A Novel Solid Dosage Form of Rifampicin and Isoniazid With Improved Functionality

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ABSTRACT

The aim of the present investigation was to develop a novel dosage form of rifampicin and isoniazid to minimize degradation of rifampicin in acidic medium and to modulate the release of rifampicin in the stomach and isoniazid in the intestine. Gastroretentive tablets of rifampicin (150 mg) were prepared by the wet granulation method using hydroxypropyl methylcellulose, calcium carbonate, and polyethylene glycol 4000. The granules and tablets of rifampicin were characterized. Hard gelatin capsules (size 4) containing a compacted mass of isoniazid (150 mg) and dicalcium phosphate (75 mg) were enteric coated. Two tablets of rifampicin and 1 capsule (size 4) of isoniazid were put into a hard gelatin capsule (size 00). The in vitro drug release and in vitro drug degradation studies were performed. Rifampicin was released over 4 hours by zero-order kinetics from the novel dosage form. More than 90% of isoniazid was released in alkaline medium in 30 minutes. The results of dissolution studies with the US Pharmacopeia XXIII method revealed that a substantial amount of rifampicin was degraded from the immediate release capsule containing rifampicin and isoniazid powder owing to drug accumulation in the dissolution vessel and also to the presence of isoniazid. The degradation of rifampicin to 3-formyl rifampicin SV (3FRSV) was arrested (3.6%-4.8% degradation of rifampicin at 4 hours) because of the minimization of physical contact between the 2 drugs and controlled release of rifampicin in acidic medium in the modified Rossett-Rice apparatus. This study concludes that the problem of rifampicin degradation can be alleviated to a certain extent by this novel dosage form.

KEYWORDS: Rifampicin, gastroretentive, isoniazid, enteric, dissolution, degradation.

INTRODUCTION

Tuberculosis (TB) has been declared a public health emergency by the World Health Organization (WHO). Rifampicin, isoniazid, pyrazinamide, and ethambutol were earlier prescribed as separate formulations in TB control. WHO and the International Union Against Tuberculosis and Lung Disease recommend the use of fixed-dose combination formulations of the essential antituberculosis drugs to ensure adequate treatment of patients.[1] The emergence of multidrug-resistant TB has threatened the efforts at TB control. The major clinical issue with TB therapy is the poor oral bioavailability of rifampicin. One of the reasons for the poor bioavailability of the fixed dose combination is enhanced degradation of rifampicin in acidic medium in the presence of isoniazid. Shishoo et al reported that isoniazid triggers the degradation of rifampicin in acidic medium.[2] Singh et al reported that the increased decomposition of rifampicin in the presence of isoniazid is due to the formation of hydrazone.[3] Mariappan and Singh reported that rifampicin is well absorbed from the stomach because of its high solubility between pH 1 and 2. They reported that isoniazid is poorly absorbed from the stomach, while it is well absorbed from all 3 segments of the intestine.[4]

Gallo and Radaelli reported that rifampicin is more soluble at low pH (pH 1.5, 1 in 5 of 0.1 M HCl, at 37°C), while it is less soluble at higher pH (pH 7.4, 1 in 100 of phosphate buffer, at 37°C).[5] Prankerd et al reported that the solubility of rifampicin at 25°C is 1 in ~10, 250, and 360 parts of water at pH 2, 5.3, and 7.5, respectively.[6] Rifampicin is hydrolyzed to 3-formyl rifampicin SV (3FRSV) and 1-amino 4 methyl piperazine under acidic pH and oxidized to rifampicin quinone in phosphate buffer (pH 7.4).[5] At pH 8.2, rifampicin forms 25-desacetyl rifampicin, which is insoluble in the alkaline medium.[7] Mariappan and Singh reported that a delivery system should release rifampicin in the gastric medium and isoniazid in the distal jejunum or ileum.[4]

The reported research underlines the importance of minimizing contact between rifampicin and isoniazid and site-specific release of the anti-TB drugs. The present work was undertaken to develop a novel solid dosage form (tablet and capsule in capsule) comprising a gastroretentive modified release rifampicin tablet and an enteric-coated isoniazid capsule. One of the objectives of the present study was to gradually release rifampicin in acidic medium to minimize the concentration-dependent degradation of rifampicin. Furthermore, enteric-coated isoniazid capsules were designed

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to prevent degradation of rifampicin in the presence of isoniazid in acidic medium.

Materials and Methods

Materials

Rifampicin Indian Pharmacopeia (IP) and isoniazid IP from Sunij Pharma Ltd, Ahmedabad, India; hydroxypropyl methylcellulose K4 M and dicalcium phosphate dihydrate from Cadila Health Care Ltd, Ahmedabad, India; calcium carbonate, chloroform, and acetone from S. D. Fine Chemicals Ltd, Mumbai, India; polyethylene glycol 4000 and anhydrous sodium sulfate from Laser Laboratories, Ahmedabad, India; Eudragit L100-55 from Degussa India Pvt Ltd (Rohm America), Mumbai, India; ascorbic acid from Dewang Corp, Ahmedabad, India; empty hard gelatin capsules from Capsule Corporation of India, Ahmedabad, India; and ethanol from Baroda Chemical Industries Ltd, Baroda, India, were used as received.

Preparation of Gastroretentive Tablet of Rifampicin

A blend of rifampicin (15 g), hydroxypropyl methylcellulose K4 M (2 g), polyethylene glycol 4000 (1.5 g), and calcium carbonate (1 g) was granulated using ascorbic acid solution (0.5% wt/vol in alcohol:acetone blend [1:3]). The wet coherent mass was passed through No 30 sieve, and the granules were dried in a microwave oven at 90°C for 2 minutes. Fines were separated by tapping granules on a No 30/60 sieve. Magnesium stearate (0.1 g) was used as a lubricant. Gastroretentive tablets of rifampicin with 200 mg average weight were prepared by compression of dried granules of rifampicin on a single station tablet machine (Cadmach Machinery Co, Ltd, Ahmedabad, India). Each tablet contained 150 mg of rifampicin. The composition of batches A1 to C4 is shown in Table 1.

Evaluation of Granules and Tablets

The flowability of rifampicin granules was estimated by Carr's index, the Hausner ratio, and the angle of repose.[8-12] The friability of granules was determined by rotating the granules in a friabilator (US Pharmacopeia [USP] XXIII, Electrolab, Mumbai, India) for 60 minutes at 25 rpm.

$$Friability\ index(FI) = \frac{Mean\ Particle\ Size\ of\ Friabilator\ Treated\ Granules}{Mean\ Particle\ Size\ of\ Untreated\ Granules} \quad (1)$$

Rifampicin tablets were characterized by crushing strength (8M tablet-hardness testing machine, Dr Schleuniger Pharmatron, Solothurn, Switzerland), percentage friability, lag time to float, and duration of floating in 0.1N HCl.

Table 1. Batches Prepared for Optimization of Gastroretentive Tablet of Rifampicin*

Optimization Stage 1			
Batch	Rifampicin (mg)	HPMC K4 M (mg)	$CaCO_3$ (mg)
A1	150	30	5
A2	150	30	10
A3	150	30	15
A4	150	20	5
A5	150	20	10
A6	150	20	15
A7	150	10	5
A8	150	10	10
A9	150	10	15

Optimization Stage 2†	
Batch	Alcohol:Acetone
B1	1:1
B2	1:2
B3	1:3
B4	1:4

Optimization Stage 3‡	
Batch	PEG 4000 (mg)
C1	5
C2	10
C3	15
C4	20

* HPMC indicates hydroxypropyl methylcellulose; PEG, polyethylene glycol.
† Batch A5 was selected for stage 2.
‡ Batch B3 was selected for stage 3.

Preparation of Enteric-Coated Isoniazid Capsule

Hard gelatin capsules (size 4) containing a compacted mass of 150 mg of isoniazid and 75 mg of dicalcium phosphate dihydrate were coated using the pan coating technique. The coating solution was prepared by dissolving 2 g of Eudragit L100-55 in 100 mL of isopropyl alcohol. Castor oil (5%, 10%, or 15% wt/wt of Eudragit L100-55) and titanium dioxide (20% wt/wt of Eudragit L100-55) were mixed with the solution under stirring at 100 rpm. The volume of coating dispersion was adjusted to 100 mL using isopropyl alcohol. The weight gain of the capsule (2.5%, 5%, 7.5%, and 10%) was attributed to the amount of Eudragit L100-55, titanium dioxide, and castor oil in the film.

Preparation of Novel Dosage Form

Two gastroretentive tablets of rifampicin (300 mg of rifampicin, 7.78-mm diameter) and an enteric-coated isoniazid capsule (150 mg of isoniazid) were put into a "00"-size hard gelatin capsule. A schematic representation of the novel

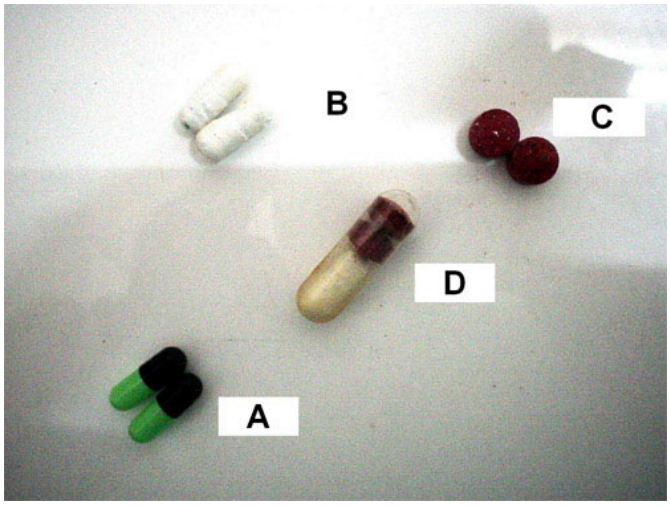

Figure 1. Schematic representation of novel dosage form: (A) uncoated isoniazid capsule; (B) enteric-coated isoniazid capsule; (C) floating tablet of rifampicin; and (D) hard gelatin capsule of B and C.

dosage form is shown in Figure 1. The novel dosage form was evaluated for in vitro drug release and in vitro drug degradation studies.

In Vitro Drug Release and In Vitro Drug Degradation Study

USP XXIII Dissolution Method

Hydrochloric acid (0.1 N, pH 1.5) and phosphate buffer (pH 7.4) were used as the dissolution media. The temperature of the dissolution medium was maintained at 37°C ± 0.5°C, and the agitation speed of the paddle was 100 rpm. Every 15 minutes, 10 mL of solution was withdrawn. The aqueous drug solution was extracted with 10 mL chloroform instantly. The aqueous medium and chloroform were separated using a separating funnel. Anhydrous sodium sulfate was used to adsorb droplets of aqueous solution from the chloroform. The volume was adjusted to 10 mL with chloroform. The isoniazid capsule was taken out of the dissolution vessel after 2 hours for further dissolution study in phosphate buffer (pH 7.4). Rifampicin and 3FRSV (degradation product of rifampicin) were determined by the dual wavelength spectrophotometric method[2] in the chloroform layer. Isoniazid was measured by the spectrophotometric method at λ_{max} 263 nm.[13]

Modified Dissolution Method

A biorelevant dissolution method for evaluation of the floating drug delivery system was adopted.[14]

In the present investigation, the drug solution coming from the bottom outlet of the beaker was immediately extracted with an organic solvent (chloroform) to monitor the drug dissolution and degradation. A modified glass beaker (Figure 2) was filled with 75 mL of 0.1 N HCl. Hydrochloric acid was added at a flow rate of 2 mL/min. The study was performed at a temperature of 37°C ± 0.5°C and an agitation speed of 75 rpm. The rifampicin was extracted with chloroform instantly. After 15 minutes, the mixture of 0.1 N HCl and chloroform was separated with a separating funnel, and simultaneously another beaker containing 10 mL chloroform was put under the bottom arm outlet of the glass beaker. Anhydrous sodium sulfate was used to adsorb droplets of the aqueous solution. The volume of extract was adjusted to 10 mL using chloroform. The amounts of undegraded rifampicin and 3FRSV were estimated by the method reported by Shishoo et al.[2] In the case of the novel dosage form, the enteric-coated isoniazid capsule was removed from the modified beaker containing 0.1 N HCl after 2 hours, and the dissolution study was continued in phosphate buffer (900 mL, pH 7.4) in the USP XXIII dissolution apparatus.

Short-Term Stability Study

The stability study (batch C3) was performed for 3 months at 45°C and 80% relative humidity. The in vitro drug release and drug degradation studies were performed every month.

Results and Discussion

Preliminary Study

Preliminary studies were performed to develop a floating matrix tablet of rifampicin that showed a lag time to float of less than 3 minutes and a duration of floating greater than 5 hours. The floating study was performed in 0.1 N HCl. Rifampicin, hydroxypropyl methylcellulose, and calcium carbonate were granulated using ethyl alcohol containing 0.5% wt/vol of ascorbic acid. Ascorbic acid was used as an antioxidant to prevent the oxidation of rifampicin. Maggi et al reported that rifampicin is converted to rifampicin quinone at higher pH but that this can be prevented by adding a reducing agent such as ascorbic acid.[7] The dried granules were lubricated with 0.5% wt/wt of magnesium

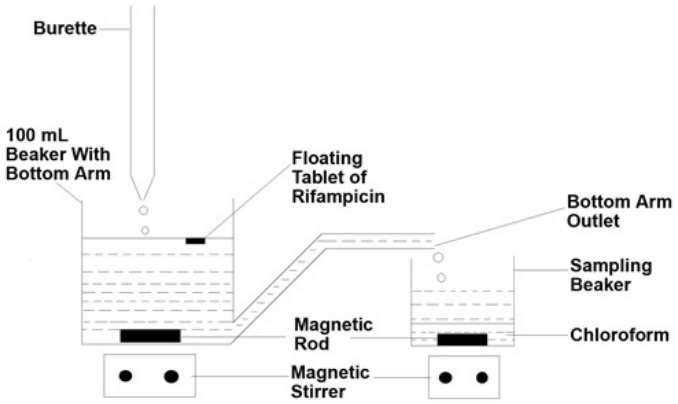

Figure 2. Schematic representation of dissolution setup.

stearate. Nine batches (A1-A9) of tablets were prepared using 10, 20, and 30 mg of hydroxypropyl methylcellulose and 5, 10, and 15 mg of calcium carbonate. The batch containing 20 mg hydroxypropyl methylcellulose and 10 mg calcium carbonate showed a desirable lag time and duration of floating. The crushing strength of the tablets of batch A5 was 80 N. From the tablets of batch A5, 27% of rifampicin was released in 4 hours in 0.1 N HCl. Rifampicin is soluble in alcohol, which might have resulted in the formation of strong tablets. Four additional batches of rifampicin tablets (B1-B4) were prepared using an alcohol:acetone blend (1:1, 1:2, 1:3, and 1:4) in place of alcohol. Acetone was selected because Gallo and Radaelli reported that rifampicin is slightly soluble in acetone.[5] The crushing strength of the tablets was 70, 60, 40, and less than 30 N, respectively. Batch B3, prepared using 1:3 alcohol:acetone, was selected for further studies because of the slight solubility of rifampicin in the solvent blend and the acceptable crushing strength of the tablets (40 N). The drug release from batch B3 was higher (52% in 4 hours) than it was for batch A5, which had been prepared using alcohol as a binder. To hasten the drug release, polyethylene glycol 4000 was used as a pore-forming agent at a level of 5, 10, 15, and 20 mg. Ninety percent of the drug was released in 4 hours from batch C3, which contained 15 mg of polyethylene glycol 4000. The formulation containing hydroxypropyl methylcellulose (20 mg), calcium carbonate (10 mg), and polyethylene glycol 4000 (15 mg) was examined for in vitro drug degradation and drug release. The procedure for making the rifampicin tablet is described in the Materials and Methods section.

The isoniazid capsule coated with Eudragit L100-55, castor oil (10% wt/wt of Eudragit), and titanium dioxide (20% wt/wt of Eudragit) showed desirable enteric qualities (no drug release in 0.1 N HCl in 2 hours and more than 90% drug release in phosphate buffer [pH 7.4] within 30 minutes). The weight gain by the capsules was 5%. This batch of isoniazid capsules was used for preparing the novel dosage form.

Table 2. Evaluation of Granules and Tablets of Rifampicin of Finalized Batch (Batch C3)

Characteristics of Granules	Observed Value	Desirable Value[8-12]
Bulk density (g/cm^3)	0.66 ± 0.14	—
Tapped density (g/cm^3)	0.73 ± 0.15	—
Hausner ratio	1.10 ± 0.28	<1.25
Carr's index	11.7 ± 1.36	5-15
Angle of repose (º)	30.0 ± 2.01	30-32
Friability index	0.94 ± 0.33	1
Characteristics of Tablets		
Friability (%)	0.71 ± 0.12	<1
Crushing strength (N)	45.0 ± 4.46	40-50
Lag time to float (minutes)	0.75 ± 0.14	<3
Duration of floating (hours)	6.0 ± 0.52	≥5 hours

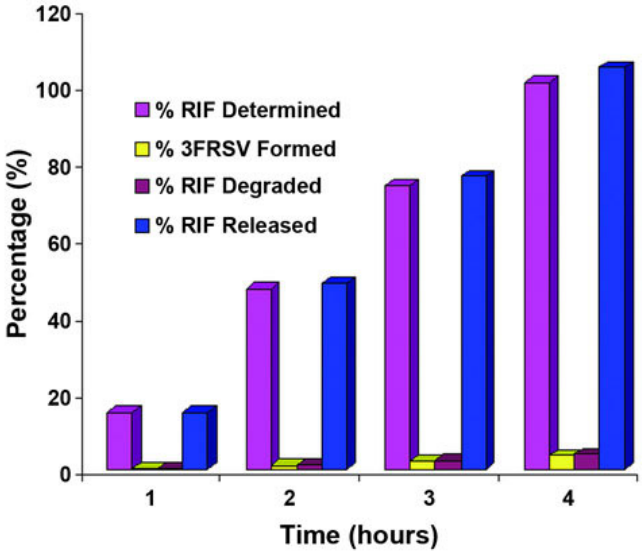

Figure 3. In vitro drug release and in vitro drug degradation from novel dosage form. RIF indicates rifampicin; and 3FRSV, 3-formyl rifampicin SV.

Evaluation of Granules and Tablets of Rifampicin

Table 2 shows the arbitrarily decided desirable values of evaluation parameters and the results of evaluation of the granules and tablets of rifampicin. The results of the Hausner ratio, Carr's index, and the angle of repose reveal that the granules exhibited good flow characteristics. The granules were nonfriable in nature (friability index = 0.94). The tablets exhibited acceptable friability, crushing strength, lag time to float, and duration of floating.

In Vitro Drug Release From Novel Dosage Form

For the dissolution study, a modified dissolution apparatus (Figure 2) was used.[14] The dissolution apparatus was designed specifically for evaluating the floating dosage form to provide biorelevant conditions. The eluted solution containing rifampicin was instantly extracted with chloroform. It was assumed that the amount of rifampicin dissolved in the eluted acidic dissolution medium is equal to the amount of rifampicin absorbed in the body. In the body, dissolution and absorption can occur concurrently. Accumulation of the dissolved drug is expected in the dissolution medium when a USP XXIII apparatus is used (ie, an inaccurate estimate of degraded drug will be made when the classical dissolution methodology is adopted).

Figure 3 shows that rifampicin was gradually released from the novel dosage form (90% release of rifampicin at 3.5-4 hours in 0.1 N HCl). The method of Bamba et al was

adopted to find the kinetics of drug release.[15] The Hixson-Crowell, Korsmeyer-Peppas, Weibull, zero-order, first-order, and Higuchi models were tested. The F value of the zero-order model was 5.5, which was significantly different from that of the other models: Hixson-Crowell (F = 25.1), Korsmeyer-Peppas (F = 261.9), Weibull (F = 34.4), first-order (F = 65.8), and Higuchi (F = 30.4).

The floating of the tablet was attributed to the presence of hydroxypropyl methylcellulose K4 M[16] and to gas formation resulting from the chemical reaction between calcium carbonate and hydrochloric acid. The gelling property of hydroxypropyl methylcellulose K4 M is responsible for sustaining drug release from the matrix tablet. The drug release from swellable and erodible hydrophilic matrices can be attributed to polymer dissolution, drug diffusion through the gel layer, or a combination of both.[17] Polyethylene glycol 4000, a water-soluble excipient, was used to modulate the drug release from the matrix tablet by increasing the porosity of the swollen matrix. A water-soluble adjuvant such as lactose is frequently used by formulation scientists in matrix tablets to modulate drug release. Sung et al reported that a greater drug release rate was observed for tablets with lower hydroxypropyl methylcellulose/lactose ratios.[18]

Isoniazid is poorly soluble in chloroform (0.1 g/100 mL).[19] Hence, it was analyzed in aqueous medium and in chloroform layer for the first 2 hours. As expected, isoniazid was not released in acidic medium from the enteric-coated isoniazid capsule. Castor oil, a hydrophobic plasticizer, prevents dissolution of the enteric coat in acidic medium. More than 90% of isoniazid was released in alkaline medium in 30 minutes.

In Vitro Drug Degradation From Novel Dosage Form

Shishoo et al reported that 12% of rifampicin degraded to 3FRSV in acidic medium in 45 minutes, while 21% of rifampicin degraded in 45 minutes when a rifampicin release study was performed in the presence of isoniazid.[2] Singh et al reported that 17% to 24% of rifampicin degraded in 0.1 N HCl at 37°C in 50 minutes when rifampicin was released with isoniazid.[3] Figure 3 shows that only 3.6% to 4.8% of rifampicin was degraded when the dosage form was tested in the modified dissolution apparatus. This reduced degradation of rifampicin could be due to the separation of rifampicin and isoniazid and/or the controlled release of rifampicin in acidic medium.

Comparative In Vitro Drug Release and In Vitro Drug Degradation Study of Different Formulations

The molecular weights of rifampicin and 3FRSV are 823 and 726, respectively. The molecular weights are dissimilar, so the method reported by Lukulay and Hokanson[20] can be used for back-calculating the amount of rifampicin that underwent degradation to 3FRSV. The following formula was used:

$$\textit{Percentage Rifampicin Degraded} = \textit{Percentage of 3 FRSV Formed} * (823/726) \quad (2)$$

The percentage of rifampicin degraded from the formulated products is shown in Figure 4. One of the objectives of the present study was to gradually release the rifampicin in acidic medium to minimize the concentration-dependent degradation of rifampicin. A hard gelatin capsule was filled with 300 mg of rifampicin to obtain an immediate release product. An in vitro dissolution study of the immediate release rifampicin capsule and the formulated floating tablet of rifampicin was performed in a USP XXIII apparatus. The results, shown in Figure 4, reveal that at 75 minutes, the percentage of 3FRSV formed from the immediate release rifampicin capsule and from the floating tablet was 22% and 7%, respectively, and the percentage of rifampicin degraded was 25% and 8%, respectively. Rifampicin is soluble in acidic medium, and it is also absorbed throughout the gastrointestinal tract (GIT).[21] Therefore, a higher percentage of rifampicin bioavailability may be expected if it is assumed that the process of rifampicin absorption is faster than the process of its dissolution. Figure 4 shows that 42% of rifampicin was degraded to 3FRSV from the immediate release capsule containing rifampicin and isoniazid at 75 minutes. On the other hand, only 7% of rifampicin was degraded from the novel dosage form containing the enteric-coated isoniazid

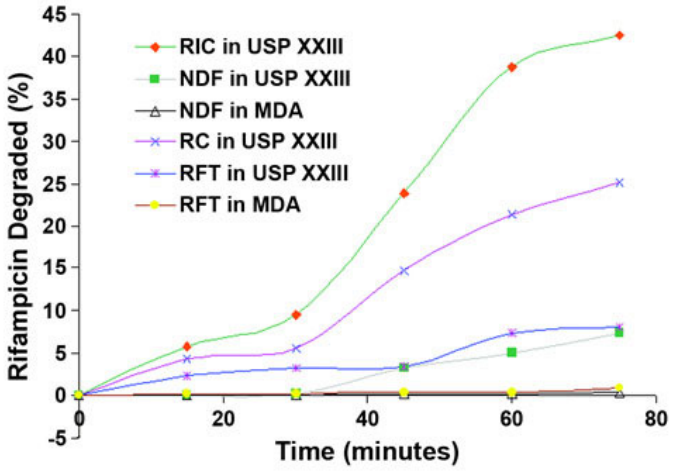

Figure 4. Comparative study of percentage of rifampicin degraded. RIC indicates rifampicin isoniazid capsule; USP, US Pharmacopeia; NDF, novel dosage form; MDA, modified dissolution apparatus; RC, rifampicin capsule; and RFT, rifampicin floating tablet.

capsule and the floating tablet of rifampicin at 75 minutes when evaluated by the USP XXIII method. The higher percentage of degradation from the immediate release rifampicin plus isoniazid capsule may be attributed to the triggering action of isoniazid as reported by Shishoo et al[2] and Singh et al.[3] The results of the present study underline the fact that minimization of contact between rifampicin and isoniazid results in less degradation of rifampicin. Enteric coating of isoniazid, therefore, is justified. It is worthwhile to note that isoniazid is well absorbed from the GIT.[21]

A modified dissolution test was performed to mimic the gastric volume and acid secretion rate. Figure 4 shows that the degradation of rifampicin was further arrested when the floating tablet of rifampicin was evaluated for in vitro drug release in the modified dissolution method (only 0.83% degradation of rifampicin at 75 minutes). The degradation of rifampicin was decreased further when the in vitro drug release and in vitro drug degradation study of the novel dosage form was performed in the modified dissolution apparatus (only 0.39% degradation of rifampicin at 75 minutes). Figure 5 shows the percentage of rifampicin released at 75 minutes from different formulations. Based on the results of the modified dissolution test, it may be concluded that the problem of rifampicin degradation in acidic medium may be addressed to a certain extent by the novel dosage form.

Food and antacids can decrease the oral absorption of rifampicin.[22,23] Hence, it is recommended that the novel dosage form be taken on an empty stomach. Figure 6 shows the results of the short-term stability study. There was no appreciable difference in drug dissolution and stability.

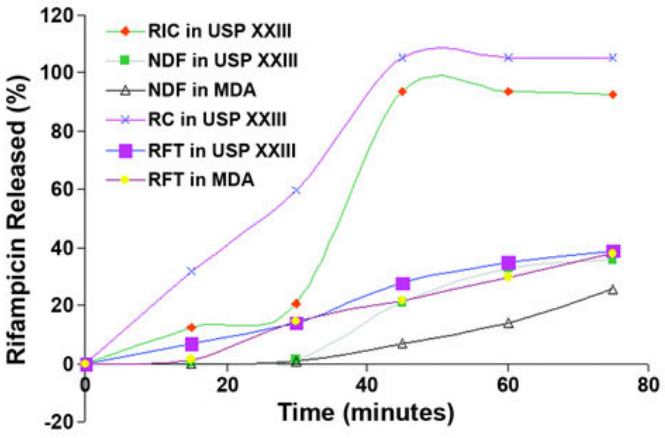

Figure 5. Comparative study of percentage of rifampicin released. RIC indicates rifampicin isoniazid capsule; NDF, novel dosage form; USP, US Pharmacopeia; MDA, modified dissolution apparatus; RC, rifampicin capsule; and RFT, rifampicin floating tablet.

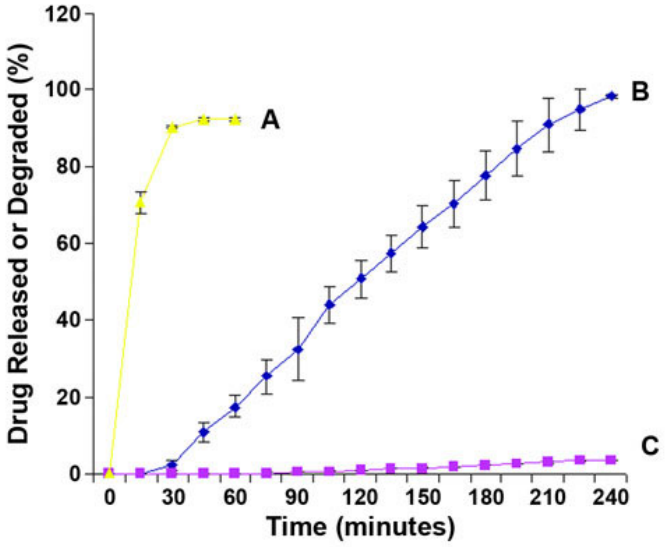

Figure 6. Stability studies of novel solid dosage form: (A) in vitro drug release of isoniazid; (B) in vitro drug release of rifampicin; and (C) in vitro drug degradation of rifampicin.

Conclusion

The minimization of contact between rifampicin and isoniazid in the presence of isoniazid and sustained release of rifampicin can alleviate the degradation of rifampicin to a certain extent from the novel dosage form. This novel dosage form will be the preferred formulation owing to less degradation of rifampicin.

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