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Research Article

# FORMULATION AND EVALUATION OFENTERIC COATED PELLETS OF RIFAMPICIN AND ISONIAZID WITH IMPROVED RIFAMPICIN STABILITY

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**ABSTRACT**

Objective: The aim of the present study is to formulate and evaluate enteric coated pellets of Rifampicin and Isoniazid with improved Rifampicin stability in *invitro* conditions.
Methodology: Two different capsule formulations of these drugs were prepared. Formulation-I contains immediate release uncoated pellets of Rifampicin and Isoniazid. Formulation-IIcontains immediate release enteric coated pellets of Rifampicin and Isoniazid. These pellets were evaluated for various physicochemical parameters. Enteric coating was mainly done to prevent the release of these drugs in acidic medium and to improve the stability of Rifampicin by preventing its interaction with Isoniazid in acidic medium. Dissolution studies for both these formulations were performed and the cumulative percentage drug release for Rifampicin was calculated.
Results: The cumulative percentage drug release for Rifampicin was found to be around 81% in formulation-I whereas it has been increased to 89% in formulation-II.
Conclusion: This study proves that Rifampicin interacts with Isoniazid and undergoes degradation to a significant extent in acidic medium. This interaction and degradation can be reduced and the stabilityof Rifampicin can be enhanced by formulating them as enteric coated dosage forms.

**Keywords:** Rifampicin, Isoniazid, Enteric coating,pellets.

## INTRODUCTION

Tuberculosiswas for centuries a major killer disease. With the development of the first line drugs, it came to be regarded as an easily curable condition. This is no longer easily curable as the bacteria Mycobacterium tuberculosis which causes it has come back to haunt us. Multidrug-resistant strains are now common and recent evidence suggests that strains with increased virulence have emerged [1]. One of the main reasons for the development of this resistance is the mono drug therapy. Thismay be due to the drug-drug interactions as the therapy includes combination of various drugs [2]. One suchcommonlyreported interaction is between Rifampicin and Isoniazid in the stomach pH,the two extensively used drugsin the treatment of Tuberculosis leading to the poor stability and bioavailability of Rifampicin [3]. The present study deals with improving the stability of Rifampicin by modifying the formulation and design of the dosage forms [4].

## MATERIALS

Rifampicin and Isoniazid were purchased from Yarrow chemicals Ltd. Eudragit L-100 was obtained from Dr. Reddy's labs Pvt. Ltd. SuperTab 11SD was obtained from DFE Pharma, Germany. Talc and Magnesium stearate were purchased from Himedia chemicals Ltd. Conc. Hydrochloric acid, Acetone, Glycerol and Isopropyl alcohol were purchased from SD-fine chemicals Ltd.

## EQUIPMENT

UV-visible spectrophotometer- UV 1601 PC, Shimadzu, Japan.

Pan coating equipment- Instacoat, Pharma R&D coater, Ideal Cures pvt. Ltd., Mumbai

Weighing balance- Model FB-200 of EssaeTeraoka Ltd.

Friabilator- Model EF-1W of Electrolab

Pelletizer-Extruder and spherodizer- UmangPharmatechpvt. Ltd., Mumbai.

Dissolution apparatus- Dissolution tester (USPII), TDT-08L, Electrolab.

Tap density tester (USP)- Electrolab.

Electromagnetic Sieve shaker - EMS-8, Electrolab

Tray dryer - Klass Engineers.

Mortar & pestle.

### Objective

The objective of the present study was to formulate once-daily oral fixed-dose combination pellets of Rifampicinand Isoniazid, which facilitates the delivery of these drugs in intestinal pH for improved Rifampicin stability.

### Methodology

To achieve the above said objective, two different formulations were manufactured.Formulation I includescapsules of Rifampicin and Isoniazid containing immediate releaseuncoated pellets and Formulation II includes capsules containing enteric coated pellets of Rifampicin and Isoniazid. The formulation ingredients of Rifampicin and Isoniazid tablets are given in the table1 and table2 respectively.EudragitL-100 was used as enteric coating polymer and the tablets were coated by pan coating technique [5].

### Preparation of the formulations

The required quantities of the drugs [6]and the excipients (as mentioned in the tables 1, 2) which include the vehicle, lubricant and glident were mixed uniformly by triturating them in a mortar and pestle. The pellets were prepared by Extrusion Spheronization method with optimized speed of 10 and 1000rpm for extrusion and spheronization respectively. Water was used as wetting liquid.The wetRifampicin and Isoniazid pellets were dried at 60°C by tray drying for 1hour. These dried pellets were evaluated for thevarious parameters like size, flow properties and friability. Then these pellets were weighed and transferred into capsule shell. The dissolution study was conducted to quantify the release of Rifampicin from the formulation I.

Then these pellets were enteric coated using the coating solution formula given in table 3 by Pan coating method [5]. The specifications of this method are mentioned in the table 4. The dissolution study was conducted again after coating to quantify the release of Rifampicin from the formulation II.

**Table 1: Rifampicin Formulation**

| Ingredients | Quantities (mg) |
|---|---|
| Rifampicin | 600 |
| Talc | 10 |
| Magnesium stearate | 10 |
| SuperTab 11SD | q.s. to 700 |

**Table 2: Isoniazid Formulation**

| Ingredients | Quantities (mg) |
|---|---|
| Isoniazid | 300 |
| Talc | 6 |
| Magnesium stearate | 6 |
| SuperTab 11SD | q.s. to 400 |

**Table 3: Enteric coating solution**

| Coating polymer | Eudragit L-100 |
|---|---|
| Plasticizer | Glycerol |
| Solvent system | Acetone + Isopropyl alcohol |

**Table 4: Pan coating specifications**

| Pan rpm | 30 |
|---|---|
| Pump rpm | 1 |
| Temperature | 40°C |
| Atomization air pressure | 20psi |
| Distance between spray gun and tablet bed was maintained at 10cm | |

**Pellet size:**Average pellet size of both Rifampicin and Isoniazid pellets was determined by sieving method.

**Friability:**The prescribed weight of uncoated pellets was placed into the friabilator and was rotated (100 rpm as per Indian Pharmacopoeia [7]) and the final weight of the pellets was noted and the percentage weight loss was computed.

**Flow properties:** Flow properties like angle of repose, carr's index and hausner ratio were determined.Angle of repose was determined by funnel method. Carr's index (C) and hausner ratio (H) were calculated from the bulk and tapped densities of these pellets by using the following equations.

$$C = 100(\rho tapped - \rho bulk)/\rho tapped$$

$$H = (\rho tapped/\rho bulk)$$

ρbulk - bulk density, ρtapped- tapped density

**Dissolution test:**Required numbers of capsules containing the pellets according to Indian Pharmacopoeia [7] wereadded into the Dissolution Test apparatus (USP II) and the release of Rifampicin was analysed at 336nm wavelength using UV-visible spectrophotometer for both Formulation I and II in 0.1N Hydrochloric acid for 2 hours. After 2 hours the formulation II was shifted to phosphate buffer of pH 6.8 and analysed for Rifampicin release.

**RESULTS**

**Pellet size:** The average pellet size for Rifampicin and Isoniazid pellets was found to be 1048µ and 982µ respectively.

**Friability:**The uncoated pellets of both the drugs have passed the IP limits for friability.The results are shown in figure1.

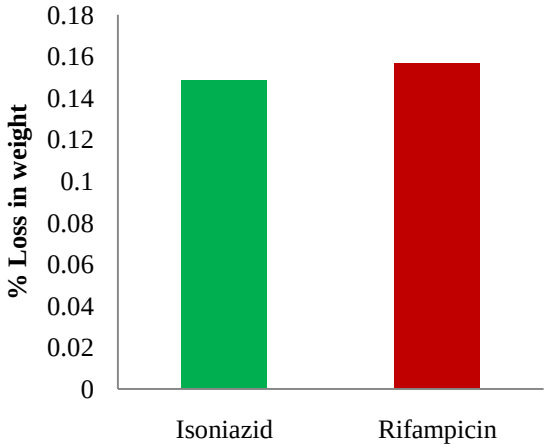


**Figure1: Friability of the pellets**

**Flow properties:** The results were given in the table 5 which indicate that the pellets have very good flow.

**Table 5: Flow properties of the pellets**

| Flow property | Rifampicin pellets | Isoniazid pellets |
|---|---|---|
| Angle of repose | 22° | 24° |
| Bulk density | 1.40 g/ml | 1.45 g/ml |
| Tapped density | 1.50 g/ml | 1.60 g/ml |
| Carr's index | 6.67% | 9.37% |
| Hausner ratio | 1.07 | 1.10 |

**Enteric coating of Isoniazid tablets:** The weight gain was found to be 10% w/w of the core combination pellet.

**Dissolution studies:** Dissolution studies were performed for Formulation I and II separately in 0.1N HCl. Then the cumulative percentage drug release for Rifampicin was calculated from the obtained data. In case of Formulation I, the cumulative percentage drug release for Rifampicin after 2hr in 0.1N HCl was found to be around 81% whereas for Formulation II did not release Rifampicin in 0.1N HCl but it has shown a phenomenal increase in release to 89% in phosphate buffer of pH 6.8.The results are given in figure2.

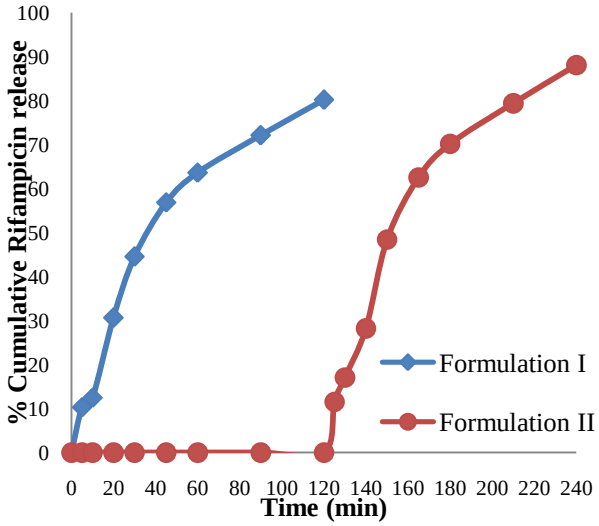


**Figure2: Dissolution studies of the formulations I and II**

**CONCLUSION**

This study proves that Rifampicin interacts with Isoniazid and undergoes degradation to a phenomenal extent in presence of Isoniazid in acidic medium of stomach. This interaction and degradation of Rifampicin can be reduced and the stability of Rifampicin can be enhanced by formulating these drugs as enteric coated pelletsso that the physical contact between these two drugs can be prevented in the acidic medium of stomach by releasing these drugsin the intestinalpH.

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