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(71) Applicant: **AMMAN PHARMACEUTICAL INDUSTRIES COMPANY** [JO/JO]; A3 street, King Abdullah II industrial city, Amman, 11512 (JO).

(72) Inventors: **KAKISH, Hanan**; Amman, 11512 (JO). **ABU ALI, Sharifeh**; Amman, 11512 (JO). **ABUSHAMALAH, Areej**; Amman, 11512 (JO). **ALATRASH, Fadi**; Amman (JO).

(74) Agent: **THE INTELLECTUAL PROPERTY COMMERCIALIZATION OFFICE/ ROYAL SCIENTIFIC SOCIETY**; Ahmed Al Tarawneh Street, Amman, P.O.Box 1438 Amman 11941 (JO).

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(54) **Title:** A PHARMACEUTICAL COMPOSITION OF SILDENAFIL AND A FORMULATION THEREOF

(57) **Abstract:** There is provided a pharmaceutical composition including sildenafil or a pharmaceutically acceptable salt thereof, a gelling and thickening agent, a water miscible co-solvent, a taste masking agent, a sweetening agent, a flavoring agent, a neutralizing agent, and water. There is also provide an oral gel formulation containing the pharmaceutical composition, for use in treating erectile dysfunction as a bioequivalent formulation to the commercially available reference film coated 100 mg tablets.

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A PHARMACEUTICAL COMPOSITION OF SILDENAFIL AND A FORMULATION THEREOF

TECHNICAL FIELD

[01] The present disclosure relates to novel pharmaceutical compositions and formulations for treating erectile dysfunction, and more particularly to a novel pharmaceutical composition and formulation of sildenafil or a pharmaceutically acceptable salt thereof.

BACKGROUND INFORMATION

[02] Penile erection is a complicated physiological process that involves the blood vessel system, as well as the endocrine and nervous systems. Patients suffering from erectile dysfunction ("ED") are increasing due to many reasons such as the expanded life span, the increase of adult diseases, change of diet, the increase of industrial and traffic accidents, and the increase of mental stress and physical fatigue resulting from complicated modern life could contribute to aggravate this manifestation.

[03] Sildenafil is one of the widely known medications that are used to temporarily treat ED, and is mainly formulated as oral tablets or as intravenous injection. Sildenafil is a selective inhibitor of cyclic guanosine monophosphate ("cGMP") specific phosphodiesterase type 5 ("PDE5") which regulates the blood flow in the penis.

[04] Some adults do not tolerate taking medications in solid oral dosage forms for reasons such as swallowing difficulties. Therefore, they tend to take medications formulated in a dosage form that are more tolerable for them. Attempts to provide alternative formulations for Sildenafil have been conducted in the art. For instance, Kamagra, is a commercially available oral gel formulation of Sildenafil, but no clinical or pharmacokinetic studies were conducted to show the bioavailability of Sildenafil compared to the approved tablets dosage form. Therefore, its safety or efficacy are not proven.

[05] Other attempts have been done in the art to provide a topical gel formulation of Sildenafil for other uses. For example, a study conducted by Koray Gusroy et al. in 2013 discloses a topical gel formulation of Sildenafil for wound healing. As another

example, a study by Shabaan K. Osman was conducted in 2016 to provide a topical gel formulation of sildenafil.

[06] The prior art solutions do not provide an oral gel formulation of sildenafil or any of its pharmaceutically acceptable salts that provide a similar bioavailability of sildenafil in the human body compared to 100 mg film coated tablet.

SUMMARY

[07] Therefore, it is an object of the present disclosure to provide a pharmaceutical composition of sildenafil or a pharmaceutically acceptable salt thereof.

[08] It is another object of the present disclosure to provide an oral gel formulation of the pharmaceutical composition of sildenafil or its pharmaceutically acceptable salt.

[09] In aspects of the present disclosure, the oral gel formulation provides a similar bioavailability of sildenafil in a human body compared to a commercially available approved 100 mg film-coated tablet of sildenafil.

[010] In aspects of the present disclosure, the pharmaceutical composition may include sildenafil or a pharmaceutically acceptable salt thereof, a gelling and thickening agent, a water miscible co-solvent, a taste masking agent, a sweetening agent, a flavoring agent, a neutralizing agent, and water.

[011] In some aspects, the pharmaceutical composition may further include a coloring agent.

[012] In aspects of the present disclosure, the pharmaceutically acceptable salt may include sildenafil citrate.

[013] In aspects of the present disclosure, the gelling and thickening agent may be a carbomer polymer having a grade selected from a group including 71G, 971, 971P, 974, 974P, 934, 934P, or combinations thereof.

[014] In aspects of the present disclosure, the water miscible co-solvent may be propylene glycol, glycerin, or a combination thereof.

[015] In aspects of the present disclosure, the taste masking agent may be a sorbitol solution, mannitol, or a combination thereof.

[016] In aspects of the present disclosure, the sweeting agent may be sucralose, sodium saccharine, or a combination thereof.

[017] In aspects of the present disclosure, the flavoring agent may be peppermint oil, orange oil, or a combination thereof or any other suitable flavoring agent.

[018] In aspects of the present disclosure, the neutralizing agent may be sodium hydroxide, potassium hydroxide, ethanolamine, or a combination thereof.

[019] In some aspects, the pharmaceutical composition may include from about 1.5% to about 3.5% by weight sildenafil or its pharmaceutically acceptable salt.

[020] In some aspects, the pharmaceutical composition may include from about 0.5% to about 2% by weight gelling and thickening agent.

[021] In some aspects, the pharmaceutical composition may include from about 15% to about 30% by weight water miscible co-solvent.

[022] In some aspects, the pharmaceutical composition may include from about 5% to about 10% by weight taste masking agent.

[023] In some aspects, the pharmaceutical composition may include from about 0.01% to about 0.4% by weight favoring agent.

[024] In some aspects, the neutralizing agent adjusts the pH of the pharmaceutical composition from about 4 to about 8.

[025] In some aspects, the pharmaceutical composition may include from about 0.005% to about 0.02% by weight coloring agent.

[026] In aspects of the present disclosure, the pharmaceutical composition is for use in treating ED.

BRIEF DESCRIPTION OF THE DRAWINGS

[027] The present disclosure will now be described with reference to the accompanying drawing, which illustrates embodiments of the present disclosure, and in which:

[028] FIG. 1 illustrates a flowchart of a method of preparing an oral gel formulation of a composition of sildenafil or a pharmaceutically acceptable salt thereof in accordance with embodiments of the present disclosure.

[029] FIG. 2 illustrates mean plasma concentrations of sildenafil in human blood plasma after taking the oral gel formulation prepared in accordance with embodiments of the present disclosure and the commercially available Reference sildenafil 100 mg film-coated tablets.

DETAILED DESCRIPTION

[030] Embodiments of the present disclosure provide a pharmaceutical composition for treating ED, the composition may include sildenafil or a pharmaceutically acceptable salt thereof, a gelling and thickening agent, a water miscible co-solvent, a taste masking agent, a sweetening agent, a flavoring agent, a neutralizing agent, and water. In some embodiments, the pharmaceutical composition may further include a coloring agent.

[031] In some embodiments of the present disclosure, the pharmaceutically acceptable salt may include sildenafil citrate.

[032] In embodiments of the present disclosure, the gelling and thickening agent may be a carbomer polymer having a grade selected from a group including 71G, 971, 971P, 974, 974P, 934, 934P, or combinations thereof.

[033] In general, carbomers designated with the letter ‘P’, e.g. Carbopol 971P, are the pharmaceutical grade polymers for oral or mucosal contact products. Table (1) illustrates characteristics of possible carbomer polymers.

Table (1)

Carbopol Polymer	Polymerization/Residual solvent	Viscosity, cP (0.5 wt% at pH 7.5)
71G NF	Ethyl Acetate	4,000 - 11,000
971P NF	Ethyl Acetate	4,000 - 11,000
974P NF	Ethyl Acetate	29,400 - 39,400
934P NF	Benzene	29,400 - 39,400

[034] In embodiments of the present disclosure, the water miscible co-solvent may be propylene glycol, glycerin, or a combination thereof.

[035] In embodiments of the present disclosure, the taste masking agent may be a sorbitol solution, mannitol, or a combination thereof.

[036] In embodiments of the present disclosure, the sweeting agent may be sucralose, sodium saccharine, or a combination thereof.

[037] In embodiments of the present disclosure, the flavoring agent may be peppermint oil, orange oil, or a combination thereof, or any other suitable flavoring agent.

[038] In embodiments of the present disclosure, the neutralizing agent may be sodium hydroxide, potassium hydroxide, ethanolamine, or a combination thereof.

[039] In some embodiments, the pharmaceutical composition may include from about 1.5% to about 3.5% by weight sildenafil or its pharmaceutically acceptable salt.

[040] In some embodiments, the pharmaceutical composition may include from about 0.5% to about 2% by weight gelling and thickening agent.

[041] In some embodiments, the pharmaceutical composition may include from about 15% to about 30% by weight water miscible co-solvent.

[042] In some embodiments, the pharmaceutical composition may include from about 5% to about 10% by weight taste masking agent.

[043] In some embodiments, the pharmaceutical composition may include from about 0.1% to about 1.0% by weight sweetening agent.

[044] In some embodiments, the pharmaceutical composition may include from about 0.01% to about 0.4% by weight favoring agent.

[045] In some embodiments, the neutralizing agent adjusts the pH of the pharmaceutical composition from about 4 to about 8.

[046] In some embodiments, the pharmaceutical composition may include from about 0.005% to about 0.02% by weight coloring agent.

[047] In embodiments of the present disclosure, the pharmaceutical composition is for use in treating ED.

[048] Embodiments of the present disclosure further provide an oral gel formulation including the pharmaceutical composition as described above.

[049] The disclosure is now further illustrated on the basis of examples and a detailed description from which further features and advantages may be taken. It is to be noted that the following explanations are presented for the purpose of illustrating and description only; they are not intended to be exhaustive or to limit the disclosure to the precise form disclosed.

Example 1

Preparation of the oral gel formulation

[050] Reference in this example is made to FIG. 1, which illustrates a flowchart of a method of preparing an oral gel formulation of a pharmaceutical composition including sildenafil or a pharmaceutically acceptable salt thereof, the method may include the steps of hydrating a gelling and thickening agent (0.8-1.2%) to provide a first mixture (process block 1-1); dispersing the sildenafil or its pharmaceutical acceptable salt (citrate salt around 2.8%) in a water miscible co-solvent (23-28%) to provide a second mixture (process block 1-2); dissolving a sweetening agent (0.3-0.5%) , a taste masking agent (6-8%), a flavoring agent (0.02-0.2%), a neutralizing agent, and a coloring agent (0.007-0.015%) in water to provide a third mixture (process block 1-3); and mixing the first, second, and third mixtures together to obtain an oral gel, followed by adjusting the pH to of the gel to become within a range from about 5 to about 7 (process block 1-4).

Example 2

Bioequivalence of the oral gel formulation with the film-coated tablets of sildenafil

[051] Reference in this example is being made to FIG. 2, which is showing the bioavailability of sildenafil in a human blood plasma after taking the oral gel formulation prepared in accordance with embodiments of the present disclosure and the commercially available reference sildenafil 100 mg film-coated tablets (VIAGRA).

[052] A comparative randomized, single dose, two-way crossover open label study to determine the bioequivalence of sildenafil 100 mg after an oral administration to healthy adults under fasting conditions was conducted to compare the absorption and disposition kinetics of the oral gel formulation of the present disclosure relative to the commercially available reference 100 mg film-coated tablet. Each healthy male subject received an oral dose of the assigned formulation, according to a randomization scheme, administered with 240 ml of water. Subject assigned for the oral gel formulation have administered the gel quantity filled in the sachet to have an equivalent amount of 100 mg Sildenafil as per the film coated tablet of the reference product, Viagra tablets. The two periods were separated by at least seven-day washout interval from the first study drug administration. 30 subjects were admitted the night before the study drug administration, supervised for at least 10 hours of overnight fasting, and confined until collecting the 24-hour sample. Safety/adverse events, laboratory evaluation, ECG, physical examination and vital signs. The study was conducted according to the "Declaration of Helsinki".

[053] Point estimates and the 90% Confidence Intervals for sildenafil transformed ratios (Test/Reference) were within the accepted limits of 80.00%-125.00% for C_{max}: 92.51 (80.90-105.79) % and for $AUC_{0\rightarrow t}$: 97.01 (90.99- 103.43)% showing bio-equivalency of the oral gel formulation to the commercially available reference film coated 100 mg tablets. Table 2 illustrates the summary of the pharmacokinetics parameters of sildenafil from the oral gel Formulation compared to reference available tablets after a single dose administration for both treatments; wherein Test Product refers to the oral gel formulation of 100 mg sildenafil prepared in accordance with embodiments of the present disclosure Reference Product refers to VIAGRA 100 mg sildenafil film coated tablet.

Table (2)

Pharmacokinetic Parameter	Treatment (Mean ± SD)	
	TEST Product	REFERENCE Product
C_{max} (ng/ml)	488.593±209.82	519.012±236.06
$AUC_{0\rightarrow t}$ (ng.h/ml)	1731.4±634.64	1756.0±622.54
$AUC_{0\rightarrow\infty}$ (ng.h/ml)	1794.1±660.32	1811.1±635.59
T_{max} (h)	0.89±0.50	1.19±0.78
$t_{½el}$ (h)	4.21±1.95	4.71±1.69
K_{el} (1/h)	0.1925±0.07	0.1705±0.07
$AUC_{0\rightarrow t}/AUC_{0\rightarrow\infty}$%	96.54±1.82	96.89±1.61

[054] FIG. 2 illustrates Sildenafil means after a single dose administration for both treatments; the oral gel formulation of 100 mg sildenafil prepared in accordance with embodiments of the present disclosure and the commercially available reference sildenafil 100 mg film-coated tablets. The point estimates mentioned above for C_{max} and for $AUC_{0\rightarrow t}$ proves comparable plasma concentrations of sildenafil. Since plasma levels are a meaningful surrogate for pharmacodynamic action and adverse events, this demonstrates that an equivalent therapeutic activity and tolerance is to be expected from the oral gel formulation as compared to film-coated tablets.

Example 3

Stability of the oral gel formulation

[055] Stability studies were conducted in accordance to ICH Q1A (R2). Long term stability for at least 24 months at 30°C and 35% relative humidity was done in addition to accelerated stability for 6 months conducted at 40°C and not more than 25% relative humidity on three batches to confirm the product stability.

[056] The assay results of sildenafil in samples stored at different storage conditions remained within the specifications throughout the time periods monitored and there was no significant decrease in its concentration throughout the time periods monitored. The results of determination of degradation products of sildenafil in the tested samples show that the percentage of these products were below the assigned allowable limits at the long term & accelerated stability studies. The oral gel formulation was also shown to be microbially stable with no significant decrease seen in the dissolution of

sildenafil from the oral gel during the 24 months long term stability or the accelerated stability. Tables 3 and 4 summarize the stability data at different conditions.

Table (3)

Stability at 30 ° C, 35% RH																		
Months	**Assay%** 90% – 110%			**Dissolution** NLT 80% at 15 minutes			**Degradation products of Sildenafil**									**Microbial testing for oral gel**		
							Sildenafil N-oxide NMT 0.2%			**Any unknown impurity** NMT 0.2%			**Total Degradation** NMT 0.5%					
	Batch 1	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**
0	105	100.	99	99	93	91	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
3	105	101	98	98	98	89	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
6	104	101	97	98	92	95	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
9	102	99	97	97	100	95	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
12	103	99	98	99	97	94	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
18	103	99	97	99	91	91	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
24	102	99	98	94	94	93	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass

*** BRL: Below Reporting limits.**

Table (4)

Stability at 40 ° C, NMT 25% RH																		
Months	**Assay%** 90% – 110%			**Dissolution** NLT 80% at 15 minutes			**Degradation products of Sildenafil**									**Microbial testing for oral gel**		
							Sildenafil N-oxide NMT 0.2%			**Any unknown impurity** NMT 0.2%			**Total Degradation** NMT 0.5%					
	Batch 1	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**
0	105	100	99	99	94	91	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
3	103	101	97	94	92	88	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass
6	102	100	98	97	97	89	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	BRL*	pass	pass	pass

*** BRL: Below Reporting limits.**

[057] The analytical methods used to determine the stability of the oral gel formulation were stability indicating validated methods capable of separating the intact compound of interest from decomposition products or from potentially interfering substances. The used methods were the USP pharmacopeia methods used for the sildenafil tablets.

[058] Tables 5 and 6 summarize the validation results of the method of analysis used for assay and degradation, respectively.

Table (5)

Validation parameters	**Limits**	**Results**	
Specificity	Peak purity= 980-100 Resolution between active Substance and adjacent peaks <2	Passed	
Linearity &Range	Range: (50-150) % of the test Conc. % intercept @ Target conc.: NMT 5% R: ≥ 0.999	Linear behavior (50-150) % of the test Conc. % intercept @ Target conc.: NMT 1% R=1.000	
Precision	RSD <2%	**Method precision**	RSD <1
		intermediate precision	RSD <1
Accuracy	average Recovery for each level (98-102)% individual Recovery (97-103)%	**Accuracy 50%**	99.2%
		Accuracy 100%	99.8%
		Accuracy 150%	100.2%
Robustness	The evaluation of System Suitability (SST) parameters	**Influence of mobile phase Flow Rate**	System Suitability meets requirements
		Influence of column Temperature	System Suitability meets requirements
Stability In Solution	% Recovery or % Assay (98-102)%	Standard Showed Stability for 48hours Sample Showed Stability for 24hours	
Filter Compatibility	% Recovery or % Assay (98-102)%	Filtered and unfiltered samples meets requirements	
System Suitability	• % RSD ≤ 2%for 5 replicates • Number of theoretical plates ≥2000 Asymmetry ≤ 2	System Suitability meets requirements	

Table (6)

Validation parameters	Limits	Results	
Specificity	Peak purity= 980-100 Resolution between active Substance and adjacent peaks <2	Passed	
Linearity &Range	Range: (LOQ -150) % of the test Conc. % intercept @ Target conc.: NMT 10% R: ≥ 0.99	Linear behavior (LOQ -150) % of the test Conc. % intercept @ Target conc.: NMT 0.45% R=1.000	
Precision	RSD <10%	**Method precision**	Sildenafil N-Oxide RSD% <5
			Sildenafil as citrate RSD%<4
	overall RSD <10%	**intermediate precision**	Sildenafil N-Oxide overall RSD% <4
			Sildenafil as citrate overall RSD% <3
Accuracy	average Recovery for each level (80-120)% individual Recovery (70-130)%	**Accuracy at LOQ**	103%
		Accuracy 50%	90.5%
		Accuracy 100%	105.3%
		Accuracy 150%	87.3%
Robustness	The evaluation of System Suitability (SST) parameters	**Influence of mobile phase Flow Rate**	System Suitability meets requirements
		Influence of column Temperature	System Suitability meets requirements
LOQ	S/N ratio (10:1)	Concentration=0.125 µg / ml S/N ratio (10.4 :1)	
LOD	S/N ratio (3:1)	Concentration=0.06 µg / ml S/N ratio (4:1)	
Stability In Solution	Recovery for standard must be (98-102) % Recovery for sample must be (80-120) %	Standard Showed Stability for 24hours Sample Showed Stability for 24hours	
Filter Compatibility	% Recovery or % Assay (80-120)%	Filtered and unfiltered samples meets requirements	
System Suitability	• % RSD ≤ 3%for 6 replicates • Number of theoretical plates ≥2000 • Asymmetry ≤ 2 • Resolution should be NLT 2.6 between Sildenafil N-Oxide and Sildenafil.	System Suitability meets requirements	

[059] While embodiments of the present disclosure have been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various additions, omissions, and modifications can be made without departing from the spirit and scope thereof.

[060] In describing and claiming the present invention, the following terminology is used.

[061] The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[062] As used herein, a plurality of items, structural elements, compositional elements, and/or materials may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a defector equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

[063] Amounts, and other numerical data may be presented herein in a range format. It is to be understood that such range format is used merely for convenience and brevity and should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. For example, a numerical range of approximately 1 to approximately 4.5 should be interpreted to include not only the explicitly recited limits of 1 to approximately 4.5, but also to include individual numerals such as 2, 3, 4, and sub-ranges such as 1 to 3, 2 to 4, etc. The same principle applies to ranges reciting only one numerical value, such as "less than approximately 4.5," which should be interpreted to include all of the above-recited values and ranges. Further, such an interpretation should apply regardless of the breadth of the range or the characteristic being described.

[064] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the presently disclosed subject matter belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or

testing of the presently disclosed subject matter, representative methods, devices, and materials are now described.

[065] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently disclosed subject matter.

[066] As used herein, the term "about", when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments ±20%, in some embodiments ±10%, in some embodiments ±5%, in some embodiments ±1%, in some embodiments ±0.5%, and in some embodiments ±0.1% from the specified amount, as such variations are appropriate to perform the disclosed method.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising sildenafil or a pharmaceutically acceptable salt thereof, a gelling and thickening agent, a water miscible co-solvent, a taste masking agent, a sweetening agent, a flavoring agent, a neutralizing agent, and water.

2. The pharmaceutical composition of claim 1, further comprising a coloring agent.

3. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable salt comprises sildenafil citrate.

4. The pharmaceutical composition of claim 1, wherein the gelling and thickening agent comprises a carbomer polymer having a grade selected from a group comprising 71G, 971, 971P, 974, 974P, 934, 934P, or combinations thereof.

5. The pharmaceutical composition of claim 1, wherein the water miscible co-solvent comprises propylene glycol, glycerin, or a combination thereof.

6. The pharmaceutical composition of claim 1, wherein the taste masking agent comprises a sorbitol solution, mannitol, or a combination thereof.

7. The pharmaceutical composition of claim 1, wherein the sweeting agent comprises sucralose, sodium saccharine, or a combination thereof.

8. The pharmaceutical composition of claim 1, wherein the flavoring agent comprises peppermint oil, or orange oil or a combination thereof, or any other suitable flavoring agent.

9. The pharmaceutical composition of claim 1, wherein the neutralizing agent comprises sodium hydroxide, potassium hydroxide, ethanolamine, or a combination thereof.

10. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 1.5% to about 3.5% by weight sildenafil or its pharmaceutically acceptable salt.

11. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 0.5% to about 2% by weight gelling and thickening agent.

12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 15% to about 30% by weight water miscible co-solvent.

13. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 5% to about 10% by weight taste masking agent.

14. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 0.01% to about 0.4% by weight favoring agent.

15. The pharmaceutical composition of claim 1, the neutralizing agent adjusts the pH of the pharmaceutical composition from about 4 to about 8.

16. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition may include from about 0.005% to about 0.02% by weight coloring agent.

17. Use of the pharmaceutical composition of claim 1 for treating erectile dysfunction.

18. An oral gel formulation comprising the pharmaceutical composition of claim 1.

AMENDED CLAIMS
received by the International Bureau on 8 September 2022 (08.09.2022)

Claims

[Claim 1] A pharmaceutical composition comprising from about 1.5% to about 3.5% by weight sildenafil or a pharmaceutically acceptable salt thereof, a gelling and thickening agent, a water miscible co-solvent, a taste masking agent, a sweetening agent, a flavoring agent, a neutralizing agent, and water to form an oral gel formulation that provides a similar bioavailability of sildenafil in a human body compared to a commercially available approved 100 mg film-coated tablet of sildenafil.

[Claim 2] The pharmaceutical composition of claim 1, further comprising a coloring agent.

[Claim 3] The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable salt comprises sildenafil citrate.

[Claim 4] The pharmaceutical composition of claim 1, wherein the gelling and thickening agent comprises a carbomer polymer having a grade selected from a group comprising 71G, 971, 971P, 974, 974P, 934, 934P, or combinations thereof.

[Claim 5] The pharmaceutical composition of claim 1, wherein the water miscible co-solvent comprises propylene glycol, glycerin, or a combination thereof.

[Claim 6] The pharmaceutical composition of claim 1, wherein the taste masking agent comprises a sorbitol solution, mannitol, or a combination thereof.

[Claim 7] The pharmaceutical composition of claim 1, wherein the sweeting agent comprises sucralose, sodium saccharine, or a combination thereof.

[Claim 8] The pharmaceutical composition of claim 1, wherein the flavoring agent comprises peppermint oil, or orange oil or a combination thereof, or any other suitable flavoring agent.

[Claim 9] The pharmaceutical composition of claim 1, wherein the neutralizing agent comprises sodium hydroxide, potassium hydroxide, ethanolamine, or a combination thereof.

[Claim 10] The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 0.5% to about 2% by weight gelling and thickening agent.

[Claim 11] The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 15% to about 30% by weight water miscible co-solvent.

[Claim 12] The pharmaceutical composition of claim 1, wherein the pharma-

ceutical composition comprises from about 5% to about 10% by weight taste masking agent.

[Claim 13] The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from about 0.01% to about 0.4% by weight favoring agent.

[Claim 14] The pharmaceutical composition of claim 1, the neutralizing agent adjusts the pH of the pharmaceutical composition from about 4 to about 8.

[Claim 15] The pharmaceutical composition of claim 1, wherein the pharmaceutical composition may include from about 0.005% to about 0.02% by weight coloring agent.

[Claim 16] Use of the pharmaceutical composition of claim 1 for treating erectile dysfunction.

[Claim 17] An oral gel formulation comprising the pharmaceutical composition of claim 1.

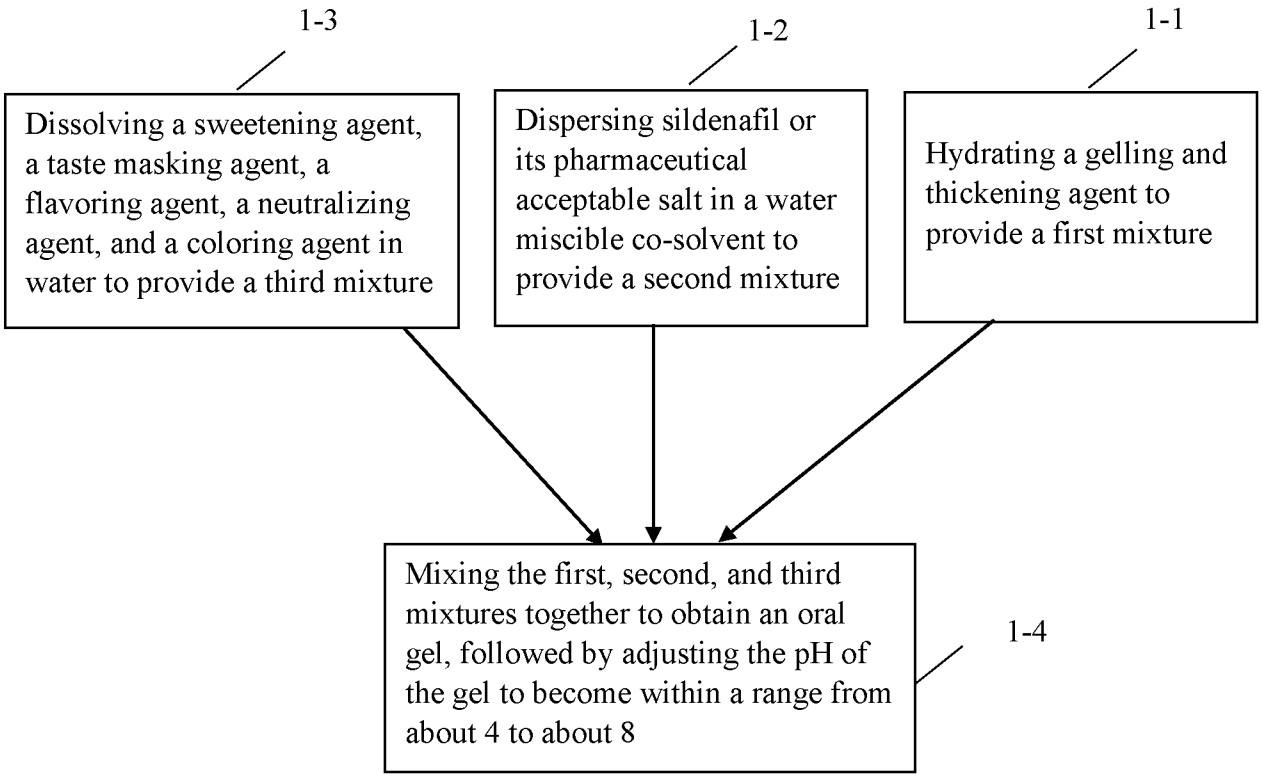
1-3
1-2
1-1
Dissolving a sweetening agent, a taste masking agent, a flavoring agent, a neutralizing agent, and a coloring agent in water to provide a third mixture
Dispersing sildenafil or its pharmaceutical acceptable salt in a water miscible co-solvent to provide a second mixture
Hydrating a gelling and thickening agent to provide a first mixture
Mixing the first, second, and third mixtures together to obtain an oral gel, followed by adjusting the pH of the gel to become within a range from about 4 to about 8
1-4

FIG. 1

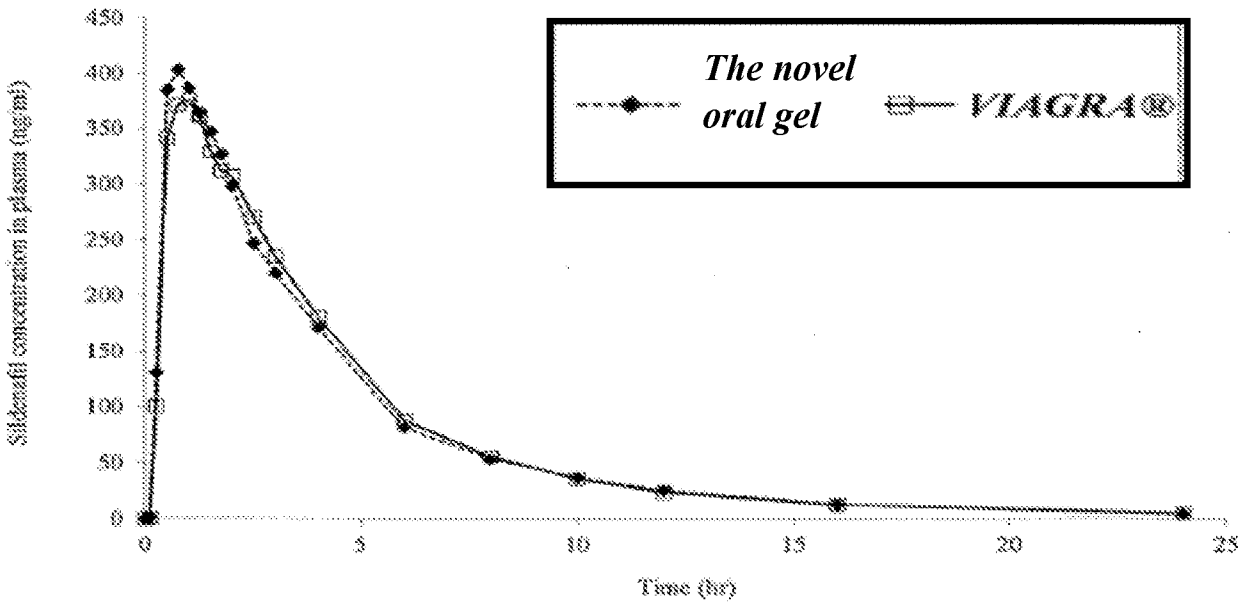
The novel oral gel
VIAGRA®
Sildenafil concentration in plasma (ng/ml)
Time (hr)
0
50
100
150
200
250
300
350
400
450
0
5
10
15
20
25

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JO 21/50012

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/05; A61K 31/19; A61K 31/198 (2021.01)

CPC - A61K 31/05; A61K 31/19; A61K 31/198

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2021/0052591 A1 (FTF PHARMA PRIVATE LIMITED) 25 February 2021 (25.02.2021) - entire document especially para [0215], [0141], [0061], [0018], [0126], [0002], [0127], and [0038]	1-18
A	US 2011/0244050 A1 (FIORE) 6 October 2011 (06.10.2011) - entire document	1-18
A	US 2005/0042177 A1 (RYDE ET AL.) 24 February 2005 (24.02.2005) - entire document	1-18
A	US 2019/0282591 A1 (BLUE GOOSE DRUGS INC.) 19 September 2019 (19.09.2019) - entire document	1-18
A	US 2020/0222544 A1 (AQUESTIVE THERAPEUTICS, INC.) 16 July 2020 (16.07.2020) - entire document	1-18
A	US 2016/0287593 A1 (INSYS DEVELOPMENT COMPANY, INC.) 6 October 2016 (06.10.2016) - entire document	1-18

☐ 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 November 2021 (19.11.2021)	DEC 20 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300