

Design, development and evaluation of Rifampicin delayed release tablets by using Sodium Lauryl Sulphate

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ABSTRACT

The purpose of the present investigation was to achieve site specific drug delivery of rifampicin using the anionic surfactant sodium lauryl sulphate as a release retardant. Drug dissolution studies were carried out in pH 1.2 and phosphate buffer pH 6.8. The results revealed that sodium lauryl sulphate offers optimum protection for rifampicin and thereby prevents its degradation in acidic environment. The prepared tablets were evaluated for thickness, content of active ingredient, friability, hardness, and disintegration. The formulations showed compliance with Pharmacopoeial standards. In vivo performance was assessed by X-ray roentgenography study. It concluded that sodium lauryl sulphate might be successfully employed for site-specific delivery of rifampicin.

Key words: Anionic surfactant, rifampicin, site-specific delivery, roentgenography

INTRODUCTION

Rifampicin is an important anti-mycobacterial agent used in the treatment of tuberculosis and leprosy. When combined with other anti-TB drugs it exhibits certain drawbacks such as stability related problems which includes changes in drug strength, increase in degradation product levels, alteration in dissolution profile, gain in moisture, etc^{1, 2}. Independent groups in India have conducted intense research in recent years, and specific reasons that explain both the bioavailability and stability problems of FDCs have been proposed. In particular, the mystery of the drop of bioavailability of Rifampicin from FDC products has been solved by showing that the problem arises due to the interdrug facile reaction of Rifampicin and Isoniazid under empty stomach conditions^{3,4,5}, whereby significant loss of drug occurs before absorption. The mechanism has also been worked out, demonstrating that Rifampicin is first hydrolyzed under acid conditions to 3-formylrifamycin, which reacts further with Isoniazid to form isonicotinyl hydrazone (HYD). The HYD converts back to Isoniazid and 3-formylrifamycin, resulting in recovery of Isoniazid, but eventually causing the loss of Rifampicin⁶. This explains why the bioavailability problem is

confined to Rifampicin alone and not Isoniazid. Thus it is clarified that 3-formylrifamycin a hydrolytic product of rifampicin plays a vital role to hamper its bioavailability. A suitable approach is therefore necessary to overcome the aforementioned problem associated with bioavailability of rifampicin. It may be achieved by enteric coating, which modifies release of rifampicin in acidic media thereby preventing formation of 3-formylrifamycin. However enteric coating is a bit costlier effort and therefore poses an urgent need to design and develop a suitable economic formulation for treatment of poverty diseases – tuberculosis. Sodium lauryl sulphate being an anionic surfactant has a strong propensity to form ion-pairs with cationic ammonium compound. The previous studies revealed the formation of aforementioned interaction of sodium lauryl sulphate with cationic polymers and gelatin which dramatically retarded their release pattern in acidic media^{7,8}. As rifampicin is a zwitterionic⁹ compound having pKa 1.7 and 7.9, which tends to behave as a cationic compound in acidic media may form hydrophobic and/or ionic interaction with sodium lauryl sulphate. Based on the aforementioned assumption the present study focuses on

suitability of sodium lauryl sulphate as an excipient to prevent release of rifampicin in acidic media.

MATERIALS AND METHODS

Rifampicin and isoniazid were obtained as a gift sample from Lupin Ltd, Pune, sodium lauryl sulphate purchased from Loba chem, Mumbai. Talc was generously gifted by Luzenac Pharma, Croscarmellose sodium from FMC Biopolymer, pregelatinized starch from Colorcon. All other chemicals used were of analytical reagent grade.

Preparation of Rifampicin-SLS powder mixture

The rifampicin-SLS powder mixture was prepared by co-grinding method under solid-state conditions. Rifampicin and SLS (equal molar ratio) were ground using a mortar and pestle. Samples were ground for up to 30 minutes at ambient conditions. The prepared mixtures were stored at airtight containers till further use.

Preparation of Rifampicin delayed release tablets

The powder mixture of rifampicin –sodium lauryl sulphate, talc, magnesium stearate, pregelatinized starch, Croscarmellose sodium were mixed and directly compressed on rotary tablet punching machine fitted with 12mm standard punch. The composition of prepared tablets is as mentioned in table no 1.

Characterization of prepared tablets.

The prepared tablets were evaluated for uniformity of thickness, hardness, friability, weight variation, content uniformity and disintegration. The results are depicted in table no.2.

In-vitro dissolution studies

In-vitro release of rifampicin tablets of different samples was determined using Veego USP dissolution test apparatus type II. 0.1N HCl and 6.8 phosphate buffer were used as dissolution medium (900 ml) and were maintained at $37 \pm 1^\circ\text{C}$. The stirring rate was 100 rpm. Samples of 5 ml were withdrawn at predetermined time intervals. The collected samples were diluted and rifampicin content was analyzed by UV spectrophotometric method at 475 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Each dissolution study was performed in triplicate.

In-vivo roentegenography studies

Amongst the prepared formulations, formulation F2 exhibited desired release profile and hence it was further studied for roentegenography studies. The core tablet F2 for in vivo studies was compressed using 100mg of barium sulphate. This formulation was labeled as formulation H. Healthy volunteers of 18-29 years of age participated in the study. They were non-alcoholic, non-smoking and were not on any drugs. The purpose of the study was fully explained and written consent

was subsequently obtained. After overnight fasting volunteers orally ingested the aforementioned formulation with 200ml of water. X-ray images of GIT were taken at different time intervals to trace movement, location and integrity of the tablet in the digestive tract.

RESULTS AND DISCUSSION:

The prepared tablet formulations were evaluated from the point of the view of the physical properties of the tablets and their in vitro releases. The tablet hardness and friability were found as per Pharmacopoeial standards. The effect of sodium lauryl sulphate was important to modify the disintegration and dissolution of rifampicin. The disintegration studies in 0.1N HCl revealed that tablets of rifampicin without sodium lauryl sulphate i.e. formulation F1 disintegrated within 30 min. Interestingly, in the same conditions the prepared tablet formulations of rifampicin in presence of sodium lauryl sulphate (Formulation F2 and H) exhibited opposite effect even at the end of 2 hour. However, the tablet formulations disintegrated completely in pH 6.8 phosphate buffer at the end of 36 min and 39 min respectively for both the formulations F2 and H. The results of dissolution studies carried in 0.1N HCl dissolution media upto 2 hours followed by pH 6.8 phosphate buffer showed that there was no release of rifampicin from formulation F2 and H in 0.1N HCl as compared to formulation F1 whereas, significant release was observed in pH 6.8 phosphate buffer (Figure 1). The delayed release of rifampicin from formulations F2 and H containing sodium lauryl sulphate in acidic medium is attributed to formation of ion-pair interaction between rifampicin and sodium lauryl sulphate. Rifampicin a zwitterionic compound ⁶, at low pH the basic piperazine nitrogen group becomes protonated with positive charge leading to cationic nitrogen have strong tendency to form ion-pairs with lauryl sulfate anion of the surfactant. (Figure2) The surfactant -drug ion-pairs formed are hydrophobic in nature and tend to precipitate in acidic media. The precipitation of the hydrophobic drug-SLS ion-pairs on the boundary layer of the tablets is hypothesized to form a hydrophobic barrier, which hinders the accessibility of the dissolution medium into the tablet matrix, a critical step for disintegration and dissolution process. The formulation F2 was selected for further in-vivo studies and formulation H was prepared with the addition of barium sulphate as a marker for monitoring the tablets through the gastrointestinal system. From the abdominal radiographs, taken at different points of time, it was seen that after 30 min the tablets were located in upper part of small intestine in all the subjects without any signs of disintegration thereby indicating that the formulations effectively resists the acidic environment of the stomach. The X-ray image

Table no 1: Composition of prepared tablets

Code	Rifampicin (mg)	SLS (mg)	Pregelatinised Starch (mg)	Cross carmalose sodium (mg)	talc (mg)	magnesium stearate (mg)	Barium sulphate (mg)
F1	150	—	68	20	10	1.5	—
F2	150	53	68	20	10	1.5	—
H	150	53	68	20	10	1.5	100

Table no 2: Characterization of prepared tablets

Code	Thickness (mm)	Drug content (%)	Hardness (kg/cm ²)	Friability (%)	Disintegration time (hrs)
F1	2.23± 0.02	99.0± 0.61	4.7 ± 0.32	0.34	0.53 ± 0.14
F2	2.26 ± 0.01	102.02± 0.83	5.1± 0.15	0.30	2.6 ± 0.36
H	2.27 ± 0.02	98.08± 0.74	4.9± 0.24	—	2.65 ± 0.27

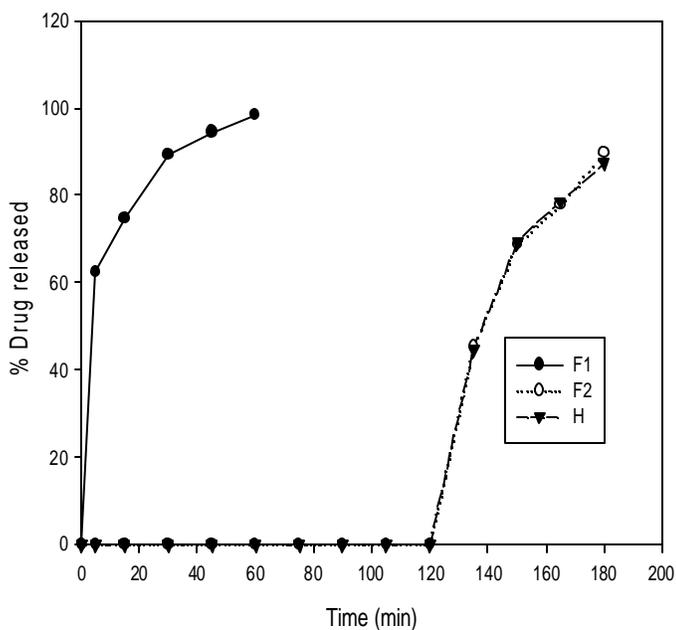


Fig.1 In-vitro release studies of Formulation F1 (0.1N HCl), F2 and H (0.1N HCl followed by pH 6.8 phosphate buffer)

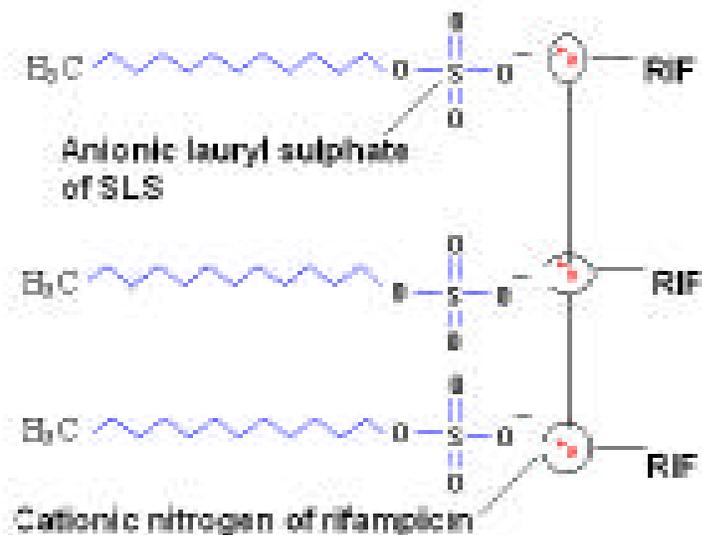


Figure 2. Proposed mechanism of ion –pair interaction of rifampicin with sodium lauryl sulphate

of tablets throughout the gastrointestinal systems is shown in Fig. 3 for subjects 1 and 2. The position of the tablet formulation reached duodenum in subjects 1, and 2. In case of subject 3 it was located in jejunum after approximately 30 min. After 1.5 hours the intensity of tablet image started to decrease in all subjects due to possible disintegration of the

tablet, and finally the tablet was not detected at the end of 2 hours because of completed disintegration of tablet. These results clearly reflect that the prepared formulation offers effective resistance in acidic environment and starts its release in the alkaline environment of small intestine. Thus, by considering the in-vitro and non-invasive in-vivo studies it was

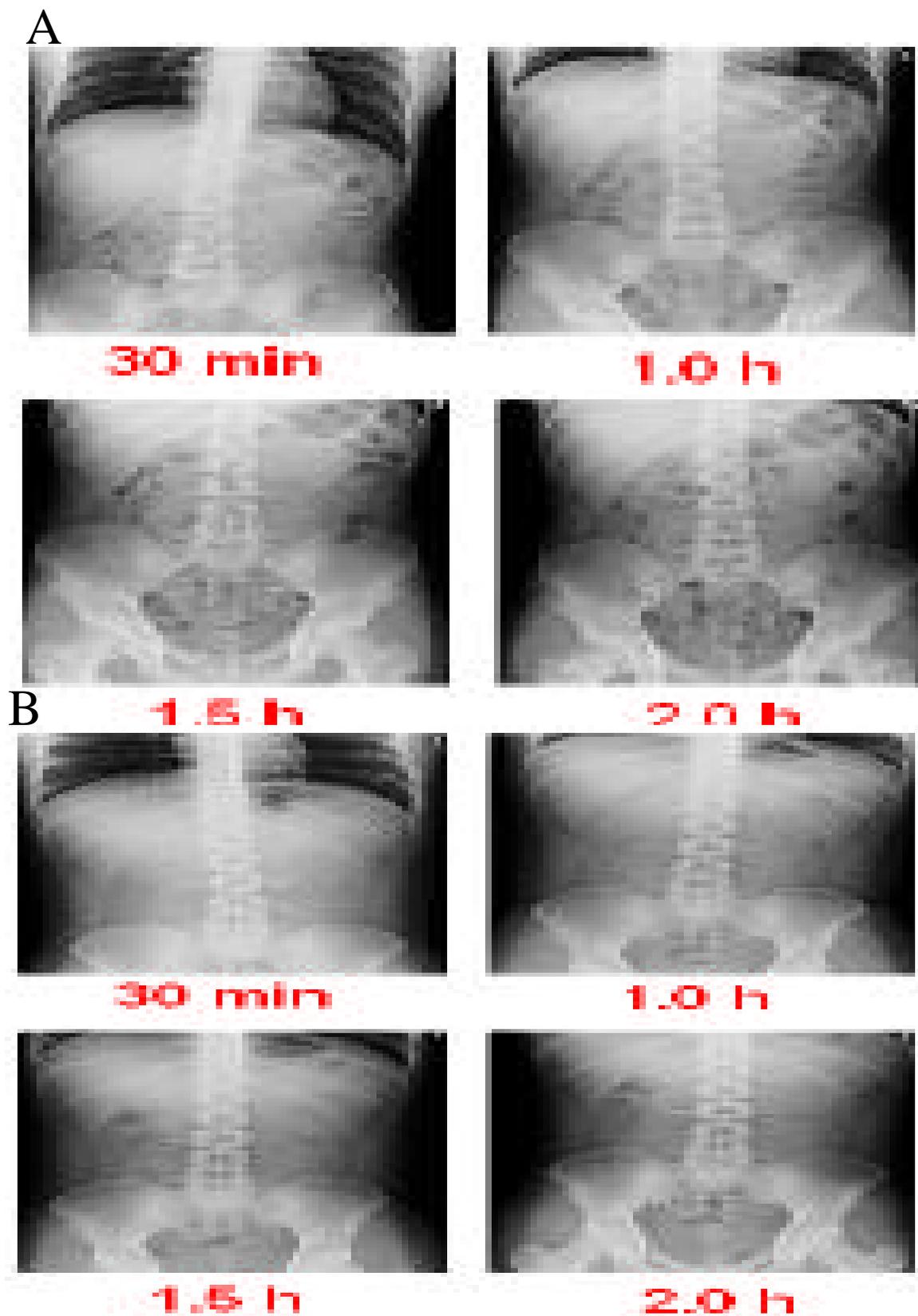


Figure 3. The localization of the tablet in the gastrointestinal tract in subject 1(A) and subject 2 (B).

concluded that sodium lauryl sulphate can be successfully employed to retard the release pattern of rifampicin and its degradation in acidic media thereby enhancing the therapeutic efficacy for the effective treatment of tuberculosis disease.

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