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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 June 2023 (22.06.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/113745 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 47/36* (2006.01)
A61K 47/26 (2006.01) *A61P 9/12* (2006.01)
A61K 47/32 (2006.01)

(21) International Application Number:
PCT/TR2022/051469

(22) International Filing Date:
10 December 2022 (10.12.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2021/019697 13 December 2021 (13.12.2021) TR

(71) Applicant: **SANOVEL ILAC SANAYI VE TICARET ANONIM SIRKETI** [TR/TR]; Istınye Mahallesı Balabandere Caddesı No:14 Sarıyer, 34460 Istanbul (TR).

(72) Inventors: **GULER, Tolga**; Istınye Mahallesı Balabandere Caddesı No:14 Sarıyer, 34460 Istanbul (TR). **PEHLIVAN AKALIN, Nur**; Istınye Mahallesı Balabandere Caddesı No:14 Sarıyer, 34460 Istanbul (TR). **SUNEL, Fatih**; Istınye Mahallesı Balabandere Caddesı No:14 Sarıyer, 34460 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, 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, 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 2023/113745 A1

(54) Title: A FILM COATED TABLET FORMULATION COMPRISING BENIDIPINE

(57) Abstract: The present invention relates to a film coated tablet comprises benidipine in the form of the free base or in the form of pharmaceutically acceptable salts and at least one pharmaceutically acceptable excipient, wherein the tablet has a hardness of between 20 N and 70 N. Furthermore, the formulation is obtained using an effective process.

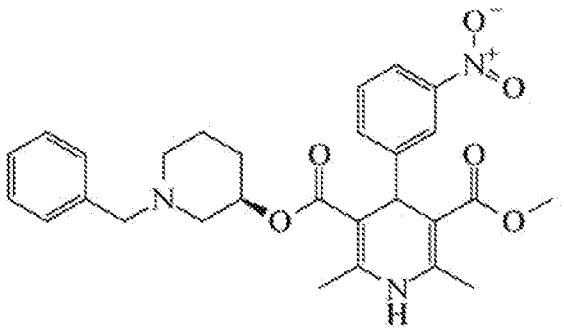
A FILM COATED TABLET FORMULATION COMPRISING BENIDIPINE

Field of the Invention

The present invention relates to a film coated tablet comprises benidipine in the form of the free base or in the form of pharmaceutically acceptable salts and at least one pharmaceutically acceptable excipient, wherein the tablet has a hardness of between 20 N and 70 N. Furthermore, the formulation is obtained using an effective process.

Background of the Invention

Benidipine has the formula 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylic acid methyl 1-(phenylmethyl)-3-piperidinyl ester hydrochloride. It is a synthetic dihydropyridine derivative that has anti-hypertensive and anti-anginal actions. It is a triple L-, T-, and N-type calcium channel blocker. The only calcium antagonist that can inhibit all the three Ca channels mentioned. Furthermore, benidipine has highly affinity with cell membrane, has vascular selectivity and renal protection effect. Therefore, it is an ideal, safe and effective agent for the treatment of hypertension and renal parenchymal hypertension and angina. Benidipine has the following chemical structure of Formula I.



Formula I: Benidipine

Benidipine is a class II drug in the BCS classification, that is, poorly water soluble. For poorly soluble drugs, its dissolution is the rate-limiting process of absorption, and is often the most important factor affecting its bioavailability. It is very soluble in formic acid, freely soluble in dimethylformamide, soluble in methanol or ethanol, slightly soluble in acetic anhydride. Furthermore, benidipine HCl presents in low amounts in the formulation so, excessive use of excipients and incompatibilities between them can adversely affect compressibility. The problem can cause also flowability and content uniformity.

Benidipine was originally disclosed with the application EP63365 B2.

In this invention, to overcome these problems mentioned above, a film coated tablet comprising benidipine in the form of the free base or in the form of pharmaceutically acceptable salts having has a hardness of between 20 N and 70 N. Also, the tablet has been developed by using standard techniques which is simple and cost-effective method.

Detailed Description of the Invention

The main object of the present invention is to eliminate problems caused by benidipine and bringing additional advantages to the relevant prior art.

Another object of the present invention is to provide a film coated tablet having a hardness of between 20 N and 70 N comprising benidipine in the form of the free base or in the form of pharmaceutically acceptable salts which is characterized by the desired compressibility and the desired dissolution rate and short disintegration time.

Another object of the present invention is to provide a formulation which is characterized by excellent pharmacotechnical properties, such as flowability and content uniformity.

Another object of the present invention is to obtain an effective process for the preparation of a film coated tablet formulation comprising benidipine which has the desired compressibility and the desired dissolution.

Hardness test was done with Erweka Tablet Hardness Tester.

According to one embodiment of the invention, a film coated tablet comprises benidipine in the form of the free base or in the form of pharmaceutically acceptable salts and at least one pharmaceutically acceptable excipient, wherein the tablet has a hardness of between 20 N and 70 N. This hardness provides the desired compressibility thus it is not brittle easily, but also provides a high dissolution rate and short disintegration time.

Tablets of lower hardness (<20 N) were observed to dissolve very quickly in the first minutes. It was observed that tablets with higher hardness (>70 N) could not be broken, so there were problems in dissolution. Thereof, It has been found that the specified values create a suitable condition for the tablet comprising benidipine.

According to this embodiment of the present invention, benidipine is in the form of is present as benidipine hydrochloride.

According to one embodiment of the present invention, the amount of benidipine hydrochloride is between 1.0% and 10.0% by weight in the total formulation. Preferably, it is between 1.0% and 6.0% by weight in the total formulation.

According to one embodiment of the invention, a film coated tablet comprises at least one pharmaceutically acceptable excipient which is selected from the group comprising fillers, binders, disintegrants, lubricants/glidants, coating agents or mixtures.

Suitable fillers are selected from the group comprising lactose monohydrate, microcrystalline cellulose, lactose, mannitol, spray-dried mannitol, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof.

According to one embodiment of the present invention, the filler is lactose monohydrate.

According to one embodiment of the present invention, the amount of fillers is between 70.0% and 88.0% by weight in the total formulation. Preferably, it is between 74.0% and 85.0% or between 77.0% and 83.0% by weight in the total formulation.

Suitable binders are selected from the group comprising polyvinylpyrrolidone, sodium carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, natural gums, sucrose, sodium alginate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxy methyl cellulose, methyl cellulose, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, alginate, alginic acid, xanthan gum, hyaluronic acid, polysaccharides, carbomer, poloxamer, polyacrylamide, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

According to one embodiment of the present invention, the binder is polyvinylpyrrolidone.

According to one embodiment of the present invention, the amount of binders is between 2.0% and 15.0% by weight in the total formulation. Preferably, it is between 2.5% and 10.0% or between 3.0% and 8.0% by weight in the total formulation.

Suitable disintegrants are selected from the group comprising pregelatinized starch, crospovidone, croscarmellose sodium, starch, low-substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose,

docusate sodium, low substituted hydroxypropyl cellulose, sodium alginate, corn starch, sodium starch glycolate, sodium glycine carbonate or mixtures thereof.

According to one embodiment of the present invention, the disintegrant is pregelatinized starch.

According to one embodiment of the present invention, the amount of disintegrants is between 3.0% and 15.0% by weight in the total formulation. Preferably, it is between 5.0% and 12.0% or between 6.0% and 10.0% by weight in the total formulation.

Suitable lubricants/glidants are selected from the group comprising magnesium stearate, sodium stearyl fumarate, talc, colloidal silicon dioxide, corn, calcium stearate, zinc stearate, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, stearic acid, fumaric acid, glyceryl palmito sulphate or mixtures thereof.

According to one embodiment of the present invention, the lubricant/glidant is magnesium stearate.

According to one embodiment of the present invention, the amount of lubricant/glidant is between 0.1% and 3.0% by weight in the total formulation. Preferably, it is between 0.5% and 2.0% by weight in the total formulation.

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

According to an embodiment of the present invention, the coating agents are hydroxypropyl methylcellulose, talc, titanium dioxide, polyethylene glycol.

According to an embodiment of the present invention, the coating agents are lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, yellow iron oxide, triacetin, ponceau, FD&C Blue.

According to an embodiment of the present invention, the amount of coating agents is 1.0% to 5.0% by weight by weight in the total formulation.

Benidipine in the form of the free base or in the form of pharmaceutically acceptable salts having the following particle sizes is important for formulation. Especially, it positively affects the dissolution properties. The obtained tablets have the desired dissolution profile.

As used here in, 'particle size' means the cumulative volume size distrubition as tested by any conventionally accepted method such as the laser diffraction method (i.e. malvern analysis). The term d (0.9) means, the size at which 90% by volume of the particles are finer. The term d (0.5) means, the size at which 50% by volume of the particles are finer.

According to this embodiment of the present invention, benidipine in the form of the free base or in the form of pharmaceutically acceptable salts has a d (0.5) particle size less than 30 µm, preferably less than 25 µm, preferably less than 20 µm, preferably less than 15 µm, preferably less than 10 µm.

According to this embodiment of the present invention, benidipine in the form of the free base or in the form of pharmaceutically acceptable salts has a d (0.5) particle size between 1 µm and 10 µm.

According to this embodiment of the present invention, benidipine in the form of the free base or in the form of pharmaceutically acceptable salts has a d (0.9) particle size less than 50 µm, preferably less than 35 µm, preferably less than 25 µm, preferably less than 18 µm.

According to this embodiment of the present invention, benidipine in the form of the free base or in the form of pharmaceutically acceptable salts has a d (0.9) particle size between 3 µm and 18 µm.

According to one embodiment of the present invention, the film coated tablet comprises;

- Benidipine hydrochloride
- Lactose monohydrate
- Polyvinylpyrrolidone

According to one embodiment of the present invention, the film coated tablet comprises;

- Benidipine hydrochloride
- Lactose monohydrate
- Pregelatinized starch
- Polyvinylpyrrolidone
- Magnesium stearate

According to one embodiment of the present invention, the film coated tablet is obtained by using a wet granulation method therefore, a simple and low-cost production method was employed. Wet granulation process efficiently counteracts segregation, so it can achieve good dissolution and disintegration properties. In the process, when a granulation solution is prepared with at least one binder and a solvent (preferably water), it was observed that the desired content uniformity is provided. Especially, the problem caused by the use of small amounts of benidipine has been prevented by the wet granulation comprising suitable excipients and steps.

According to one embodiment of the present invention, a process for the preparation of the film coated tablet comprising benidipine comprises the following steps:

a) Mixing benidipine hydrochloride, at least one filler and at least one disintegrant and then sieving,
b) Dissolving at least one binder in water,
c) Granulating the mixture at step (a) with the granulation solution at step (b),
d) Sieving the wet granule and drying the wet granule at fluid bed dryer,
e) Sieving the dry granule,
f) Adding at least one lubricant/glidant and then mixing,
g) Compressing the prepared mixture to form tablets
h) Coating these tablets with coating agents.

According to one embodiment of the present invention, a process for the preparation of the film coated tablet comprising benidipine comprises the following steps:

a) Mixing benidipine hydrochloride, lactose monohydrate and pregelatinized starch and then sieving,
b) Dissolving polyvinylpyrrolidone in water,
c) Granulating the mixture at step (a) with the granulation solution at step (b),
d) Sieving the wet granule and drying the wet granule at fluid bed dryer,
e) Sieving the dry granule,
f) Adding magnesium stearate and then mixing,
g) Compressing the prepared mixture to form tablets
h) Coating these tablets with coating agents.

Example 1: Film coating tablet

Ingredients	**Amount (% by weight of the total formulation)**
Benidipine hydrochloride	1.0 – 10.0
Lactose monohydrate	70.0 – 88.0
Pregelatinized starch	3.0 – 15.0
Polyvinylpyrrolidone K-30	2.0 – 15.0
Magnesium stearate	0.1 – 3.0
Film coating	1.0 – 5.0
TOTAL	**100**

Example 2: Film coating tablet

Ingredients	**Amount (% by weight of the total formulation)**
Benidipine hydrochloride	2.0
Lactose monohydrate	81.5
Pregelatinized starch	7.5
Polyvinylpyrrolidone K-30	5.0
Magnesium stearate	1.0
Film coating • *HPMC 2910 (Hypromellose) % 72.55* • *Titanium dioxide (E 171) % 18.15* • *Talc (E553b) % 5.45* • *Macrogol (PEG 4000) % 3.85*	3.0
TOTAL	**100**

5

Example 3: Film coating tablet

Ingredients	**Amount (% by weight of the total formulation)**
Benidipine hydrochloride	4.0
Lactose monohydrate	79.5
Pregelatinized starch	7.5
Polyvinylpyrrolidone K-30	5.0
Magnesium stearate	1.0
Film coating • *Lactose monohydrate % 21.00* • *HPMC 6 cP % 40.00* • *Titanium dioxide % 24.25* • *PEG 3000 Powder % 8.00* • *Yellow iron oxide %0.737* • *Triacetin %6.00* • *Ponceau 4R %0.011* • *FD&C Blue No 2 %0.002*	3.0
TOTAL	**100**

A process for example 2 or 3;

a) Mixing benidipine hydrochloride, lactose monohydrate and pregelatinized starch and then sieving,
b) Dissolving polyvinylpyrrolidone in water,
c) Granulating the mixture at step (a) with the granulation solution at step (b),
d) Sieving the wet granule and drying the wet granule at fluid bed dryer,
e) Sieving the dry granule,
f) Adding magnesium stearate and then mixing,
g) Compressing the prepared mixture to form tablets
h) Coating these tablets with coating agents.

CLAIMS

1. A film coated tablet comprising benidipine in the form of the free base or in the form of pharmaceutically acceptable salts and at least one pharmaceutically acceptable excipient, wherein the tablet has a hardness of between 20 N and 70 N.

2. The film coated tablet according to claim 1, wherein benidipine is in the form of is present as benidipine hydrochloride.

3. The film coated tablet according to claim 1, wherein the amount of benidipine hydrochloride is between 1.0% and 10.0% by weight in the total formulation.

4. The film coated tablet according to claim 1, wherein at least one pharmaceutically acceptable excipient which is selected from the group comprising fillers, binders, disintegrants, lubricants/glidants, coating agents or mixtures.

5. The film coated tablet according to claim 4, wherein fillers are selected from the group comprising lactose monohydrate, microcrystalline cellulose, lactose, mannitol, spray-dried mannitol, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof.

6. The film coated tablet according to claim 5, wherein the filler is lactose monohydrate.

7. The film coated tablet according to claim 5, wherein the amount of fillers is between 70.0% and 88.0% by weight in the total formulation.

8. The film coated tablet according to claim 4, wherein binders are selected from the group comprising polyvinylpyrrolidone, sodium carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, natural gums, sucrose, sodium alginate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxy methyl cellulose, methyl cellulose, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, alginate, alginic acid, xanthan gum, hyaluronic acid, polysaccharides, carbomer, poloxamer, polyacrylamide, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

9. The film coated tablet according to claim 4, wherein disintegrants are selected from the group comprising pregelatinized starch, crospovidone, croscarmellose sodium, starch, low-substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose,

calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, low substituted hydroxypropyl cellulose, sodium alginate, corn starch, sodium starch glycolate, sodium glycine carbonate or mixtures thereof.

10. The film coated tablet according to claim 9, wherein the disintegrant is pregelatinized starch.

11. The film coated tablet according to claim 1, wherein benidipine in the form of the free base or in the form of pharmaceutically acceptable salts has a d (0.5) particle size less than 30 µm, preferably less than 25 µm, preferably less than 20 µm, preferably less than 15 µm, preferably less than 10 µm.

12. The film coated tablet according to claim 1, wherein benidipine in the form of the free base or in the form of pharmaceutically acceptable salts has a d (0.9) particle size less than 50 µm, preferably less than 35 µm, preferably less than 25 µm, preferably less than 18 µm.

13. The film coated tablet according to claim 1, wherein the film coated tablet comprising;

- Benidipine hydrochloride
- Lactose monohydrate
- Polyvinylpyrrolidone

14. A process for the preparation of the film coated tablet comprising benidipine comprises the following steps:

a) Mixing benidipine hydrochloride, at least one filler and at least one disintegrant and then sieving,
b) Dissolving at least one binder in water,
c) Granulating the mixture at step (a) with the granulation solution at step (b),
d) Sieving the wet granule and drying the wet granule at fluid bed dryer,
e) Sieving the dry granule,
f) Adding at least one lubricant/glidant and then mixing,
g) Compressing the prepared mixture to form tablets
h) Coating these tablets with coating agents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2022/051469

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/20 (2006.01)i; A61K 47/26 (2006.01)i; A61K 47/32 (2006.01)i; A61K 47/36 (2006.01)i; A61P 9/12 (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 9/20; A61K 47/26; A61K 47/32; A61K 47/36; A61P 9/12

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 112807284 A (SHANDONG WELLSO PHARMACEUTICAL CO LTD) 18 May 2021 (2021-05-18) Abstract, claims, examples	1-14
X	JP 2012162502 A (FUJIFILM CORP) 30 August 2012 (2012-08-30) Claims	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
08 February 2023	**08 February 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**	**Nurgül SIKI** Telephone No. **+903123031622**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/TR2022/051469

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
CN 112807284 A	18 May 2021	NONE	
JP 2012162502 A	30 August 2012	JP 5710301 B2	30 April 2015
		WO 2012108266 A1	16 August 2012