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Research Article

FORMULATION AND EVALUATION OF FIXED DOSE COMBINATION PRODUCTS OF RIFAMPICIN AND ISONIAZID WITH IMPROVED RIFAMPICIN STABILITY

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ABSTRACT

Introduction: One of the main reasons for the development of the resistance in the therapy for Tuberculosis is the mono drug therapy. This may be due to the drug-drug interactions as the therapy includes combination of various drugs leading to poor bioavailability of these drugs. One such reported interaction is between Rifampicin and Isoniazid which leads to poor bioavailability of Rifampicin.

Objective: The aim of the present study is to formulate and evaluate fixed dose combination tablets of Rifampicin and Isoniazid with improved Rifampicin stability in *invitro* conditions.

Methodology: Rifampicin and Isoniazid were formulated separately as immediate release tablets. Then these tablets were evaluated for the various physical parameters like appearance, weight variation, hardness, friability and disintegration. Then the Isoniazid tablets were enteric coated with Eudragit L-100 using pan coating technique. Dissolution studies for the Rifampicin tablets were performed along with uncoated Isoniazid (Formulation I) and as well in combination withenteric coated Isoniazid (Formulation II) tablets separately.

Results: The cumulative percentage drug release for Rifampicin was found to be around 80% in case of Formulation I (when it was taken along with uncoated immediate release Isoniazid tablets) whereas it has been increased to91% for Formulation II (when it is with enteric coated Isoniazid tablets).

Conclusion: This study proves that Rifampicin interacts with Isoniazid and undergoes degradation to a phenomenal extent in presence of Isoniazid at pH 1.2. This interaction and degradation of Rifampicin can be reduced and the stability can be enhanced by enteric coating of Isoniazid with suitable polymers.

Keywords: Rifampicin, Isoniazid, Enteric coating, Fixed dose combination products.

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 fixed dose ofdrugs leading to poor bioavailability [2]. One such commonly reported interaction is between Rifampicin and Isoniazid, the two extensively used drugs in 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 by enteric coating the Isoniazid tablets [4]. Only Isoniazid was enteric coated instead of Rifampicin as Rifampicin has shown more solubility and permeability when it is released in the stomach [5].

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.

Tablet compression machine- Rimek Mini Press, Karnavati Engineering Ltd., Ahmedabad

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

Disintegration Tester- Model ED-2L of Electrolab

Hardness Tester- Monsanto of Tab machines

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

Mortar and pestle

Objective

The objective of the present study was to formulate once-daily oral fixed-dose combination tablets of Rifampicin and Isoniazid, which facilitates the segregated delivery of these drugs for improved Rifampicin stability.

Methodology

To achieve the above said objective, two different formulations were manufactured. Formulation I includes Rifampicin and Isoniazid as immediate release uncoated tablets and Formulation II includes Rifampicin in uncoated form and Isoniazid in enteric coated form. The formulation ingredients of Rifampicin and Isoniazid tablets are given in the table1 and table2 respectively. Eudragit L-100 was used as enteric coating polymer and the tablets were coated by pan coating technique [9].

Preparation of the formulations

The required quantities of the drugs [10] and the excipients (as mentioned in the tables 1and 2) which include the directly compressible vehicle, lubricant and glident were mixed uniformly by triturating them in a mortar and pestle. After adjusting the die cavity in the tablet compression machine with respect to the weight required by the vehicle, the tablets were prepared by direct compression method [6, 7]. The prepared Rifampicin and Isoniazid tablets were evaluated for the physical parameters like hardness, weight variation, friability, disintegration and dissolution.

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

Weight Variation

Uncoated tablets of Rifampicin and Isoniazid were weighed and the % deviation of each and every tablet from the mean weight was calculated. The procedure for weight variation was followed as per Indian Pharmacopoeia (IP) [8].

Hardness

The tablets were carefully placed in the hardness tester, the pressure was applied and the pressure at which the tablets break was noted.

Friability

The prescribed number of tablets were weighed and placed into the friabilator and were rotated at 100 rpm as per IP [8] and the final weight of the tablets was noted and the percentage weight loss was computed.

Disintegration Test

Required numbers of tablets as per IP [8] were added into the Disintegration Test apparatus and the disintegration time was noted.

Dissolution test

Required numbers of tablets according to IP [8] were added into the Dissolution Test apparatus (USP II) and the release of the drug Rifampicin was analysed at 336nm wavelength using UV-visible spectrophotometer for both Formulation I and II in 0.1N Hydrochloric acid.

Enteric coating of Isoniazid tablets [9]

Polymer: Eudragit L-100

Plasticizer: Glycerol

Solvent system: Acetone & Isopropyl Alcohol (IPA)

Technique: Pan Coating Technique

Enteric coating process parameters

Atomization air pressure:20psi

Pan RPM: 30

Pump RPM: 1

Inlet air temperature: 40 ºC

Distance between spray gun and tablet bed was maintained at 10cm

RESULTS

Hardness

The average hardness of Isoniazid tablets was found to be 4.1kg/cm^2 whereas it was 4.5kg/cm^2 for Rifampicin tablets. The results are tabulated in table3 and figure1.

Table 3: Hardness

	Average hardness (Kg/cm2)
Isoniazid	4.1
Rifampicin	4.5

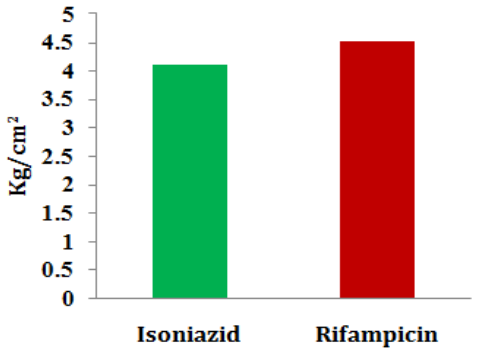

Fig.1: Hardness

Friability

The tablets of both the drugs have passed the IP limits [8] for friability. The results are shown in table4 and figure2.

Table 4: Friability

	% loss in weight
Isoniazid	0.1421
Rifampicin	0.1255

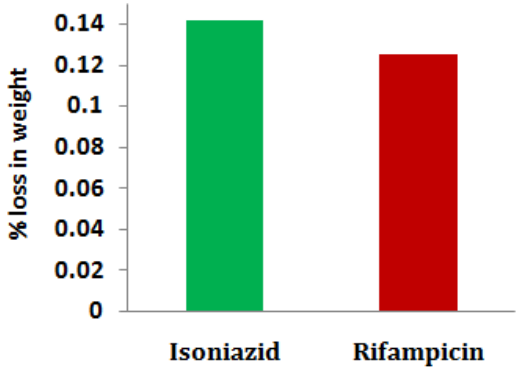

Fig. 2: Friability

Weight variation

All the uncoated tablets were within the limits as per IP [8] with respect to weight variation test. The results are shown in the figure3.

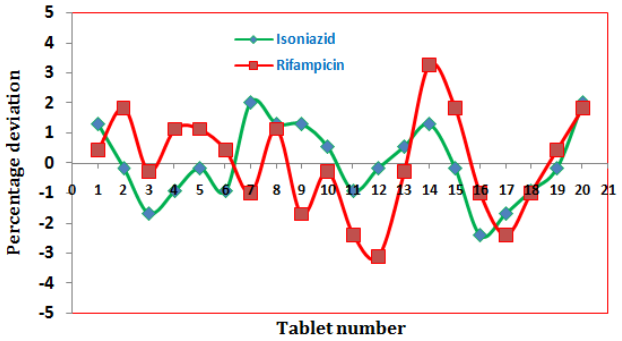

Fig. 3: Weight variation

Disintegration test

The disintegration time of uncoated tablets of both the drugs confirmed to IP specifications [8]. The results are shown in table5 and figure4.

Table 5: Disintegration test

	Disintegration time (min)
Isoniazid	8.37
Rifampicin	13.12

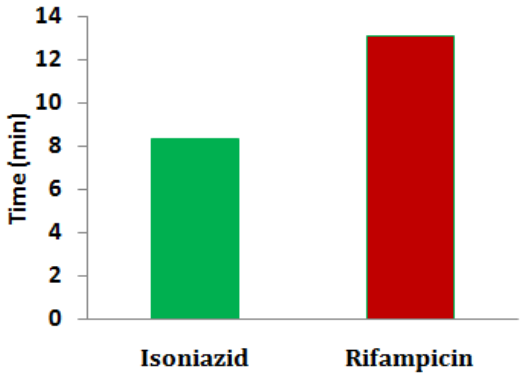

Fig. 4: Disintegration test

Enteric coating of Isoniazid tablets

The weight gain was found to be 10% w/w of the core tablet of Isoniazid.

Dissolution studies

Dissolution studies for the Rifampicin tablets 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 80% whereas for Formulation II release of Rifampicin is phenomenally increased to 91%.The results are given in table6 and figure5 respectively.

Table 6: Dissolution test

Time (min)	Rifampicin + Uncoated Isoniazid	Rifampicin+ Enteric coated Isoniazid
0	0	0
5	10.31±2.10	9.56±2.04
10	12.5±1.82	14.1±1.66
20	30.66±2.34	28.26±1.59
30	44.56±1.78	41±2.42
45	56.88±1.22	58.55±1.31
60	63.68±1.48	68.22±1.92
90	72.14±2.11	80.42±2.32
120	80.22±2.06	90.81±1.54

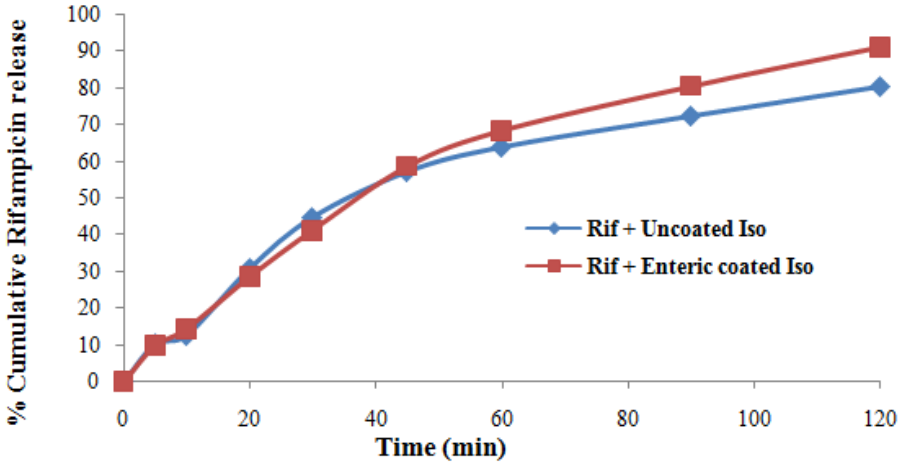

Fig. 5: Dissolution studies

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 coating Isoniazid with enteric coating polymers so that the physical contact between these two drugs can be prevented in the stomach by modifying the release of Isoniazid in intestinal pH.

REFERENCES

1. Rang, H.P, Dale, M.M, Ritter, J.M. Pharmacology. Antibacterial drugs. Fourth edition, page no. 703. Churchill livingstone publishers Ltd, 2000.
2. Sankar, R, Nishi Sharda, Saranjit Singh. Behavior of decomposition of rifampicin in the presence of isoniazid in the pH range 1–3. Drug Dev. Ind. Pharm. 2003; 29(7), 733–738.
3. Shishoo, C.J, Shah, S.A, Rathod, I.S, Savale, S.S, Kotecha, J.S, Shah, P.B. Stability of rifampicin in dissolution medium in presence of isoniazid. Int. J. Pharm. 1999; 190, 109–123.
4. Saranjit Singh, Mariappan, T.T, Sankar, R,Sarda, N, Baljinder Singh. A critical review of the probable reasons for the poor/variable bioavailability of rifampicin from anti-tubercular fixed-dose combination (FDC) products, and the likely solutions to the problem. Int. J. Pharm. 2001; 228, 5–17.
5. Mariappan, T.T, Singh, S. Regional gastrointestinal permeability of rifampicin and isoniazid (alone and their combination) in the rat. Int. J. Tuberc. Lung Dis. 2003; 7(8), 797-803.
6. William CG, Joseph LK. Tablets. The Theory and Practice of Industrial Pharmacy. Edited by Leon Lachman, Herbert AL and Joseph LK. New York. 1976: 2nd edition: pp.321-358.
7. Peter D. Oral solid dosage forms. Pharmaceutical Preformulation and Formulation. Edited by Mark Gibson, UK.2001: 1st Indian edition: pp. 379 – 456.
8. Pharmaceutical Methods, General Chapters, Indian Pharmacopoeia, 2007, 5th edition, Vol-1, pp. 177-183.
9. John RE, Elliot BP, Anton HA. Tablet Coating. The Theory and Practice of Industrial Pharmacy. Edited by Leon Lachman, Herbert AL and Joseph LK. New York. 1976: 2nd edition: pp.359-388.
10. Standardized treatment regimens. Treatment of Tuberculosis: guidelines for national programmes, World Health Organization, Geneva, 2003, 3rd edition, pp 27- 39.