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(54) Title: COMPOSITIONS OF ANTIVIRAL COMPOUND

(57) Abstract: An oral pharmaceutical composition comprising free flowing ribavirin and one or more pharmaceutically acceptable excipients, wherein the free flowing ribavirin is prepared by agglomerating the non-free flowing ribavirin using a solvent or by controlling the crystallization during synthesis of ribavirin.

COMPOSITIONS OF ANTIVIRAL COMPOUND

Field of the invention

The present invention relates to composition of an anti-viral compound. More particularly, the present invention relates to compositions comprising free flowing ribavirin.

The present invention also relates to a process for the preparation of compositions comprising free flowing ribavirin.

Background of the invention

Ribavirin is a synthetic nucleoside analog with broad-spectrum antiviral activity and known to be useful in the treatment of hepatitis C as well as various other disease states. Chemically, ribavirin is 1-(β)-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and is commercially available in the US as tablets under the trade name of Copegus®; as capsule and oral solution under the trade name of Rebetol® and as inhalation solution under the trade name of Virazole®. Ribavirin is currently indicated for use as a combination therapy with interferon for Hepatitis C. As such, ribavirin is administered in large dosages, e.g., a dose as large as 1200 mg per day, together with interferon injections.

Ribavirin is a colorless, water-soluble, stable material and is known to have two polymorphic forms. It is very fluffy, non- free flowing powder, which makes it difficult for filling in capsules or as such compressing into tablets. Even after mixing ribavirin with fillers and lubricants, the composition cannot have sufficient flow and density of blend is not suitable for filling into capsules or compressing into tablets.

US patent Nos. 5,914,128; 5,916,594; 6,051,252; 6,335,032; and 6,337,090 disclose rapidly dissolving compacted ribavirin composition comprising ribavirin and disintegrant and further disclose the composition having a tap density of at least about 0.6 g/mL. Dry compaction utilizes high pressure to form a ribbon of ribavirin that is subsequently reduced to a free

flowing powder by milling. The undesirable side effects of manufacturing ribavirin by dry compaction include creation of excessive dust, a potential health hazard, as well as the risk that high pressure, which can produce high heat, may change the polymorphic forms of ribavirin, which are unacceptable for obtaining health registration.

It is disclosed in US 5,914,128 patent that ribavirin is marketed in Canada as capsules under trade name Virazole®. The ribavirin composition used in Virazole® capsules is a non-free flowing powder with low and variable tap densities in the range of 0.320 to 0.449 g/mL, and comprises lactose monohydrate, microcrystalline cellulose, and magnesium stearate as excipients. It is further disclosed that it would be desirable for the ribavirin composition to have a uniformly high tap density of at least 0.6 g/mL to fill any capsule and to avoid excessive weight variation and suggested the dry compaction method to improve the flow.

There are few other patents/publications which disclose ribavirin formulation technologies, some of them are as given below:

US patent No. 6,720,000 disclose a process for preparing ribavirin pellets by extrusion and spheronization. However, the pellets prepared by this method are costlier and time consuming.

US 2003/0104050 disclose quick dissolving ribavirin composition prepared by a process comprising mixing ribavirin, disintegrant, filler to form an homogenous mixture; granulating the mixture with water; drying the granules; and mixing the dried granules with disintegrant and lubricant.

WO 2004/096187 disclose a pharmaceutical composition containing ribavirin as active substance in the mixture with at least one pharmaceutically acceptable excipient characterized in that it is a freely flowing granulate prepared by wet granulation of a mixture of ribavirin, wetted with water, and at least one pharmaceutically acceptable filler selected from the group including

cellulose and its derivatives and carbonates, phosphates, sulfates and silicates of metals, and optionally at least one pharmaceutically acceptable excipient.

EP 1455801 discloses a process for preparing ribavirin granules, comprising preparing granulate solution which involves mixing of a binding agent with an isopropanol/water or ethanol/water-mixture, then stirring the granulate solution into a mixture of ribavirin-powder with sieving and drying the granulates.

The above prior art references discloses various technologies for preparing ribavirin composition. However, still there is a need for making ribavirin composition, which involves simple process and does not involve high pressure compaction process and costlier pelletization technique. The inventors of the present invention during their continuous effort to develop ribavirin compositions, found that blending of free flowing ribavirin with other excipients produces composition which have uniform dissolution profile and does not cause the formation of undesired ribavirin polymorphic forms.

Objective of the invention

Accordingly, the main objective of the present invention is to provide composition comprising free flowing ribavirin.

Yet, another embodiment of the present invention is to provide simple, cost effective and efficient process for preparing ribavirin composition.

Yet another objective of the present invention is to provide ribavirin composition in such a way that it will comply with the reference product in terms of *in vitro* parameters like dissolution, disintegration, etc and *in vivo* parameters like bioequivalence.

Summary of the Invention

Accordingly, to the main embodiment, the invention provides a composition comprising free flowing ribavirin and one or more pharmaceutically acceptable excipients, wherein the free flowing ribavirin is prepared by

agglomerating the non-free flowing ribavirin using a solvent or by controlling the crystallization during synthesis of ribavirin.

The invention also provides a process for preparing ribavirin compositions wherein the composition is prepared by mixing free flowing ribavirin with one or more excipients and finally filling into capsules or compressing into tablets.

Detailed description of the invention

The present invention describes a composition comprising free flowing ribavirin prepared by a simple process from non free flowing ribavirin without using any excipients or procedures where high pressure is required such as compaction.

The free flowing ribavirin is prepared by dissolving ribavirin crude product in a mixture of water and methanol at 65 to 70 °C. The resulting mixture is treated with charcoal and cooling the filtrate slowly at 50 to 70 °C, at which temperature the product starts crystallizing resulting into a slurry. Maintaining such slurry at this temperature without agitation for 15-20 min for formation of crystals and stirring for 2.0 hrs and drying the product to obtain free flowing crystals of ribavirin.

The free flowing ribavirin is also prepared by adding solvent to non-free flowing ribavirin powder in a mixer, kneading the wet mass, sieving the wet agglomerate, and drying the wet agglomerate at 60 to 80 °C. The dried granules are shifted through suitable sieves to obtain free flowing ribavirin.

In an embodiment of the present invention, the free flowing ribavirin used according to the present invention has bulk density not less than 0.36g/ml and not more than 0.66g/ml, tapped density of not less than 0.4g/ml and not more than 0.8g/ml.

In yet another embodiment of the present invention, the particle size of the free flowing ribavirin used is not more than 600 μm.

The ribavirin prepared by process of the present invention is uniform, free flowing, and have adequate bulk and tapped density for processing into capsules or tablets. Furthermore, the ribavirin compositions are substantially free of polymorphic forms of ribavirin, i.e., there are no signs of change in polymorphic nature of ribavirin.

In an embodiment, the ribavirin composition of the present invention may be filled into capsules, compressed into conventional or sustained release tablets.

In an embodiment, the ribavirin composition of the present invention comprises one or more pharmaceutically acceptable excipients selected from fillers, disintegrants, binders, lubricants, glidants, polymers and the like.

The sustained release tablets further comprise polymers selected from hydoxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, and polyethylene oxide or a combination thereof.

The ribavirin composition of present invention complies with the reference product in terms of *in vitro* parameters like dissolution, disintegration, etc and *in vivo* parameters like bioequivalence.

Suitable solvents used for preparing free flowing ribavirin include water, acetonitrile, acetone, chloroform, methylene chloride, methanol, ethanol, and isopropanol or a combination thereof.

Suitable fillers used according to the present invention are selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, dibasic calcium phosphate dihydrate, calcium carbonate, dextrose, sucrose, mannitol, and sorbitol or a combination thereof.

Suitable disintegrants used according to the present invention are selected from croscarmellose sodium, sodium starch glycolate, crospovidone, pregelatinized starch, and sodium carboxymethyl cellulose or a combination thereof.

Suitable binders of the invention are selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, starch, pregelatinized starch or a combination thereof.

Suitable lubricants used according to the present invention are selected from magnesium stearate, calcium stearate, zinc stearate, talc, stearic acid, vegetable oil, and sodium lauryl sulfate or a combination thereof.

Suitable glidants used according to the present invention are selected from magnesium trisilicate, talc, and colloidal silicon dioxide or a combination thereof.

The following examples further exemplify the invention and are not intended to limit the scope of the invention. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.

Example 1

Ribavirin capsules

S. No.	Ingredient	Qty/capsule
1	Free flowing Ribavirin	200 mg
2	Lactose Monohydrate	20 to 40 mg
3	Microcrystalline cellulose	20 to 50 mg
4	Croscarmellose sodium	6 to 30 mg
5	Povidone	1.5 to 9 mg
6	Magnesium Stearate	3 to 6 mg

The processing steps involved in manufacturing ribavirin capsules are :

i) free flowing ribavirin was loaded in a blender,

ii) lactose, microcrystalline cellulose, croscarmellose sodium and povidone were added to free flowing ribavirin and mixed,

iii) lubricated the blend obtained from step (ii) with magnesium stearate, and

iv) filled the uniform blend into capsules.

The capsules disclosed in the following examples are prepared by similar process described in example 1.

Example 2

Ribavirin capsules

S. No.	Ingredient	Qty/capsule
1	Free flowing Ribavirin	200 mg
2	Lactose Monohydrate	20 to 40 mg
3	Microcrystalline cellulose	20 to 50 mg
4	Sodium starch glycolate	6 to 30 mg
5	Povidone	1.5 to 9 mg
6	Magnesium Stearate	3 to 6 mg

Example 3

Ribavirin capsules

S. No.	Ingredient	Qty/capsule
1	Free flowing Ribavirin	200.00mg
2	Lactose Monohydrate	45.00mg
3	Microcrystalline cellulose	50.50mg
4	Povidone	1.50mg
5	Magnesium Stearate	3.00mg

Example 4

Immediate release ribavirin tablets

S. No.	Ingredient	Qty/capsule
1	Free flowing Ribavirin	200 mg
2	Pregelatinized starch	20 to 50 mg
3	Microcrystalline cellulose	50 to 100 mg
4	Sodium starch glycolate	6 to 30 mg

5	Povidone	1.5 to 9 mg
6	Magnesium Stearate	3 to 6 mg

The processing steps involved in manufacturing ribavirin immediate release tablets are :

i) free flowing ribavirin was loaded in a blender,

ii) pregelatinized starch, microcrystalline cellulose, croscarmellose sodium and povidone were added to free flowing ribavirin and mixed the blend,

iii) lubricated the blend obtained from step (ii) with magnesium stearate, and

iv) compressed the blend to obtain tablets.

The immediate release tablets disclosed in the following examples are prepared by similar process described in example 4.

Example 5

Immediate release ribavirin tablets

S. No.	Ingredient	Qty/capsule
1	Free flowing Ribavirin	200 mg
2	Pregelatinized starch	20 to 50 mg
3	Microcrystalline cellulose	50 to 100 mg
4	Croscarmellose sodium	6 to 30 mg
5	Povidone	1.5 to 9 mg
6	Magnesium Stearate	3 to 6 mg

Example 6

Immediate release ribavirin tablets

S. No.	Ingredient	Qty/capsule
1	Free flowing Ribavirin	200.00mg
2	Pregelatinized starch	37.00mg

3	Microcrystalline cellulose	97.40mg
4	Sodium starch glycolate	12.00mg
5	Povidone	8.00mg
6	Magnesium Stearate	3.60mg
7	Colloidal silicon dioxide	2.00mg

Example 7

Sustained release Ribavirin tablets

S. No.	Ingredient	Qty/capsule
1	Free flowing Ribavirin	200 mg
2	Pregelatinized starch	20 to 50 mg
3	Microcrystalline cellulose	50 to 100 mg
4	Polymers	6 to 30 mg
5	Povidone	1.5 to 9 mg
6	Magnesium Stearate	3 to 6 mg

The processing steps involved in manufacturing ribavirin sustained release tablets are:

i) free flowing ribavirin was loaded in a blender,

ii) pregelatinized starch, microcrystalline cellulose, polymers, and povidone were added to free flowing ribivirin of step (i) and mixed the blend,

iii) lubricated the blend obtained from step (ii) with magnesium stearate, and

iv) compressed the blend to obtain sustained release tablets.

Dissolution profile :

The dissolution studies were performed in 900 ml of water, at 100 RPM by USP I method. The release profile (% of drug released in minutes) is given in table 1.

Table I

S. No.	Time in min.	% Drug release	
		Ex 3	Ex 6
1	5	50	93

2	10	87	96
3	20	102	98
4	30	103	99
5	45	102	100

We claim :

1. A composition comprising free flowing ribavirin and one or more pharmaceutically acceptable excipients, wherein the free flowing ribavirin is prepared by agglomerating the non-free flowing ribavirin using a solvent or by controlling the crystallization during synthesis of ribavirin.

2. The free flowing ribavirin as claimed in claim 1, prepared by crystallization process.

3. The crystallization process as claimed in claim 2, comprises the steps of dissolving ribavirin crude product in a mixture of water and methanol at 65 to 70 °C, treating the resulting mixture with charcoal, cooling the filtrate slowly at 50 to 70 °C to form a slurry, maintaining the slurry at this temperature without agitation for 15-20 min to form crystals, stirring for 2.0 hrs and drying the crystals.

4. The free flowing ribavirin as claimed in claim 1, prepared by agglomeration process.

5. The agglomeration process as claimed in claim 4, comprises the steps of adding solvent to non free flowing ribavirin powder in a mixer, kneading the wet mass, sieving the wet agglomerate, drying at 60 to 80 °C and sifting the dried the granules through sieves.

6. The process as claimed in claim 3, wherein the solvent used is selected from water, acetonitrile, acetone, chloroform, methylene chloride, methanol, ethanol, isopropanol or a combination thereof.

7. The free flowing ribavirin as claimed in claim 1, having bulk density not less than 0.36g/ml and not more than 0.66g/ml, tapped density of not less than 0.4g/ml and not more than 0.8g/ml and

8. The free flowing ribavirin as claimed in claim 1, has a particle size of less than 600 μm.

9. The composition as claimed in claim 1, wherein pharmaceutically acceptable excipient is selected from fillers, disintegrants, binders, glidants and lubricants.

10. The composition as claimed in claim 9, wherein filler is selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, dibasic calcium phosphate dihydrate, calcium carbonate, dextrose, sucrose, mannitol, sorbitol or a combination thereof.

11. The composition as claimed in claim 9, wherein disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, pregelatinized starch, sodium carboxymethyl cellulose or a combination thereof.

12. The composition as claimed in claim 9, wherein lubricant is selected from magnesium stearate, calcium stearate, zinc stearate, talc, stearic acid, vegetable oil, sodium lauryl sulfate or a combination thereof.

13. The composition as claimed in claim 1, is in the form of capsules, immediate release tablets or sustained release tablets.