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Research Article

FORMULATION AND EVALUATION OF MULTIPARTICULATE SYSTEMS OF RIFAMPICIN AND ISONIAZID WITH IMPROVED RIFAMPICIN STABILITY

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ABSTRACT

Context: One of the main reasons for the development of resistance to Tuberculosis is the drug-drug interactions as the therapy includes combination of various drugs. One such commonly reported interaction is between Rifampicin and Isoniazid, the two extensively used drugs in the treatment of Tuberculosis in the stomach pHleading to the poor stability and bioavailability of Rifampicin.

Objective: The aim of the present study is to formulate and evaluate pellets of Rifampicin and Isoniazid with improved Rifampicin stability in *in vitro* conditions.

Methods: Two different capsule formulations of these drugs were prepared. Formulation-I contains immediate release uncoated pellets of Rifampicin and Isoniazid. Formulation-IIcontains immediate release pellets of Rifampicin and enteric coated pellets of Isoniazid. These pellets were evaluated for various physicochemical parameters. Enteric coating was mainly done to prevent the release of Isoniazid in acidic medium and to improve the stability of Rifampicin by preventing their interaction in stomach. 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 92% 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 Isoniazid as enteric coated pellets.

Keywords: Enteric coating, Pellets, Drug-drug interactions.

INTRODUCTION

Tuberculosis was 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 leading to poor bioavailability of these 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 design of the dosage forms [4].

MATERIALS AND METHODS

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.

Electromagnetic Sieve shaker- EMS 8, Electrolab

Tap density tester (USP)- Electrolab.

Tray dryer - Klass Engineers.

Mortar & pestle.

Objective

The objective of the present study was to formulate once-daily oral multiparticulate systems (pellets) of Rifampicinand Isoniazid, which facilitates thesegregated delivery of these drugs in GITfor 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 uncoated immediate release pellets of Rifampicin and enteric coated pellets ofIsoniazid. The formulation ingredients of Rifampicin and Isoniazid pellets are given in the table1 and table2 respectively.EudragitL-100 was used as enteric coating polymer and the pellets 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 50°C by tray drying for 1hr. Then these pellets were evaluated for thevarious parameters like size, flow properties, friability, drug content and dissolution. Then these pellets were weighed and transferred into hard gelatincapsule shells of sizes 00 and 0 for Rifampicin and

Isoniazid pellets respectively. The dissolution study was conducted to quantify the release of Rifampicin from the formulation I.

Then Isoniazid pellets were enteric coated using the coating solution formula given in table 3 by Pan coating method. The specifications of this method are mentioned in the table 4. After coating the pellets of Isoniazid were transferred into hard gelatin capsule shell. The dissolution study was conducted againto 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 pellet bed was maintained at 10cm	

Sieve analysis: Average pellet size of both Rifampicin and Isoniazid pellets was determined by sieving method and the pellets lying in the range of 900 – 1200µwas considered as yield value.

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

Drug content: Required quantity of the uncoated pellets of these drugs were taken separately and crushed in porcelain mortar and pestle. From that 100mg of powder was taken separately into 100ml volumetric flask and thoroughly mixed with distilled water and sonicated in bath sonicator.

Then the dispersion is filtered through whatman membrane filterpaper. The filtrate was diluted and analysed for their drug contents at 336nm wave length for Rifampicin and 265nm for Isoniazid respectively using UV-visible spectrophotometer.

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.

RESULTS

Sieve analysis: The average pellet size for Rifampicin and Isoniazid pellets was found to be 1042µ and 1096µ respectively and the yield value was 96.48% and 97.32% respectively.

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

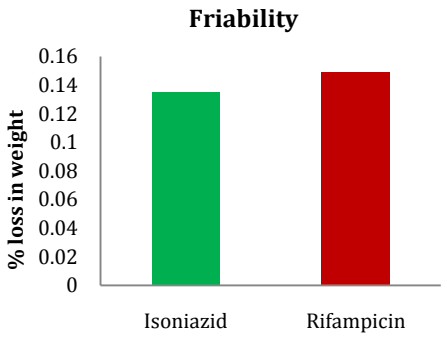

Fig.1: Friability studies of Isoniazid and Rifampicin pellets

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

Table 5: Flow properties

Flow property	Rifampicin pellets	Isoniazid pellets
Angle of repose	24°	26°
Bulk density	1.40 g/ml	1.35 g/ml
Tapped density	1.55 g/ml	1.50 g/ml
Carr's index	9.67%	10%
Hausner ratio	1.107	1.111

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

Drug content: The drug content was 98.34% and 98.58% of theoretical yield for Rifampicin and Isoniazid respectively.

Table 6: Cumulative % release of Rifampicin

Time (min)	Formulation I	Formulation II
0	0	0
5	10.12±0.92	11.52±1.11
10	14.7±1.26	18.54±1.32
20	30.18±1.31	31.08±1.42
30	45.21±1.51	48.94±1.56
45	58.33±1.32	64.56±1.26
60	66.26±1.48	74.61±1.34
90	73.81±1.72	82.84±1.58
120	80.89±1.28	92.02±1.54

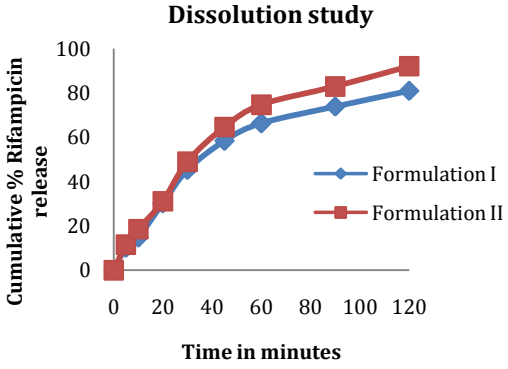

Fig. 2: Dissolution studies of the formulations

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 it has shown a phenomenal increaseup to 92%.The results are given in table6 and figure2 respectively.

DISCUSSION

From the results obtained, the pellets prepared showed very good flow properties with a good yield value and average pellet size. The friability was well within the IP limits. With respect to the drug content, there is no much loss during the preparation steps for both the drugs. The major finding and difference was observed with the release of Rifampicin in the formulations. As expected there is phenomenal increase in the release of Rifampicin in formulation II where the Isoniazid pellets were enteric coated.

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 can be enhanced by segregating the delivery of these drugs by formulating Isoniazid as enteric coated pelletsso that it is released in Intestine the physical contact between these two drugs can be prevented in the acidic medium of stomach.

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