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Original Research Article

MANUFACTURING OF NEW FORMULATION OF RIBAVIRIN 200MG CAPSULES

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ABSTRACT

Ribavirin are used for the treatment of chronic hepatitis C with compensated liver disease, in the present study we manufactured the new formulations of Ribavirin capsules by using Microcrystalline cellulose PH 102, Di-calcium phosphate, Povidone K 30, Crospovidone, Aerosil 200 and Magnesium stearate. This study is alienated into two phases. The first phase of the study comprises of new formulation of Ribavirin capsules which were prepared. Whereas in the 2nd phase of study new formulation is evaluated for their physical parameters like average weight, weight variation, disintegration time and also evaluated the chemical analysis like dissolution behaviour and assay. All quality control parameters: average weight, weight variation test, disintegration test, dissolution test and assay were carried out specified by BP/USP (British and United state Pharmacopoeia) for capsules. The results showed that all parameters of new formulations are in accordance with the BP/USP limits.

Keywords: Ribavirin, New Formulations, Disintegration, Dissolution.

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INTRODUCTION

Ribavirin (RBN) is categorized as an antihepaciviral, nucleoside (Anti-HCV); it inhibits replication of RNA and DNA viruses. Chemically it is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide (Figure 1) [1]. It is a broad spectrum antiviral agent [2]. It is a white, crystalline powder, freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is C₈H₁₂N₄O₅ and the molecular weight is 244.21. It is used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor [3]. It is used to treat chronic hepatitis C virus infection [4-7], Crimean-congo hemorrhagic fever [8-9] and lassa fever [10]. It is also used for treatment of respiratory syncytial virus infection in children [11], also used as an anti cancer therapy [12].

Ribavirin nasal and oral inhalation used for treatment of severe lower respiratory tract infections (i.e., bronchiolitis, pneumonia) caused by RSV in hospitalized infants and young children. The primary toxicity of ribavirin is hemolytic anemia [13-15] Reductions in hemoglobin levels occurred within the first 1-2 weeks of oral therapy. It Absorbed rapidly from GI tract; peak plasma concentrations achieved within 1–3 hours, bioavailability is 64%. Ribavirin and/or its metabolites accumulate in erythrocytes [16-17].

The manufacturing of Pharmaceutical dosage form, from formulation development to finished product, is very difficult process. This includes interactions of various types between process conditions and raw materials. These interactions are of great importance for the process ability and quality of the finished product, so these interactions should be taken into account earlier, such that to save later loss of time and money [18].

In this present study we developed a new formulation of Ribavirin and all of the physical and chemical parameters were analyzed i.e. average weight, weight variation, disintegration, dissolution and assay as per USP [1].

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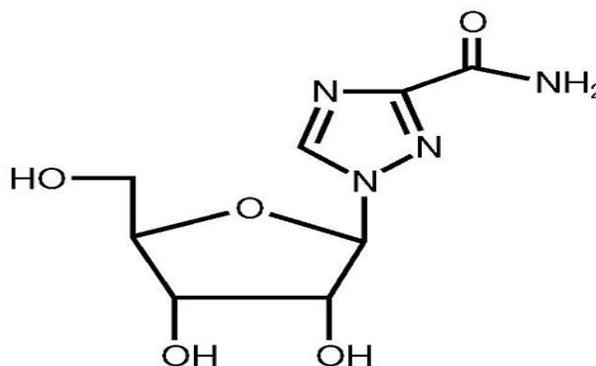


Figure: 1 Structure of Ribavirin

EXPERIMENTAL METHODOLOGY

Materials and reagents

The API and excipients used in the formulation were Ribavirin, Microcrystalline cellulose PH 102, Lactose monohydrate, Crocarmellose sodium and Povidone K 30. All of them were of pharmaceutical grade. For quantitative analysis, the standards used were Ribavirin (Potency 99-101%).

Manufacturing of New Formulations

Accurately weigh all the ingredients of capsules. Pass the Ribavirin, Microcrystalline cellulose PH 102, Di-calcium phosphate and Crospovidone through mesh 0.5 mm. add the PVP K-30 in purified water and make a clear solution. Add this solution to the above sieved materials and made a granules. Dry the wet mass at 60 °C and check the moisture which should be not more than 1.00 %. Pass these dried granules through 1.00 mm mesh and then add Aerosil 200 and Magnesium stearate after passing through mesh 0.5 mm, then transferred them into suitable food grade polyethylene bag. Ingredients were mixed by tumbling action in a large size poly bag for 5 minutes. Finally adjust the capsules shell into the capsules filling machine carefully so the body adjust in the lower hole. The head of capsules were unlocked by adjusting the lever. Fill the blended powder in the body of capsule. Place the upper plate carrying head of the capsules and locked them on the body with the help of the lever.

Capsules Specifications

After manufacturing of a new formulation of capsules all of the described parameters were analyzed i.e. average weight, weight variation, disintegration, dissolution and assay [1].

Average Weight and Weight Variation Test

Weight Variation is the in-process test which ensures that the content of each dosage units is uniform during encapsulation process. 20 capsules of new formulation were accurately weighed on Electronic Balance Metler AL-204. Calculate the weight of each capsule that must be within official limits. USP/ BP states that the capsules containing 130-324 mg of the total weight may be outside $\pm 7.5\%$ of the average (NMT two capsules out of the sample) and all must be within 20%.

Disintegration Test

Disintegration of the new formulation of capsules was tested by using apparatus Pharmatest Disintegration Tester Series Type PTZ Auto. Place one capsule in each of the six tubes of the basket and add a disc. Using water as the immersion fluid, operate the apparatus by maintaining its temperature at 35- 39 °C. Finally at the specified time, pick up the basket from the fluid and check

whether all of the capsules have disintegrated completely. The test is repeated on 12 extra capsules if one or two capsules fail to disintegrate. The requirements are met when out of 18 capsules 16 are disintegrated. According to USP, capsule should disintegrate in not more than thirty minutes.

Dissolution test

Dissolution test was carried out on Dissolution Tester AT7 Smart dissolution apparatus. Assemble the equipment, pour 900ml of DI water in each of the vessel and maintain the temperature of vessels at $37 \pm 0.5^\circ\text{C}$. Place one capsule of new formulation in an each vessel before rotation. The rotation of the basket was set at 100 RPM. A sample of 10 ml is withdrawn after 30 minutes. The sample must be taken from a zone midway between the surface of the dissolution medium and the top of the rotating basket, at least 10 mm from the vessel wall and not less than 10 mm below the surface. The quantity of Ribavirin dissolved was determined as specified in USP [1].

Assay

Assay was performed on High Performance Liquid Chromatography (HPLC) Shimadzu, with Auto sampler. Sample and standard were prepared as specified in the USP and tested was carried out at UV 207 nm, Column: 7.8-mm \times 15-mm; 7- μm packing L17, Column temperature: 65°C , Flow rate: 1 mLmin⁻¹, and Injection volume: 10 μL as per USP [1].

RESULTS AND DISCUSSION

Average Weight and Weight Variation Test

Average weight and Wt. variation test of new formulated capsules proved statistically that all the capsules were in accordance to the BP/USP requirements. (Table 1, 2)

Table 1. Statistical Weight variation

No. of Capsules	Average (mg)	Standard deviation	Upper limit (X+3S)	Lower limit (X-3S)
20	280.00	0.003	289.95	268.89

Table 2. Weight variation test

No. of Capsules	Average (mg)	BP/USP Specification	Deviation from BP/USP Specification
20	280.00	Deviation should be $\pm 7.5\%$	Within specified limit

Table 3. Disintegration test

Disintegration time (min.:sec.)	USP Specification	Deviation from USP Specification
3 min: 18 sec	NMT 30 Min	Passes

Table 4. Dissolution Test

No. of Capsules	Results (%) Ribavirin	USP Spec	Deviation from USP
6	97.37	Not less than 80%(Q) of the labeled amount dissolved in 30 min	Passes

Table 5. Assay Test

No. of Capsules	Results (%) Ribavirin	USP Spec	Deviation from USP
20	102.12	90.0%–110.0%	Passes

Disintegration Test

Disintegration test was conducted on newly developed formulation and our results were in accordance to BP/USP (Table 3).

In vitro dissolution studies

The percentages of the labeled amount of Ribavirin dissolved in 30 minutes are shown in Table-4. As per USP official limits for Ribavirin capsules, dissolved amount of Ribavirin should NLT 80% (Q) of the labeled amount in 30 minutes and new formulation is under the specified limit.

Pharmaceutical assay

The assays described are the official methods upon which the standard of the pharmacopoeia depend. By using HPLC assay was carried out on the newly developed formulation of Ribavirin Capsules contain an amount of Ribavirin equivalent to NLT 90.0% and NMT 110.0% each of the labeled amount of Ribavirin during the study. All capsules have potencies in accordance of required specification (Table 5).

In the present study new formulation of Ribavirin capsule was manufactured. All parameters of (average weight, weight variation, dissolution, disintegration time and assay) of new formulation were tested and results showed that they are in accordance with the BP/USP limits. In our trials Disintegration time was found to be 3 minutes 18 seconds which is within specified BP/USP limit. And the dissolved amount of Ribavirin should NLT 80% (Q) of the labeled amount in 30 min. Potency of the Ribavirin equivalent to NLT 90.0% and NMT 110.0% each of the labeled amount of Ribavirin. Our research group has done these types of formulation studies.

CONCLUSION

All parameters (average weight, weight variation, dissolution, disintegration time, and assay) of new formulations were tested and results showed that average weight, weight variation, disintegration time, dissolution and assay are in accordance with BP/USP limits. The advantage of this formulation is that this formulation is a quite simple; less time consuming, economical and achieved all qualitative and quantitative characteristics which were required by pharmaceutical industry for a dosage form.

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