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Oral matrix tablet formulations for concomitant controlled release of anti-tubercular drugs: Design and in vitro evaluations

Praveen S. Hiremath*, Ranendra N. Saha

Pharmacy Group, Birla Institute of Technology and Science, Pilani, Rajasthan, India

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ABSTRACT

The aim of the present investigation was to develop controlled release (C.R.) matrix tablet formulations of rifampicin and isoniazid combination, to study the design parameters and to evaluate in vitro release characteristics. In the present study, a series of formulations were developed with different release rates and duration using hydrophilic polymers hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC). The duration of rifampicin and isoniazid release could be tailored by varying the polymer type, polymer ratio and processing techniques. Further, Eudragit L100-55 was incorporated in the matrix tablets to compensate for the pH-dependent release of rifampicin. Rifampicin was found to follow linear release profile with time from HPMC formulations. In case of formulations with HPC, there was an initial higher release in simulated gastric fluid (SGF) followed by zero order release profiles in simulated intestinal fluid (SIFsp) for rifampicin. The release of isoniazid was found to be predominantly by diffusion mechanism in case of HPMC formulations, and with HPC formulations release was due to combination of diffusion and erosion. The initial release was sufficiently higher for rifampicin from HPC thus ruling out the need to incorporate a separate loading dose. The initial release was sufficiently higher for isoniazid in all formulations. Thus, with the use of suitable polymer or polymer combinations and with the proper optimization of the processing techniques it was possible to design the C.R. formulations of rifampicin and isoniazid combination that could provide the sufficient initial release and release extension up to 24 h for both the drugs despite of the wide variations in their physicochemical properties.

1. Introduction

Although current chemotherapeutic agents for tuberculosis treatment are effective and well tolerated, a number of problems still remain. Fixed dose anti-tubercular products combine the most effective drugs in one formulation; this minimizes the adaptation of monotherapy by patients and hence reduces the chances of developing drug resistances (Blomberg and Fourie, 2003). However, these conventional formulations have been associated with many serious drawbacks like development of microbial drug resistance, improper bioavailability of drugs and, toxico-allergic side effects. These problems can be alleviated by the use of controlled release (C.R.) drug delivery systems (Batyrbekov et al., 1997).

Some combined C.R. formulations of rifampicin and isoniazid have been reported in the literature, which can be summarized as follows. Alginate hydrogel microparticles were developed for oral controlled delivery of anti-tubercular drugs isoniazid, rifampicin and pyrazinamide alone and in combination (Ain et al., 2003). An oral C.R. formulation has been developed based on poly (DL-lactide-*co*-glycolide) microparticles for the delivery of isoniazid, rifampicin, and pyrazinamide either individually or in combination (Ain et al., 2002). A colloidal dosage form for the oral delivery of rifampicin and isoniazid in combination was developed with the aid of artificial neural network (ANN) data modeling (Kustrin et al., 2003). Sustained release capsular systems of rifampicin and isoniazid (an osmotically regulated multi-drug oral delivery system) comprising asymmetric membrane coating and dense semipermeable membrane coating were developed to reduce the potential side effects and enhance the patient compliance (Prabhakaran et al., 2004).

On extensive literature survey, no report has been found in the area of polymer matrix tablet based oral drug delivery systems for rifampicin and isoniazid combination. Also, there is a continuous need for the development of C.R. formulations for concomitant delivery of combination drugs like rifampicin and isoniazid with the technology that is cost effective, reproducible and, easy to manufacture and scale-up in an industry with minimum set-up/facility. This would especially be of great interest for

* Corresponding author. Present address: Product Development, Pharmaceutics International, Inc., 10819 Gilroy Road, Hunt Valley, MD 21031, USA.
Tel.: +1 410 584 0001x3021; fax: +1 410 584 0007.
E-mail address: phiremath@pharm-int.com (P.S. Hiremath).

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under-developed or developing countries with minimum industrial set-up and manufacturing capabilities and, also for countries with economic restrictions as tuberculosis is considered to be a "poor/underprivileged man's disease".

Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form, and ease of scale-up and process validation (Verma et al., 2004). Hydrophilic polymers have been paid considerable attention in the formulation of C.R. formulations for various drugs. Hydroxypropyl methylcellulose (Velasco et al., 1999; Maggi et al., 1999; Ford et al., 1985) and hydroxypropyl cellulose (Alderman, 1984; Ranga Rao et al., 1988; Nakagami and Nada, 1988) are the hydrophilic polymers, which have been extensively used in the formulation of C.R. systems. Their broad FDA acceptance, cost effectiveness, nontoxic property, ease of handling, ease of compression, ability to accommodate a large percent of drug, negligible influence of the processing variables on drug release rates and relatively simple tablet manufacturing technology make them excellent carrier materials for oral matrix tablets (Alderman, 1984; Lee et al., 1999). Eudragit L and S grades are anionic polymers based on the combination of methacrylic acid and methyacrylic acid esters, which are useful in the development of pH-dependent systems to achieve linear release profiles or to balance pH-dependent drug solubility. There are several studies reported in the literature that substantiate the use of Eudragit polymers in the development of C.R. matrix tablets (Al-Taani and Tashtoush, 2003; Gohel et al., 2003; Rao et al., 2003).

It has been reported that approximately 80–100 mg of rifampicin should be released orally to achieve the minimum effective concentration (MEC) to elicit required therapeutic effect in the body. Thus, an initial release of 20–30% (of total 450 mg dose) of rifampicin from C.R. release formulations as a loading dose may fulfill this biopharmaceutical requirement (Prabhakaran et al., 2004). It has also been reported that, to get best results, the C.R. formulations in case of isoniazid should release approximately 37% initially as a loading dose and, 63% as a maintenance dose in a controlled manner (Eidus and Hodgkin, 1975).

In this regard, we have reported the oral C.R. formulations of rifampicin (Hiremath and Saha, 2004, 2008) and there are some unpublished reports/works from our lab on rifampicin and isoniazid C.R. formulations. This is a continuation of research efforts from our group to further design rifampicin and isoniazid combination C.R. formulations. In light of the above discussed aspects, the main objective of our present research endeavor was to formulate the C.R. matrix tablets for the concomitant C.R. of rifampicin and isoniazid, first line anti-tubercular drugs widely used in the treatment of the mycobacterium tuberculosis infection. The thirst of the investigation was also to study the effect of various formulation factors and processing parameters on the release characteristics and release mechanism of both rifampicin and isoniazid from the matrix tablet formulations. Further, the attempt has been made to optimize these various parameters to achieve the concomitant C.R. from the single matrix tablet of these two anti-tubercular drugs, which differ significantly in their physicochemical characteristics (especially, solubility). The present research aimed as well at developing once a day C.R. formulation which provides both initial release (loading dose) and controlled release (maintenance dose) of rifampicin and isoniazid from a single C.R. matrix tablet required for better therapeutic efficacy. It was also an important objective of our research endeavor to develop these formulations by using relatively simple manufacturing technology which can be easily adopted in industrial units on a commercial scale, and thus providing formulations that are advantageous or preferred over reported delivery systems.

2. Materials

Rifampicin and isoniazid were generously provided by Lupin Laboratories, India. HPMC K4M (4000 cPs) was purchased from Sigma–Aldrich, Germany. Hydroxypropyl cellulose (HPC) (Klucel LF) was purchased from Sigma–Aldrich, India. Eudragit L100-55 was received as a gift from Zydus Cadila Research Center, India. All other chemicals and reagents used were of pharmaceutical or analytical grade and were used as received.

3. Methods

3.1. Formulation of C.R. matrix tablets containing rifampicin and isoniazid combination

Some preliminary studies were carried out before choosing suitable polymer combinations, polymer proportions and method of granulation. On the basis of experiments and results of C.R. formulations of individual drugs, specific formulations were designed and studied. Only the formulations and studies relevant for the present investigation are presented here.

Accurately weighed quantity of isoniazid and hydrophilic polymer (HPMC K4M or HPC Klucel LF) (passed through 60# mesh) were mixed uniformly and granulated with isopropyl alcohol (IPA) followed by drying in a tray drier at 60 °C. To the dried granules was added weighed quantity of rifampicin (passed through 60# mesh) and mixed properly to assure homogeneity. Finally this mixture was blended with talc (1%, w/w) and magnesium stearate (1%, w/w) and compressed with Cadmach 16 station tablet compression machine using 16/32″ round FFBE (Flat faced beveled edges) punches at a compression force required to produce tablets of about 7–8 kg/cm^2 hardness. Three batches of tablets were prepared for each formulation with each tablet containing 450mg of rifampicin and 300 mg of isoniazid.

3.2. Physical characterization of the tablets

Formulated tablets were subjected to different physical characterization studies. The drug content of each batch of the formulated tablets was determined in triplicate. The weight variation was determined on 20 tablets using electronic balance (Afcoset). Tablet hardness was determined for minimum 6 tablets of each batch using Monsanto (Standard type) tablet hardness tester. Friability was determined with 20 tablets in a Cambell Electronic Friabilator for 4 min at 25 rpm.

3.3. In vitro release studies

The dissolution medium specified in USP-24 (United States Pharmacopoeia-XXIV) for rifampicin and isoniazid capsules has been reported to be unsuitable, as it has been observed that rifampicin degrades in this medium from 17% to 22% in presence of isoniazid. Also, other reported dissolution methods found to be unsuitable especially for combination C.R. formulations of rifampicin and isoniazid. Hence, it was decided to develop a dissolution method for the combined C.R. formulations of rifampicin and isoniazid. The details of dissolution method development is not discussed here which is beyond the scope of the present study.

Release studies were carried out using in-house developed and validated dissolution method. This was done using type 1 method (basket) at 37 ± 1 °C with the stirring speed set at 100 rpm. The release medium was 350 ml simulated gastric fluid, pH 1.2 (SGF) for initial 2 h of the study, and then the total SGF media was replaced with 900 ml simulated intestinal fluid, pH 6.8 (SIFsp) in the later hours (3–24 h). At predetermined time intervals 10 ml of sample

was withdrawn and replaced with fresh dissolution medium. After appropriate dilutions, the samples were analyzed. Cumulative percent of drug released was calculated, and mean of six tablets from three different batches was used in the data analysis.

The mechanism of drug release was analyzed using Korsmeyer–Peppas model. The release profiles were also analyzed for f_2 (similarity) factor values to assess the similarity or difference in the release profiles. The following variations in tablet formulae were done and their effect on in vitro release rate, release mechanism and nature of release was studied.

3.3.1. Effect of polymer proportion

The polymer proportion is reported as a percent weight by weight (%, w/w) of the isoniazid present in the formulation. Formulations were made containing 20%, 40%, and 80% of HPMC. However, the results are discussed only for 40% and 80% HPMC (RH2 and RH3) formulations as 20% polymer formulation (RH1) could control the isoniazid release only up to 1 h. Tablets were also manufactured containing 40% (RH5), and 80% (RH6) of HPC.

In case of HPC formulations one more formulation, RH7, was prepared with 20% ethyl cellulose (EC) as an additional polymer (compared to RH5) to study the effect of addition of hydrophobic EC polymer on release profile of drugs. But, this modification did not provide any significant results and hence this formulation is not further discussed.

Effect of addition of Eudragit L100-55 was studied in case of both HPMC and HPC formulations. In case of HPMC formulations, 60% Eudragit was added to RH3 formulation intra-granularly along with isoniazid and HPMC to produce RH4 formulation. In case of HPC formulations, two different formulae were prepared by modifying RH6;

- First formula, RH8, was prepared by adding 30% Eudragit intra-granularly along with isoniazid and HPC. In this case HPC proportion was also reduced from 80% to 60% to know combined out-come of this modification.
- Second formula, RH9, was prepared by adding 60% Eudragit intra-granularly along with isoniazid and HPC.

3.3.2. Effect of change in the release media

For this study, RH2 (HPMC) and RH5 (HPC) formulations were used. The release studies were done only in SIFsp for 24 h and same formulations were also subjected for the release studies in SGF (pH 1.2) for first 2 h followed by SIFsp for 3–24 h.

3.3.3. Effect of change in the manufacturing/formulation process

The study was carried out in case of RH4 (HPMC) formulations. In this case, rifampicin was added intra-granularly along with isoniazid and HPMC, to produce a modified-RH4 formulation, instead of adding it extragranularly along with talc and magnesium stearate.

The study was also carried out in case of RH9 (HPC) formulations. Two small changes were done in the formulation process, with the formula remaining same. In first case, instead of adding whole 60% Eudragit L100-55 with isoniazid intra-granularly, only 30% was added and remaining 30% was added extragranularly along with rifampicin to produce RH10. In second case, rifampicin was granulated separately with IPA and mixed with isoniazid granules, to produce RH11, instead of adding it extragranularly along with talc and magnesium stearate.

3.3.4. Effect of presence of one drug on the release of other drug

The study was carried out for the RH10 formulations (HPC). In one case total isoniazid was replaced by rifampicin to produce RH12 and, in other case total rifampicin was replaced by isoniazid to produce RH13. Nonetheless, the care was taken to not to change/alter other formulation and processing parameters.

4. Results and discussions

4.1. Formulation of C.R. matrix tablets of rifampicin and isoniazid combination

It was observed from the preformulation studies that both rifampicin and isoniazid were sensitive to the moisture. It is also a known fact that the hydrolytic degradation of rifampicin triggers in the presence of isoniazid. Thus, for both of these drugs, it was decided to use either direct compression or non-aqueous granulation method for the preparation of the C.R. tablet formulations. It was observed from our initial studies with rifampicin alone C.R. tablet formulations (data not shown) that direct compression found to give better quality tablets with higher viscosity HPMC (K4M and K15M) and HPC (Klucel LF) polymers. Whereas, for the formulation of isoniazid C.R. tablets, non-aqueous granulation with IPA found to provide better quality tablets with higher viscosity HPMC (K4M, K15M and K100M) and HPC (Klucel LF) polymers.

So, same basic approach was used to manufacture combined drug formulations. The formulations prepared thus found to have good physicochemical properties (Tables 1 and 2) and found to control the drug release for both the drugs when in vitro release studies were carried out. Further, to know the effect of processing techniques on release characteristics, rifampicin was granulated along with isoniazid and, separately granulated and added to isoniazid granules.

As the drug doses (for isoniazid and rifampicin) were high, no attempt was made to incorporate the excipients (such as microcrystalline cellulose, lactose, dicalcium phosphate, etc.) other than C.R. polymers into the tablet matrices to increase the bulk further or to improve the granule properties. The amount of polymer used was also restricted (to the possible extent) so as to make the formulations practically useful for the purpose of administration in terms of tablet weight, height and thickness.

4.2. Physical characterization of the tablets

Physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all formulations were found to be satisfactory as can be observed from the data in Tables 1 and 2 for

Table 1
Formula and physical properties of rifampicin and isoniazid combination matrix tablets prepared with HPMC K4M

Formulations	RH 1	RH 2	RH 3	RH 4
Components[a]				
Rifampicin (mg)[b]	450	450	450	450
Isoniazid (mg)	300	300	300	300
HPMC[c] (%)	20	40	80	80
Eudragit L100-55[c] (%)	–	–	–	60
Physical properties				
Drug content (%) (R)[d]	102.5 ± 1.4	101.6 ± 1.7	99.0 ± 1.5	101.8 ± 1.9
Drug content (%) (H)[d]	99.3 ± 1.2	100.4 ± 1.8	102.4 ± 1.6	98.7 ± 1.1
Weight variation (%)[e]	±2.6	±2.9	±1.9	±3.1
Hardness (kg/cm^2)[f]	7.6 ± 0.6	7.8 ± 0.7	7.5 ± 0.8	7.9 ± 0.4
Friability (%)	<0.8	<0.8	<0.8	<0.8

[a] Also contains 1% (w/w) of talc and 1% (w/w) of magnesium stearate as additives.
[b] Added extragranularly.
[c] % (w/w) of the isoniazid and added along with isoniazid during granulation.
[d] % label claim (mean of triplicate with S.D.).
[e] ±Max % variation from the mean.
[f] Mean of 20 tablets.

Table 2
Formula and physical properties of rifampicin and isoniazid combination matrix tablets prepared with HPC (Klucel LF)

Formulations	RH 5	RH 6	RH 7	RH 8	RH 9
Components[a]					
Rifampicin (mg)[b]	450	450	450	450	450
Isoniazid (mg)	300	300	300	300	300
HPC[c] (%)	40	80	40	60	80
EC[c] (%)	–	–	20	–	–
Eudragit[c] L100-55 (%)	–	–	–	30	60
Physical properties					
Drug content (%) (R)[d]	98.5 ± 1.3	102.2 ± 1.5	99.3 ± 1.8	101.9 ± 1.7	102.6 ± 1.1
Drug content (%) (H)[d]	102.4 ± 1.2	100.4 ± 1.9	102.6 ± 1.4	101.4 ± 1.1	98.8 ± 1.2
Weight variation (%)[e]	±1.8	±2.7	±1.6	±3.2	±3.0
Hardness (kg/cm^2)[f]	7.7 ± 0.5	7.4 ± 0.7	7.8 ± 0.7	7.5 ± 0.8	7.6 ± 0.6
Friability (%)	<0.8	<0.8	<0.8	<0.8	<0.8

[a] Also contains 1% (w/w) of talc and 1% (w/w) of magnesium stearate as additives.
[b] Added extragranularly.
[c] % (w/w) of the isoniazid and added along with isoniazid during granulation.
[d] % label claim (mean of triplicate with S.D.).
[e] ±Max % variation from the mean.
[f] Mean of 20 tablets.

HPMC (K4M) and HPC (Klucel LF) formulations respectively. These results indicate that the method of preparation of formulation is an acceptable method for preparing good quality matrix tablets of rifampicin and isoniazid combination.

4.3. In vitro release studies

4.3.1. Effect of polymer and its proportion

4.3.1.1. HPMC formulations. Plots of percent cumulative drug released vs. time for HPMC K4M matrix tablet formulations, RH2 (40%) and RH3 (80%), are shown in Fig. 1. It can be observed from the graph that increase in the polymer proportion resulted in decrease in the release for both rifampicin and isoniazid. Rifampicin found to follow linear release profile with time. Whereas, the isoniazid release found to follow Higuchi's square root kinetics as the plots of percent cumulative drug released vs. square root of time found to be linear (data not shown). Since the drug release was less (for rifampicin) in the initial hours, for these formulations a separate loading dose would be required to attain the desired drug levels in the initial hour to meet biopharmaceutical requirement. In case of isoniazid, however, sufficient amount of drug was released during initial hours to meet loading dose requirement. For poorly soluble drug like rifampicin the erosional release would be dominant and diffusional contribution would be very minimum as the drug particles merely exist in the soluble form within the matrix. Thus, the rifampicin release was mainly because of the matrix erosion, which occurred at a constant rate resulting in the zero order release. The reason for initial higher release and decrease in the rate of isoniazid release with time can be explained as follows. As the drug (isoniazid) was highly soluble in the release media, the drug particles close to matrix surface might have been released before the surrounding polymer reached the polymer disentanglement concentration. Within this time major amount of the drug was released resulting in the initial higher release in case of isoniazid. There was a clear distinction between the isoniazid and rifampicin release profiles, this might be due to difference in their solubility. Isoniazid being a highly soluble drug released at much faster rate compared to poorly soluble rifampicin. The presence of poorly soluble rifampicin drug particles along with isoniazid (in a same tablet matrix) did not seem to decrease the initial release of isoniazid.

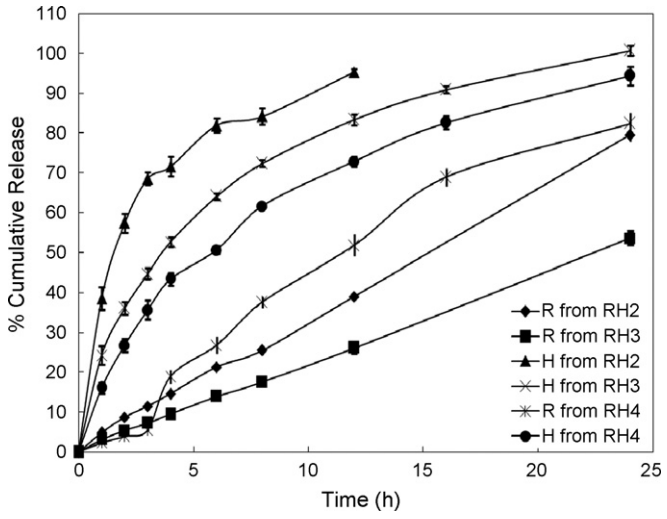

Fig. 1. Comparative release profiles of rifampicin and isoniazid from RH2, RH3 and RH4 (HPMC K4M) formulations in SGF (0–2 h) followed by SIFsp (3–24 h) media (Each data point represents the average of six tablets from three batches with S.D.).

The release mechanism and kinetics of the release profiles were analyzed by Korsmeyer–Peppas model, $M_t/M_\infty = K.\ t^n$, up to 60% release (Korsmeyer et al., 1983; Ritger and Peppas, 1987). The values of K, n, $t_{50\%}$ (time for 50% of drug release) and r (correlation coefficient) obtained for various formulations are listed in Table 3. These n values indicated that the rifampicin release was predominantly by erosion mechanism. However, the n values for isoniazid release demonstrated that the release was predominantly by Fickian diffusion. In case of Higuchi's model, n is 0.5, thus the release profiles found to follow Higuchi's square root kinetics. The difference in the release mechanisms between rifampicin and isoniazid was again because of difference in their solubility.

From our preformulation studies, rifampicin, a zwitterionic molecule with two pK_a values (1.7 and 7.9), found to exhibit a highly pH-dependent solubility profile. It was observed that rifampicin was more soluble in acidic SGF (pH 1.2) medium, solubility being 102.5 mg/ml, and less soluble in alkaline SIFsp (pH 6.8) medium, solubility of 2.6 mg/ml. However, isoniazid being a Class-I drug according to biopharmaceutical classification system (BCS), showed good solubility in both SGF (326.0 mg/ml) and SIFsp (274.4 mg/ml). Thus, to overcome/reduce the effect of pH on rifampicin release, pH dependant polymer Eudragit L100-55 was used in the study. It can be observed from Fig. 1 that rifampicin release decreased in SGF and increased in SIFsp in pres-

Table 3
Release kinetics parameters for C.R. formulations of rifampicin and isoniazid combination

Formulations	Release kinetics parameters			
	n[a]	K[b] (h^{-n})	$t_{50\%}$[c] (h)	r[d]
Rifampicin				
RH2	0.86	0.046	15.77	0.995
RH3	0.89	0.029	24.56	0.996
RH4	1.02	0.052	11.34	0.944
RH5	0.89	0.358	1.47	0.916
RH6	0.74	0.198	3.55	0.889
RH8	0.60	0.154	7.14	0.995
RH9	0.67	0.126	7.83	0.993
RH10	0.68	0.111	9.10	0.996
RH11	1.12	0.028	11.56	0.984
RH12	0.75	0.073	12.98	0.986
Isoniazid				
RH2	0.54	0.389	1.61	0.996
RH3	0.53	0.248	3.77	0.998
RH4	0.64	0.169	5.47	0.990
RH5	0.86	0.421	1.22	0.999
RH6	0.51	0.378	1.73	0.962
RH8	0.42	0.363	2.15	0.984
RH9	0.63	0.229	3.46	0.972
RH10	0.53	0.225	4.56	0.980
RH11	0.45	0.213	6.56	0.990
RH13	0.64	0.224	3.50	0.995

[a] Diffusional exponent indicative of the release mechanism.
[b] Release rate constant.
[c] Time for 50% of the drug release.
[d] Correlation coefficient.

ence of Eudragit. This might be due to pH-dependent solubility of the Eudragit. Eudragit L100-55 is an anionic polymer based on methacrylic acid and methacrylic acid esters that dissolve above pH 5.5 by salt formation. In SGF, as the polymer was insoluble, it closed the pores available for the media infiltration in to the matrix. This caused the delay in the matrix hydration, swelling and ultimately erosion. Thus, the rifampicin release was slightly lower in presence of the Eudragit in SGF. When the release study was continued in SIFsp, the rifampicin release got enhanced because of the increased solubility and release of the Eudragit in SIFsp that resulted in the significant increase in the matrix porosity. Whereas, isoniazid release was decreased both in SGF and SIFsp in presence of Eudragit. In SGF, Eudragit acted as an insoluble mass that reduced the matrix porosity and thus decreased the diffusivity of isoniazid molecules.

4.3.1.2. HPC formulations. Plots of percent cumulative drug released vs. time for HPC matrix tablet formulations, RH5 (40%) and RH6 (80%), are shown in Fig. 2. It can be seen from Fig. 2 that there was initial higher release in SGF up to 2 h followed by a decrease in the release when the media changed to SIFsp. But in SIFsp, rifampicin exhibited a linear release profile with time. Similarly, isoniazid also had shown a higher initial release in SGF followed by relatively slower rate of release in SIFsp. In case of both the drugs, the initial release was higher indicating no necessity of incorporation of a separate loading dose to attain the desired drug levels in the initial hour. In this case also, isoniazid being a highly soluble drug released at much faster rate compared to poorly soluble rifampicin.

The main difference in the in vitro release profiles of drugs from HPMC and HPC formulations was observed in the initial release of rifampicin. It was already discussed that the initial amount of rifampicin released was less in case of HPMC formulations. This might be due to the formation of thick hydrated gel layer once the tablet came in contact with the release medium in case of high

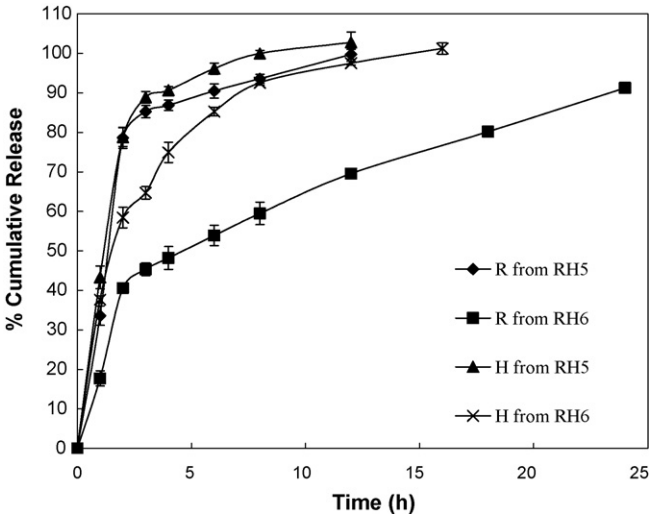

Fig. 2. Comparative release profiles of rifampicin and isoniazid from RH5 and RH6 (HPC formulations) in SGF (0–2 h) followed by SIFsp (3–24 h) media (Each data point represents the average of six tablets from three batches with S.D.).

viscosity (4000 cPs) HPMC K4M formulations. This stable gel layer prevented the initial release of rifampicin because of the reduced tendency of the matrix to undergo erosion that prevented the initial release (which is erosional release). Whereas, the HPC used was of low viscosity and was having less swelling tendency. Thus, the hydrated gel layer formed was not stable enough to resist erosion. Hence, during initial hours the matrix started eroding along with that substantial amount of the rifampicin has been released leading to higher initial release of rifampicin in case of HPC based formulations. Whereas, isoniazid being a soluble drug, exhibited an initial burst release effect leading to higher release from both HPMC and HPC formulations with the burst effect being higher in case of HPC formulations.

The n values (Table 3) showed that the rifampicin release was predominantly by erosion mechanism. Similarly, isoniazid was also released predominantly by erosion of the matrix. HPC being a low viscosity polymer shown a relatively low swelling tendency and hence, the diffusion contribution towards release was not significant. However, at higher polymer proportion, isoniazid found to exhibit diffusional release probably due to increased resistance of matrix to undergo erosion.

Effect of addition of Eudragit L100-55 was studied in two formulations, RH8 and RH9 and the results are shown in Fig. 3. Rifampicin release was decreased in SGF and enhanced in SIFsp in presence of Eudragit from both RH8 and RH9 formulations. However, the f_2 factor value of 76.11 for rifampicin release between RH8 and RH9 formulations indicated that there was no significant difference in the release profiles. Thus, the replacement of 20% HPC with 30% Eudragit L100-55 was sufficient enough to decrease the initial release of rifampicin in SGF and, to obtain complete release (within 24 h) in SIFsp. However, the effect was slightly different in case of isoniazid release. There was no significant difference in the isoniazid release profiles between RH6 and RH8 formulations (f_2 = 64.08). Thus, the replacement of 20% HPC with 30% Eudragit L100-55 was not ample to exert significant effect on isoniazid release. Nevertheless, there was significant difference in the isoniazid release profiles between RH6 and RH9 formulations (f_2 = 39.35). Isoniazid release was decreased both in SGF and SIFsp from RH9 compared to RH6. Hence, it could be said that, it was not only the presence of Eudragit but also the amount of HPC was a significant factor for decreasing the release of isoniazid, which was not true in case of rifampicin release. Addition of Eudragit to

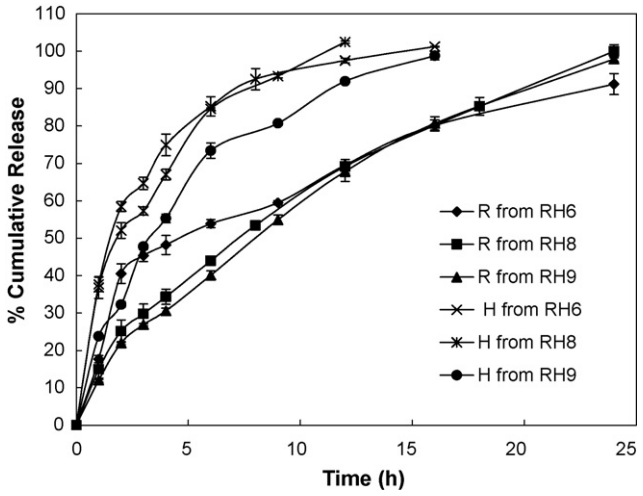

Fig. 3. Effect of addition of Eudragit L10055 on release profiles of rifampicin and isoniazid from HPC formulations in SGF (0–2 h) followed by SIFsp (3–24 h) media (Each data point represents the average of six tablets from three batches with S.D.).

HPC formulations had no significant impact on the mechanism of release for both rifampicin and isoniazid.

4.3.2. Effect of change in the release medium on release profile

4.3.2.1. HPMC formulations. It can be seen from Fig. 4 that, there was no significant difference in the release profiles of rifampicin due to change in medium for first 2 h. The f_2 factor value of 68.54 between the rifampicin release profiles in SIFsp medium alone and in SGF followed by SIFsp for RH2 formulations showed that there was no significant difference in the release profiles.

There was marginal decrease in the release of isoniazid when initial release was also studied in SIFsp instead of SGF medium. The f_2 factor value (58.53) also showed insignificant difference in the release profiles in SGF and SIFsp. The results suggested that change in release medium for first 2 h did not change release of both rifampicin and isoniazid from formulations with HPMC K4M polymer. This study indicated that HPMC formulations were robust towards the effect of change in the release medium.

4.3.2.2. HPC formulations. It can be seen from Fig. 5 that, there was a significant decrease in the release profile of rifampicin and isoniazid, with more impact on rifampicin release, when initial release also studied in SIFsp medium. The f_2 factor value of 9.75 for rifampicin release established the difference in release profiles. The rifampicin release was extended from 12 h to more than 24 h when SGF was replaced with SIFsp for first 2 h. Also, there was a huge difference in the initial amount of the rifampicin released. This might be due to strong dependence of rifampicin solubility on pH of the release media and effect of release media on polymer. Due to high solubility of rifampicin in pH 1.2, there was an initial burst release of rifampicin from low viscosity HPC (Klucel LF) formulation (at low polymer ratio) in SGF.

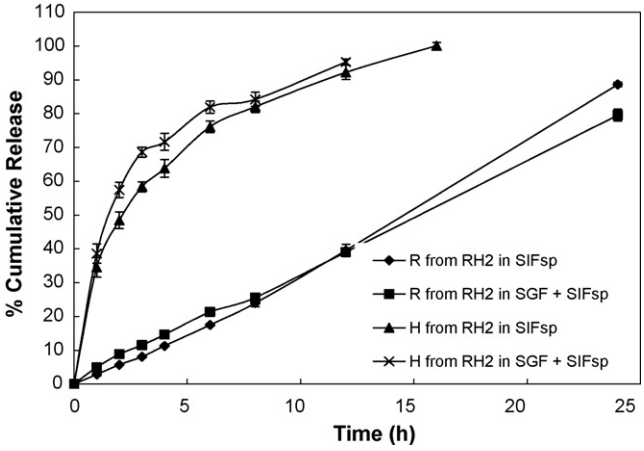

Fig. 4. Effect of release media on release profiles of rifampicin and isoniazid from RH2 (HPMC K4M formulations) (Each data point represents the average of six tablets from three batches with S.D.).

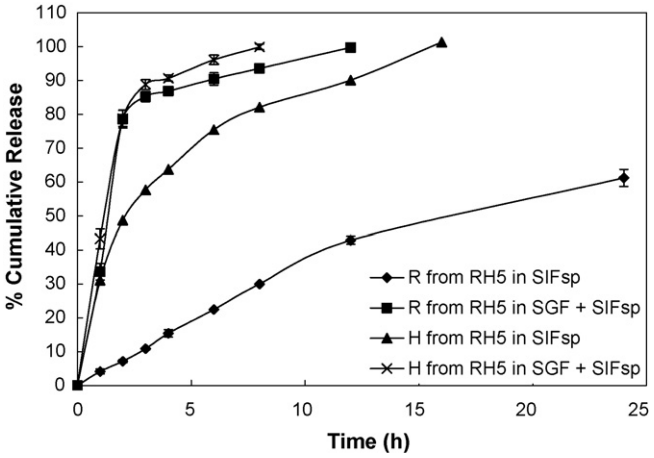

Fig. 5. Effect of release media on release profiles of rifampicin and isoniazid from RH5 (HPC formulations) (Each data point represents the average of six tablets from three batches with S.D.).

There was also a significant difference in the isoniazid release in changed medium. Release was decreased when initial medium changed from SGF to SIFsp. The f_2 factor value of 30.86 established the effect of media change on isoniazid release. The isoniazid release was extended only up to 8 h in case SGF followed by SIFsp compared to 16 h in SIFsp alone. There was also a significant difference in the initial amount of the isoniazid released. This might again be due to difference in the rifampicin solubility in SGF and in SIFsp and effect of media pH on polymer (HPC). The release in SGF was much higher due to excess solubility of rifampicin creating of large number of pores in the tablet matrix. Whereas, the poorly soluble rifampicin hindered the isoniazid release by closing the micropores in the matrix structure and increasing the tortuosity in SIFsp. From this study it could be said that, HPC formulations were more sensitive to the effect of change in release media compared to HPMC. Therefore, addition of Eudragit to minimize the effect of pH on release of rifampicin and isoniazid was found to be more beneficial in case of HPC formulations compared to formulations made with HPMC.

4.3.3. Effect of change in the manufacturing/formulation process

4.3.3.1. HPMC formulations. The release of both rifampicin and isoniazid decreased from modified-RH4 formulations where rifampicin existed intra-granularly along with isoniazid (Fig. 6). The f_2 factor values of 38.21 and 28.83 for rifampicin and isoniazid release respectively between modified-RH4 and RH4 formulations further proved that the variations in the formulation processing had a significant influence on drug release.

There was no change observed in the initial release of rifampicin (0–2 h), the release was changed in the later phase due to change in the availability of rifampicin for diffusion and erosion. Presence of rifampicin in intragranular space made its availability less with increased tortuosity and increased diffusional path length. However, the polymer matrix presented a lower resistance for the

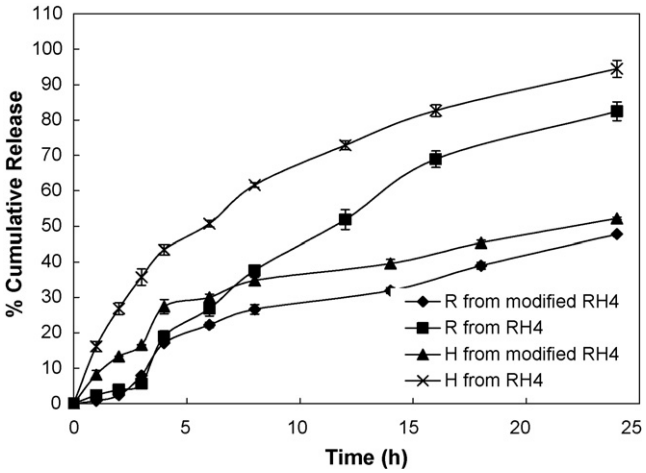

Fig. 6. Effect of change in manufacturing process on release profiles of rifampicin and isoniazid from HPMC K4M formulations in SGF (0–2 h) followed by SIFsp (3–24 h) media (Each data point represents the average of six tablets from three batches with S.D.).

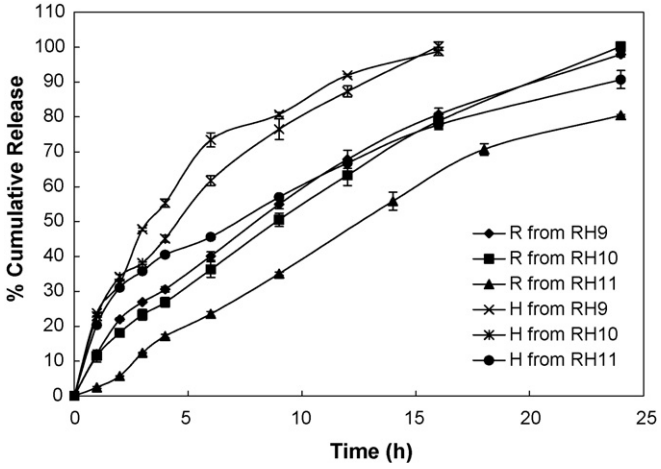

Fig. 7. Effect of change in manufacturing process on release profiles of rifampicin and isoniazid from HPC formulations in SGF (0–2 h) followed by SIFsp (3–24 h) media (Each data point represents the average of six tablets from three batches with S.D.).

release media infiltration in formulations containing extragranular rifampicin leading to quicker polymer hydration, swelling and erosion. Thus, in case of RH4 formulations the erosional release of rifampicin was comparatively higher than that from modified-RH4 formulations.

The initial release of isoniazid was more drastically affected compared to rifampicin when the formulation processing was changed. The possible explanation for such observation might be given as follows. In the modified-RH4 formulation the isoniazid was present along with the rifampicin (intra-granularly). Swelling and erosion tendency of the hydrated matrix was reduced due to the presence of the poorly soluble (compared to isoniazid) rifampicin particles within the matrix. Here, the rifampicin acted merely as an insoluble filler or excipient in the matrix that reduced the porosity of the matrix and decreased the diffusivity of the isoniazid molecules. Thus, the isoniazid release decreased in the SGF in presence of intragranular rifampicin from modified-RH4 formulations. The rate and extent of the reduction in the isoniazid release was much more pronounced in SIFsp release media. This might be due to very poor solubility of the rifampicin in SIFsp compared to SGF. Thus, there might be more number of insoluble rifampicin particles in the matrix structure at any time point in SIFsp compared to that in SGF. Hence, process variation in terms of adding rifampicin intra or extra granularly had significant impact on release profiles of both rifampicin and isoniazid from HPMC formulations.

4.3.3.2. HPC formulations. It can be observed from Fig. 7 that there was no significant difference in the release profile of rifampicin between RH9 and RH10 formulations (f_2 = 72.31). Thus, the process variation in terms of the adding Eudragit L100-55 totally inside the granules along with isoniazid or partly along with rifampicin extragranularly, did not significantly influence the release of rifampicin. Whereas, the rifampicin release was decreased in case of RH11 formulations compared to RH9 in both SGF and SIFsp (f_2 = 45.46). Thus, the IPA granulation of rifampicin significantly reduced its release compared to when it was present as a simple mixture (direct compression) extragranularly.

It can be seen from Fig. 7 that there was no significant difference in the release profile of isoniazid between RH9 and RH10 formulations (f_2 = 57.83). The isoniazid release from RH11 was slower compared to RH9 formulations (f_2 = 36.40). The reason for decrease in the isoniazid release from RH11 formulations compared to RH9 formulations might be again due to the presence of intragranular rifampicin. Similar to HPMC formulations, process variation in terms of adding rifampicin intra or extra granularly had significant impact on release profiles of both rifampicin and isoniazid from HPC formulations.

4.3.4. Effect of presence of one drug on another drug release

It can be observed from Fig. 8 that the rifampicin release occurred at a lower rate in case of RH12 formulations containing rifampicin alone compared to RH10 formulations containing rifampicin in combination with the isoniazid. This was further proved by the f_2 factor value of 48.61. The decrease in the rifampicin release from RH12 formulations was more pronounced in SIFsp. This might be due to the fact that the solubility of rifampicin in SGF was high enough to achieve sufficient initial release and thus the presence or absence of another soluble drug (isoniazid) did not affect the rifampicin release in SGF. But, rifampicin was poorly soluble in SIFsp thus the presence of isoniazid (along with the rifampicin in the same matrix) resulted in the increased rifampicin release (due to increased matrix porosity and erosion) compared to when the total matrix was covered with the insoluble rifampicin.

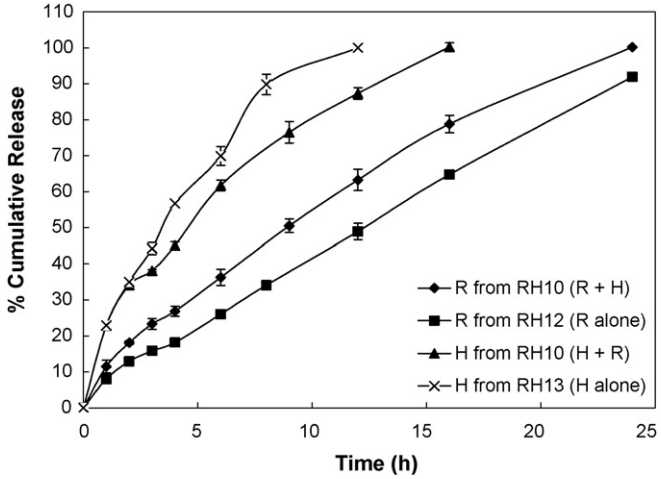

Fig. 8. Effect of presence of one drug on the release of other drug from RH10 (HPC formulations) in SGF (0–2 h) followed by SIFsp (3–24 h) media (Each data point represents the average of six tablets from three batches with S.D.).

In case of isoniazid release, the results were exactly opposite. There was a decrease in the release profile of isoniazid from RH10 (when present along with the rifampicin) compared to RH13 (where isoniazid was present alone in the tablet matrix). This was further demonstrated by the f_2 factor value of 48.28. There was no significant difference in the isoniazid release profiles between RH10 and RH13 in SGF. But in SIFsp the isoniazid release was decreased in case of RH10 formulations compared to RH13. This might again be due to lower solubility of rifampicin in SIFsp that decreased the isoniazid release from RH10 formulations. Whereas, isoniazid release was not significantly affected in SGF as rifampicin was having good solubility in this medium.

5. Conclusions

C.R. formulations are better over conventional multidose delivery systems, particularly for long-term therapeutic effect and for the treatment of chronic diseases. Thus, there is a scope of using multidrug C.R. formulations for the treatment of tuberculosis. In the present investigation, an attempt has been made to develop oral concomitant C.R. release formulations of rifampicin and isoniazid by matrix tablet technology using different polymers or polymer combinations and by optimizing the various formulation factors and processing parameters. Surprisingly we found that the proper combination of non-ionic and anionic polymers and, careful selection of formulation and process parameters could provide concomitant C.R. of rifampicin and isoniazid from a single matrix tablet. The designed matrix tablets of rifampicin and isoniazid combination showed good and reproducible physical properties indicating that the methods of preparation of formulation are suitable and acceptable for preparing good quality matrix tablets. The tablet manufacturing method was relatively simple and can be easily adopted in conventional tablet manufacturing units in industries on a commercial scale.

From our studies it was observed that the C.R. formulations containing 80% HPC and 60% Eudragit (RH9) found to be of good quality and provided required release profile for both rifampicin and isoniazid. These formulations gave good initial release for rifampicin (about 100 mg in 2 h) and isoniazid (about 34% of the total dose in 2 h) and also, the release of both rifampicin and isoniazid were extended up to 18–24 h. Thus, the optimized formulation of the present study provided both required initial release for rifampicin (80–100 mg) and isoniazid (36% of the dose) as loading dose and controlled release of rifampicin and isoniazid as maintenance dose from a single C.R. matrix tablet. Therefore, as discussed in the introductory section, these formulations might fulfill the biopharmaceutical requirement for once a day C.R. formulation of rifampicin and isoniazid combination. The results are also promising as there are very few reports on the use of low viscosity HPC (Klucel LF) as a C.R. matrix forming polymer, especially for combination drugs like rifampicin and isoniazid. Nevertheless the in vitro release methodology, although selected with the proper care, does not always reflect the exact conditions that prevail in the gastrointestinal tract (GIT). Especially the hydrodynamics of the GIT is really a tough and challenging aspect to correlate. Hence, our attempt was to develop the bunch of formulations with different release rates and duration so that these formulations could further be assessed from the in vivo bioavailability studies. From our in vitro studies, these formulations found to be promising and could further be considered for in vivo bioavailability studies in suitable animal models or human volunteers to assess their in vivo performance and bioavailability.

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