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(54) Title: PHARMACEUTICAL COMPOSITION OF PRAMIPEXOLE

(57) Abstract: A pharmaceutical composition comprising pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof, sugar alcohol (s) and a pharmaceutically acceptable carrier medium substantially free of polyvinyl pyrrolidone.

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PHARMACEUTICAL COMPOSITION OF PRAMIPEXOLE

The present invention relates to a pharmaceutical composition comprising pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof.

BACKGROUND OF THE INVENTION

Pramipexole, (S)-2-amino-4, 5, 6, 7 - tetrahydro-6-(propylamino) benzole, is a non ergot dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 subfamily of dopamine receptors. It is indicated in the treatment of signs and symptoms of idiopathic Parkinson's disease.

United States Patent number 4,886,812 ('812 patent) claims the markush class of compounds covering pramipexole. However, the patent does not teach or suggest the use of specific excipients to prepare stable pramipexole composition.

Pramipexole is available in five strengths (0.125, 0.25, 0.50, 1.00 and 1.50 mg per tablet), marketed under the brand name of Mirapex® having mannitol, corn starch, colloidal silicon dioxide, povidone and magnesium stearate as the pharmaceutical excipients. We have found that compositions prepared according to the ingredients of Mirapex® (Physician Desk Reference, Edition 54, page no 2467), when stored at a temperature of about 40° C $\pm$ 2 ^{0}C and relative humidity of about 75 % $\pm$ 5 % for the period of three months showed a drop in the content of pramipexole dihydrochloride monohydrate, to below 95 % of the labeled amount.

United States patent application number 20060051417 ('417 patent application) discloses an extended release tablet formulation comprising pramipexole or its pharmaceutically acceptable salt in a matrix comprising of pregelatinised starch and an anionic polymer.

United States patent application number 20070129329 ('329 patent application) discloses a stabilized pharmaceutical composition of pramipexole comprising one or more dextrin.

SUMMARY OF INVENTION

The present invention provides a pharmaceutical composition comprising a mixture of pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof, sugar alcohol (s) and a pharmaceutically acceptable carrier medium substantially free of polyvinyl pyrrolidone.

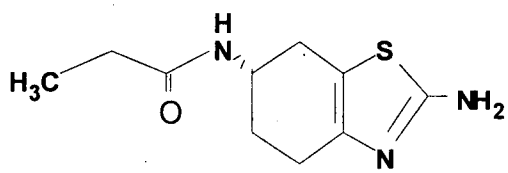
DETAILED DESCRIPTION OF THE INVENTION

The term 'labeled amount' as used herein, refers to the amount of therapeutically active ingredient present in a pharmaceutical product. When a unit dose of the therapeutically active ingredient is present in the pharmaceutical product, it is often termed as a unit dosage form. Detailed monographs, often called label, of the

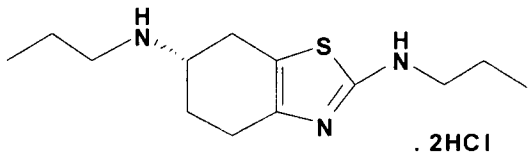
marketed dosage form contain its description, pharmacology, clinical studies, indication, contraindications, warnings, precautions, adverse events, dosage and administration and other details of the marketed product. The dosage form may be available in various doses, specified in the label, for example, pramipexole tablets are available as 0.125, 0.25, 0.5, 1.0 and 1.5 mg of pramipexole dihydrochloride monohydrate. These various doses in the tablets are herein referred to as the 'labeled amount' of pramipexole dihydrochloride monohydrate.

The dosage form should be chemically 'stable' and retain the labeled amount of the therapeutically active ingredient upon storage and the impurities in the pharmaceutical product should remain low. We have found a 'stable' pharmaceutical composition comprising a mixture of pramipexole or its pharmaceutically acceptable salts or hydrates or solvates thereof, sugar alcohol (s) and a pharmaceutically acceptable carrier medium substantially free of polyvinyl pyrrolidone. These compositions when stored in high density polyethylene containers at a temperature of about 40^0 C $\pm$ 2^0 C and relative humidity of about 75 % $\pm$ 5 % for a period of three months, showed the content of pramipexole dihydrochloride monohydrate ranging from about 95 % to about 105 % by weight of the labeled amount of pramipexole dihydrochloride monohydrate and the total impurities (known and unknown) were less than 1 % of the labeled amount of pramipexole dihydrochloride monohydrate. Particularly the content of the known impurities, i.e, impurity A (I), impurity B (II) and Impurity C (III) respectively did not increase when the pharmaceutical composition of the present invention was stored at a temperature of about 40^0C $\pm$ 2^0 C and relative humidity of about 75 % $\pm$ 5 % for about three months. On the contrary, we found a marginal increase in content of impurity A, impurity B and impurity C in compositions containing polyvinyl pyrrolidone. Particularly the unknown impurities increased to greater extent in the presence of polyvinyl pyrrolidone compared to compositions of the present invention.

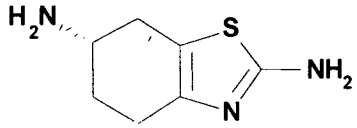
The known impurities, as described above were identified by chemical structures I, II and III and were termed as impurity A, impurity B and impurity C respectively. Their structures are given as follows:



I



II



III

According to one embodiment of the present invention, these impurities were separated by High performance liquid chromatography (HPLC) and quantified by measuring the absorption in the ultraviolet region. Although HPLC was preferred, any other suitable analytical method may also be employed to determine the pramipexole content and to quantify the known and unknown impurities.

Accordingly, the composition of the present invention comprises a mixture of pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof, sugar alcohol (s) and a pharmaceutically acceptable carrier medium substantially free of polyvinyl pyrrolidone.

The term 'mixture' as used herein means pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof is intimately blended or is in physical contact with the pharmaceutically acceptable carrier medium.

The pharmaceutical composition of the present invention is considered to be 'stable' when the pharmaceutical composition upon storage in suitable containers with or without desiccants at a temperature of about 40^0 C ± 2^0 C and a relative humidity of about 75 % ± 5 %, shows the pramipexole dihydrochloride monohydrate content in the range of about 95 % to about 105 % of the labeled amount and total impurities are less than about 1 % by weight of pramipexole dihydrochloride monohydrate.

The composition of the present invention comprises pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof. The pharmaceutically acceptable acid salts of pramipexole, include, but are not limited to, acid addition salts of inorganic acids or organic acids such as hydrobromide, sulfuric, phosphoric, lactic, citric, tartaric, succinic, maleic and formic acid and the like. In preferred embodiment of the present invention, the pramipexole is used as the dihydrochloride salt, more preferably pramipexole is used as dihydrochloride monohydrate.

In this embodiment, the amount of pramipexole dihydrochloride monohydrate ranges from about 0.05 mg to about 2.0 mg per tablet. More preferably, the amount of pramipexole dihydrochloride monohydrate ranges from about 0.09 mg to about 1.8 mg per tablet.

The composition of the present invention comprises a pharmaceutically acceptable carrier medium substantially free of polyvinyl pyrrolidone. Although it may be possible to prepare a stable pharmaceutical composition with trace amount of polyvinyl pyrrolidone, preferably the composition is completely devoid of polyvinyl pyrrolidone.

According to the present invention, the pharmaceutical composition comprises sugar alcohol (s) as one of the fillers or diluents. The sugar alcohols that are used may be in any stereoisomers or geometric isomers or/and optical isomers forms. They may be straight chain or cyclic in nature. The straight chain sugar alcohols may be trihydric to hexahydric sugar alcohol. Examples of the straight chain sugar alcohols that may be used in the composition of the present invention include, but are not limited to, hexitols such as sorbitol, mannitol, glycerol, allitol, talitol, glucitol, iditol and dulcitol; pentitols such as xylitol, adonitol (also called ribitol) and arabitol; tetritols such as erythritol and threitol; and triols such as glycerol. Examples of cyclic sugar alcohol that may be used include, but are not limited to, inositol and the like.

In one embodiment of the present invention, mannitol is used as the sugar alcohol. The amount of mannitol used in the composition may range from about 60 % to about 90 %, preferably from about 70 % to about 80 % and most preferably about 75 % by weight of composition. It is advantageous to use a sugar alcohol particularly for the low dose drugs like pramipexole dihydrochloride monohydrate for uniform distribution of the drug. In one preferred embodiment, the mannitol having a mean particle size ranging from about 5 microns to about 70 microns, preferably from about 10 microns to about 50 microns, most preferably from about 15 microns to about 30 microns is used.

Other examples of fillers or diluents that may be used in the pharmaceutically acceptable carrier medium substantially free of polyvinyl pyrrolidone, include, but are not limited to, starch and its derivatives like corn starch, pregelatinized starch and the like, calcium phosphate dibasic, calcium phosphate tribasic, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, lactose, dextrose, dextrin, sugar compressible and the like and mixture thereof. The amount of fillers that may be used in the pharmaceutical composition of the present invention ranges from about 5 % to about 90 % by weight of the composition, preferably 15 % to about 30 % by weight of the composition.

Examples of the binders that may be used include, but are not limited to, methyl cellulose, hydroxypropyl cellulose, gelatin, tragacanth, sodium alginate and the like and mixture thereof. The amount of binder that may be used ranges from about 0 % to about 10 % by weight of the composition. In one preferred embodiment of the present invention, purified water is used as the sole granulating agent.

Examples of lubricants/ glidants that may be used include, but are not limited to, silicon dioxide, colloidal silicon dioxide, magnesium stearate, calcium stearate, sodium stearyl fumarate, stearic acid, zinc stearate, talc and the

like, or mixture thereof. The amount of lubricants/glidants that may be used in the pharmaceutical composition of the present invention, ranges from about 0.1 % to about 5 %, preferably about 2 % by weight of the composition.

In one embodiment of the present invention, the pharmaceutical composition comprises one or more antioxidants. Examples of the antioxidants that may be used in the pharmaceutical composition includes, but are not limited to, butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, fumaric acid, malic acid, alpha tocopherol, ascorbic acid palmitate, propyl gallate, sodium ascorbate, sodium metabisulfite and the like and mixture thereof. Preferably antioxidants used in the composition of the present invention are butylated hydroxytoluene and/or butylated hydroxyanisole. The amount of antioxidant used may range from about 0 % to about 1 % by weight of the composition.

In one preferred embodiment of the present invention, the pharmaceutical composition consists essentially of a mixture of pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof, starch or its derivatives, sugar alcohol (s) and a pharmaceutically acceptable carrier medium. In this embodiment, the pharmaceutically acceptable carrier medium is substantially free of polyvinyl pyrrolidone. Although it may be possible to prepare a stable pharmaceutical composition with trace amounts of polyvinyl pyrrolidone, preferably the composition is completely devoid of polyvinyl pyrrolidone.

The composition of the present invention may be prepared in the form of powders, granules, capsules, sachets and tablets using conventional methods, involving mixing, granulation, drying, blending and compression. Preferably, it is recommended that the mixing of the drug with excipients be designed according to known methods in the art that result in a uniform mixing of the drug with the excipients. For example, mixing of the drug with excipients in geometric proportions may be preferred or for instance when granulating, wet granulation may be preferred over dry granulation or direct compression into tablets. When water is used in the granulation fluid, the granules are preferably dried to moisture content not more than about 4 % by weight of the dried granules.

The examples that follow are provided as illustrations only and do not limit the scope of the present invention.

Examples 1-5

Compositions of examples 1-5 of the present invention were prepared using the ingredients listed in table no. 1. Pramipexole dihydrochloride monohydrate, mannitol, corn starch and pregelatinized starch were sifted through 40 # mesh. Mannitol (Part B) was first loaded to the rotating mixture granulator followed by Pramipexole dihydrochloride monohydrate, remaining portion of mannitol (Part A), corn starch and a portion of pregelatinised starch. The ingredients were dry mixed for about 5 minutes. The mixture was then granulated with water. The wet mass was screened and the granules were dried and milled. The moisture content of the dried granules was about 3.0 % by weight of the dried granules. Remaining portion of pregelatinized starch was added to dried, milled granules and the blend was lubricated with colloidal silicon dioxide and magnesium stearate. This mixture was then compressed into tablets.

Table 1

Ingredients	Example 1		Example 2		Example 3		Example 4		Example 5	
	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w
Pramipexole dihydrochloride monohydrate	0.125	0.156	0.25	0.313	0.50	0.313	1.00	0.625	1.50	0.625
Mannitol (Mannitol 25) (Part A)	29.475	36.84	29.35	36.69	58.70	36.69	57.20	35.75	86.80	36.16
Mannitol (Mannitol 25) (Part B)	30.00	37.50	30.00	37.50	60.00	37.50	60.00	37.50	90.0	37.50
Corn starch	10.00	12.50	10.00	12.50	20.00	12.5	20.00	12.5	30.0	12.50
Pregelatinized starch (Intraganular)	6.40	8.00	6.40	8.00	12.80	8.00	12.800	8.0	19.20	8.00
Pregelatinized Starch (Extragranular)	2.40	3.0	2.40	3.00	4.80	3.00	4.80	3.0	7.20	3.00
Colloidal silicon dioxide	0.40	0.50	0.40	0.50	0.80	0.50	0.80	0.80	1.20	0.80
Magnesium stearate	1.20	1.50	1.20	1.50	2.40	1.50	2.40	2.40	3.60	2.40
Total weight	80.00		80.00		160.00		160.00		240.00	

The compositions prepared according to Example 1, 2, 5 were packed and sealed in high density polyethylene containers with desiccant and were stored at a temperature of about 40^0C ± 2^0 C and relative humidity of about 75 % ± 5 % for three months. The compositions were analyzed for the pramipexole content by High performance liquid chromatography (HPLC). Related substances were separated by HPLC and quantified by measuring the absorption in the Ultraviolet region. The details of the results are given in table 2.

Table 2

Stability conditions	Example 1		Example 2		Example 5	
	Initial	40°C/75 % RH	Initial	40°C/75 %RH	Initial	40°C/75 %RH
Duration	0 time	3M	0 time	3M	0 time	3M
Assay of pramipexole	100.7	98.1	101.6	100.8	102.2	100.2
Related substances in % by weight						
Impurity A	0.05	0.01	ND	0.01	ND	ND
Impurity B	0.04	0.02	0.02	0.03	ND	0.01
Impurity C	0.01	0.03	0.01	0.03	0.01	0.02
Max. unknown	0.02	0.10	0.02	0.1	0.03	0.07
Total unknown	0.10	0.52	0.05	0.49	0.10	0.30
Total impurity	0.20	0.58	0.08	0.53	0.11	0.33

ND- Not detected

Examples 6-9

Compositions of examples 6 to example 9 of the present invention were prepared using the ingredients listed in table no. 3. The tablets were prepared according to the procedure described in examples 1-5 except the addition of butylated hydroxyl anisole and butylated hydroxyl toluene dissolved in a mixture of isopropyl alcohol and water.

Table 3

Ingredients	Example 6		Example 7		Example 8		Example 9	
	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w
Pramipexole dihydrochloride monohydrate	0.125	0.156	0.25	0.3125	1.00	0.625	1.50	0.625
Mannitol (Mannitol 25) (Part A)	29.275	36.59	29.15	36.44	57.80	36.125	86.70	36.125
Mannitol (Mannitol 25) (Part B)	30.00	37.50	30.00	37.50	60.00	37.50	90.00	37.50
Corn starch	10.00	12.50	10.00	12.50	20.00	12.50	30.00	12.50
Pregelatinized starch (intragranular)	6.40	8.00	6.40	8.00	12.80	8.00	19.20	8.00
Butylated hydroxy anisole	0.10	0.125	0.10	0.125	0.20	0.125	0.30	0.125
Butylated hydroxyl toluene	0.10	0.125	0.10	0.125	0.20	0.125	0.30	0.125
Pregelatinized starch (Extargranular)	2.40	3.00	2.40	3.00	4.80	3.00	7.20	3.00
Colloidal silicon dioxide	0.40	0.50	0.40	0.50	0.80	0.50	1.20	0.50
Magnesium stearate	1.20	1.50	1.20	1.50	2.40	1.50	3.60	1.50
Total weight	80.00		80.00		160.00		240.00	

Composition prepared according to examples 6-9 were packed and sealed in black lined high density polyethylene containers with desiccant and was in stored at a temperature of about 40^0C ± 2^0 C and relative humidity of about 75 % ± 5 % for three months. The compositions were analyzed for the pramipexole dihydrochloride monohydrate content by HPLC techniques. Related substances were separated by HPLC and quantified by measuring the absorption in the UV region. The details of the results are given in table 4.

Table 4

Stability conditions	Example 6		Example 7		Example 8		Example 9	
	Initial	40°C/75 %RH	Initial	40°C/75 %RH	Initial	40°C/75 %RH	Initial	40°C/75 %RH
Duration	0 time	3M	0 time	3M	0 time	3M	0 time	3M
Assay of pramipexole	98.9	96.0	99.9	95.5	100.9	97.5	100.5	97.6
Related substances in % by weight								
Impurity A	ND	0.02	ND	0.01	ND	ND	ND	ND
Impurity B	ND	0.03	ND	0.03	ND	0.04	ND	0.04
Impurity C	0.02	0.01	ND	0.01	ND	0.01	0.01	0.00
Max. unknown	0.02	0.12	0.10	0.13	0.02	0.05	0.02	0.07
Total unknown	0.02	0.38	0.13	0.74	0.02	0.18	0.04	0.30
Total impurity	0.04	0.44	0.13	0.79	0.02	0.23	0.05	0.37

ND - Not detected

Comparative Examples 1-5

Composition according to Comparative examples 1-5 were prepared using the ingredients listed in Table no. 5. Pramipexole dihydrochloride monohydrate, mannitol, corn starch and pregelatinized starch were sifted through 40 number mesh. Mannitol (Part B) was first loaded to the rotating mixture granulator followed by pramipexole dihydrochloride monohydrate, remaining portion of mannitol (Part A), corn starch and a portion of pregelatinised starch. The ingredients were dry mixed for about 5 minutes. The mixture was granulated with water. The wet mass was screened and the granules were dried till the moisture content was about 3.0 % by weight of the dried granules. The dried granules were milled. Remaining portion of pregelatinized starch was added to dried granules and the blend was lubricated with colloidal silicon dioxide and magnesium stearate. This mixture was then compressed into tablets.

Table 5

Ingredients	Comparative Example 1		Comparative Example 2		Comparative Example 3		Comparative Example 4		Comparative Example 5	
	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w	mg per tablet	% w/w
Pramipexole dihydrochloride monohydrate	0.125	0.156	0.25	0.3125	0.50	0.3125	1.00	0.625	1.50	0.625
Mannitol (Mannitol 25) (Part A)	29.475	36.844	29.35	36.69	58.70	36.69	57.20	35.75	86.80	36.167
Mannitol (Mannitol 25) (Part B)	30.00	37.50	30.00	37.50	60.00	37.50	60.00	37.50	90.00	37.50
Corn starch	10.00	12.50	10.00	12.50	20.00	12.50	20.00	12.50	30.00	12.50
Povidone	3.15	3.94	3.15	3.94	6.30	3.94	6.30	3.94	9.45	3.94
Corn starch	2.40	3.00	2.40	3.00	4.80	3.00	4.80	3.00	7.20	3.00
Colloidal silicon dioxide	0.40	0.50	0.40	0.50	0.80	0.50	0.80	0.50	1.20	0.50
Magnesium stearate	1.20	1.50	1.20	1.50	2.40	1.50	2.40	1.50	3.60	1.50
Total weight	80.00		80.00		160.00		160.00		240.00	

The composition according to comparative examples 1-5 of pramipexole were packed and sealed in black-lined high density polyethylene containers without desiccant and were stored at a temperature of about 40°C ± 2° C and relative humidity of about 75 % ± 5 % for three months. The compositions were analyzed for the pramipexole content by high performance liquid chromatography (HPLC). Related substances were separated by HPLC and quantified by measuring the absorption in the ultraviolet region. The details of the results are given in table 6.

Table 6

Stability conditions	Comparative Example 1		Comparative Example 2		Comparative Example 3		Comparative Example 4		Comparative Example 5	
	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH
Duration	0 time	3M	0 time	3M	0 time	3M	0 time	3M	0 time	3M
Assay of pramipexole	101.1	84.3	98.50	84.9	99.40	90.6	98.20	94.1	98.60	92.5
Related Substances (in % by weight)										
Impurity A	ND	ND	ND	0.03	ND	ND	ND	ND	ND	ND
Impurity B	0.02	0.04	0.03	0.05	0.03	0.09	0.03	0.05	0.03	0.11
Impurity C	0.02	0.08	0.02	0.06	0.01	0.04	ND	0.03	ND	0.04
Max. unknown	0.04	0.59	0.03	0.50	0.02	0.46	0.01	0.31	0.02	0.37
Total unknown	0.11	3.85	0.10	3.64	0.03	2.99	0.04	0.82	0.06	1.21
Total impurity	0.15	3.97	0.15	3.78	0.07	3.12	0.07	0.90	0.09	1.36

ND - Not detected

Comparative Examples 6-10

Compositions of comparative examples 6-9 were prepared using the ingredients listed in table no. 7 and the composition of comparative example 10 was prepared using the ingredients given in table no. 8. The tablets were prepared according to the procedure described in comparative examples 1-5 except use of butylated hydroxyl anisole and butylated hydroxyl toluene dissolved in mixture of isopropyl alcohol and water instead of purified water alone.

Table 7

Ingredients	Comparative Example 6		Comparative Example 7		Comparative Example 8		Comparative Example 9	
	mg per tablet	%w/w	mg per tablet	%w/w	mg per tablet	%w/w	mg per tablet	%w/w
Pramipexole dihydrochloride monohydrate	0.125	0.156	0.25	0.3125	0.50	0.3125	1.50	0.625
Mannitol (Mannitol 25) (Part A)	29.475	36.84	29.35	36.69	58.70	36.69	86.80	36.167
Mannitol (Mannitol 25) (Part B)	30.00	37.50	30.00	37.50	60.00	37.50	90.00	37.50
Corn starch	10.00	12.50	10.00	12.50	20.00	12.50	30.00	12.50
Povidone	3.15	3.94	3.15	3.94	6.30	3.94	9.45	3.94
Butylated hydroxy anisole	0.10	0.125	0.10	0.125	0.20	0.125	0.30	0.125
Butylated hydroxyl toluene	0.10	0.125	0.10	0.125	0.20	0.125	0.30	0.125
Corn starch	2.40	3.00	2.40	3.00	4.80	3.00	7.20	3.00
Colloidal silicon dioxide	0.40	0.50	0.40	0.50	0.80	0.50	1.20	0.50
Magnesium stearate	1.20	1.50	1.20	1.50	2.40	1.50	3.60	1.50
Total weight	80.00		80.00		160.00		240.00	

Comparative Example 10

Table 8

Ingredients	Comparative Example 10	
	mg per tablet	%w/w
Pramipexole dihydrochloride monohydrate	0.25	0.3125
Mannitol (Mannitol 25)	35.00	43.75
Corn starch	32.00	40.00
Pregelatinised starch (intragranular)	3.00	3.75
Povidone	3.15	3.94
Pregelatinised starch (Extragranular)	5.00	6.25
Corn starch	5.00	6.25
Colloidal silicon dioxide	0.40	0.50
Magnesium stearate	1.20	1.5
Total weight	80.00	

The composition according to comparative examples 6-9 of pramipexole were packed and sealed in black lined high density polyethylene containers without desiccant and were stored at a temperature of about 40^0C ± 2^0 C and relative humidity of about 75 % ± 5 % for a period of three months. The composition of the comparative example 10 was packed and sealed in white high density polyethylene bottles and was stored at a temperature of about 40^0C ± 2^0 C and relative humidity of about 75 % ± 5 % for three months. The compositions were analyzed

for the pramipexole dihydrochloride monohydrate content by HPLC techniques. Related substances were separated by HPLC and quantified by measuring the absorption in the UV region. The details of the results are given in table 9.

Table 9

Stability condition	Comparative example 6		Comparative example 7		Comparative example 8		Comparative example 9		Comparative example 10	
	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH	Initial	40°C/ 75%RH
Duration	0 time	3M	0 time	3M	0 time	3M	0 time	3M	0 time	3M
Assay	102.00	90.3	97.00	89.0	97.60	89.3	96.50	94.7	101.00	87.2
Related Substances (in % by weight)										
Impurity A	ND	0.02	ND	ND	ND	ND	ND	ND	-	-
Impurity B	0.03	0.03	0.02	0.05	0.02	0.03	0.02	0.01	-	-
Impurity C	0.01	0.06	0.03	0.03	0.01	ND	0.01	ND	-	-
Max. unknown	0.03	0.29	0.02	0.18	0.02	0.16	-	0.12	0.11	0.76
Total unknown	0.10	2.42	0.04	1.76	0.05	1.19	-	1.07	0.44	3.19
Total impurity	0.14	2.53	0.09	1.84	0.08	1.22	0.03	1.08	0.44	3.19

ND- Not detected. – Not determined.

As seen from example 1-9 of the present invention in comparison to prior art composition comprising polyvinyl pyrrolidone, it was found that when the compositions were packed and sealed in high density polyethylene containers with desiccants and stored at a temperature of about 40^0 C ± 2^0 C and relative humidity of about 75 % ± 5 % for a period of three months, the compositions showed the content of pramipexole dihydrochloride monohydrate within the range of about 95 % to about 105 % of the labeled amount and the total impurity did not exceed 1 % by weight of pramipexole dihydrochloride monohydrate.

Claims:

1. A pharmaceutical composition comprising a mixture of pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof, sugar alcohol (s) and a pharmaceutically acceptable carrier medium substantially free of polyvinyl pyrrolidone.

2. A pharmaceutical composition as claimed in claim 1 wherein the sugar alcohol is mannitol and is present in the amount ranging from about 60 % to about 85 % by weight of the composition.

3. A pharmaceutical composition as claimed in claim 2 wherein the particle size of mannitol ranges from about 15 microns to about 35 microns.

4. A pharmaceutical composition as claimed in claim 1 wherein the composition is in the form of granules.

5. A pharmaceutical composition as claimed in claim 4 wherein the moisture content of the granules is not more than about 4 % by weight of the dried granules.

6. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically acceptable carrier medium comprises starch or its derivatives.

7. A pharmaceutical composition as claimed in claim 6 wherein the corn starch is present intragranularly and pregelatinized starch is present intragranularly and extragranularly.

8. A pharmaceutical composition as claimed in claim 7 wherein the amount of corn starch present intragranularly ranges from about 10 % to about 15 % by weight of the composition and the amount of pregelatinised starch present intragranularly ranges from about 5 % to about 10 % by weight of the composition and the amount of pregelatinised starch present extragranularly ranges from about 1 % to about 5 % by weight of the composition.

8. A pharmaceutical composition as claimed in claim 1 wherein the composition comprises one or more antioxidants.

9. A pharmaceutical composition consisting essentially of a mixture of pramipexole or its pharmaceutically acceptable salts or its hydrates or solvates thereof, starch or its derivatives, sugar alcohol(s) and a pharmaceutically acceptable carrier medium.

10. A pharmaceutical composition as claimed in claim 1 wherein said pharmaceutical composition when stored at a temperature of about 40 ^{0}C ± 2 ^{0}C and relative humidity of about 75 % ± 5 % in high density polyethylene container showed the content of pramipexole dihydrochloride monohydrate in the range of about 95 % to about 105 % of the labeled amount and the total impurities less than about 1 % by weight of pramipexole dihydrochloride monohydrate.