmellose sodium, crospovidone, sodium starch glycollate, sodium alginate, gums, starch, magnesium aluminum silicate or a mixture thereof.

3) The pharmaceutical bilayer tablet according to claim 1, wherein the disintegrant is croscarmellose sodium.

4) The pharmaceutical bilayer tablet according to claim 1, wherein the amount of disintegrants is 0.1% to 15.0% by weight, preferably 0.1% to 10.0% by weight in the first layer composition.

5) The pharmaceutical bilayer tablet according to claim 1, wherein the amount of disintegrants is 3.0% to 10.0% by weight, preferably 3.0% to 5.0% in the second layer composition.

6) The pharmaceutical bilayer tablet according to claim 1, further comprises at least one pharmaceutically acceptable excipient which is selected from fillers, glidants/lubricants or mixtures thereof.

7) The pharmaceutical bilayer tablet according to claim 6, wherein fillers are selected from the group comprising microcrystalline cellulose, lactose, anhydrous lactose, starch, mannitol, calcium hydrogen phosphate dihydrate, dicalcium hydrogen phosphate anhydrate, calcium phosphate trihydrate, neutral pellets, magnesium carbonate, magnesium oxide, maltodextrin, maltose, medium chain triglycerides or mixtures thereof.

8) The pharmaceutical bilayer tablet according to claim 6, wherein the filler is microcrystalline cellulose or lactose or mixtures thereof.

9) The pharmaceutical bilayer tablet according to claim 6, wherein the filler is microcrystalline cellulose in the first layer, the filler is lactose in the second layer.

10) The pharmaceutical bilayer tablet according to claim 6, wherein the amount of fillers is 5.0% to 50.0% by weight in the first layer composition.

11) The pharmaceutical bilayer tablet according to claim 6, wherein the amount of fillers is 70.0% to 85.0% by weight in the second layer composition.

12) The pharmaceutical bilayer tablet according to claim 6, wherein glidants/lubricants are selected from the group comprising colloidal silicon dioxide, magnesium stearate, sodium stearyl fumarate, magnesium oxide, starch, silica colloidal anhydrous, talc, polyethylene glycol, stearic acid, aluminum silicate, magnesium silicate, colloidal silica or mixtures thereof.

13) The pharmaceutical bilayer tablet according to claim 1, wherein comprises;

a) Metformin HCl
b) Empagliflozin
c) Microcrystalline cellulose
d) Croscarmellose sodium
e) Colloidal silicon dioxide
f) Magnesium stearate
g) Lactose

14) A process for the preparation of the bilayer tablet comprises the following steps:

First layer

a) Sieving metformin HCl through 2 mm,
b) Mixing Metformin HCl, microcrystalline cellulose and croscarmellose sodium,
c) Sieving the mixture through 630 µ and then mixing,
d) Adding colloidal silicon dioxide and magnesium stearate and then mixing, and obtained a mixture for the first layer.

Second layer

e) Mixing empagliflozin, lactose and croscarmellose sodium and sieving,
f) Granulating the mixture at step (e) with a solvent (for example; pure water),
g) Drying at fluid bed dryer and sieving,
h) Adding colloidal silicon dioxide and magnesium stearate and then mixing, and obtained a mixture for the second layer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2023/050469

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/155 (2006.01)i; A61K 31/7048 (2006.01)i; A61K 9/24 (2006.01)i

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)

Epodoc

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 20210084053 A (HUONS CO LTD [KR]) 07 July 2021 (2021-07-07) Paragraphs 23, 26; claims 1, 5-6	1-14
X	CN 107432869 A (TIANJIN INST PHARMACEUTICAL CO LTD) 05 December 2017 (2017-12-05) Paragraphs 30-36; claim 4	1-14
X	WO 2017093419 A1 (BOEHRINGER INGELHEIM INT [DE]) 08 June 2017 (2017-06-08) Page 29, the second paragraph; claim 1	1-14

☐ Further documents are listed in the continuation of Box C. ☑ 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
"D" document cited by the applicant in the international application
"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
19 July 2023	**19 July 2023**

Name and mailing address of the ISA/TR	Authorized officer
Turkish Patent and Trademark Office (Turkpatent) **Hipodrom Caddesi No. 13** **06560 Yenimahalle** **Ankara** **Türkiye** Telephone No. **+903123031000** Facsimile No. **+903123031220**	**Kübra KILIÇ AKALIN** Telephone No. **+903123031637**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/TR2023/050469

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
KR 20210084053 A	07 July 2021	NONE	
CN 107432869 A	05 December 2017	NONE	
WO 2017093419 A1	08 June 2017	US 2018344647 A1	06 December 2018
		US 2022105043 A1	07 April 2022