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Research Article

Controlled Release Hydrophilic Matrix Tablet Formulations of Isoniazid: Design and *In Vitro* Studies

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Abstract. The aim of the present investigation was to develop oral controlled release matrix tablet formulations of isoniazid using hydroxypropyl methylcellulose (HPMC) as a hydrophilic release retardant polymer and to study the influence of various formulation factors like proportion of the polymer, polymer viscosity grade, compression force, and release media on the *in vitro* release characteristics of the drug. The formulations were developed using wet granulation technology. The *in vitro* release studies were performed using US Pharmacopoeia type 1 apparatus (basket method) in 900 ml of pH 7.4 phosphate buffer at 100 rpm. The release kinetics was analyzed using Korsmeyer–Peppas model. The release profiles were also analyzed using statistical method (one-way analysis of variance) and f_2 metric values. The release profiles found to follow Higuchi's square root kinetics model irrespective of the polymer ratio and the viscosity grade used. The results in the present investigation confirm that the release rate of the drug from the HPMC matrices is highly influenced by the drug/HPMC ratio and viscosity grade of the HPMC. Also, the effect of compression force and release media was found to be significant on the release profiles of isoniazid from HPMC matrix tablets. The release mechanism was found to be anomalous non-Fickian diffusion in all the cases. In the present investigation, a series of controlled release formulations of isoniazid were developed with different release rates and duration so that these formulations could further be assessed from the *in vivo* bioavailability studies. The formulations were found to be stable and reproducible.

KEY WORDS: controlled release; dissolution; rifampicin and isoniazid; spectroscopy.

INTRODUCTION

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. This is reflected by the large number of patents filed each year and by the commercial success of a number of novel drug delivery systems based on matrix technologies (1). In matrix devices, the drug is homogeneously dispersed in either a hydrophobic or hydrophilic polymer matrix. The release rate from matrix systems remains unaffected by thin spots, pinholes, and other similar defects, which can be a serious problem with reservoir systems (2). Hydroxypropyl methylcellulose (HPMC), a semisynthetic derivative of cellulose, has its popularity for the formulation of controlled release (CR) dosage forms as a swellable and hydrophilic polymer (3–5). Its 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 it an excellent carrier material (6). Various formulation factors influence the drug release form HPMC matrices, viz., polymer viscosity, polymer particle size, drug/polymer ratio, drug solubility, drug particle size, drug loading, compression force, tablet shape, formulation excipients, coatings, processing techniques, as well as the testing medium (7).

Tuberculosis kills more people worldwide than any other single infectious disease (8). Isoniazid is one of the most important "first-line" anti-tubercular drugs used in the treatment of tuberculosis (9). One of the major drawbacks in the use of isoniazid for the treatment of tuberculosis is the severe toxic/adverse effects associated with it (10–11). These severe toxic effects lead to discontinuation of the therapy because of the lack of patient compliance. Isoniazid reported to undergo appreciable pre-systemic (first pass) metabolism in the wall of the small intestine and liver, resulting in the concentrations in the plasma of rapid acetylators which are half those in slow acetylators after normal dose of 300 mg of the drug (12). This results in subtherapeutic concentrations of the drug in the blood, which leads to treatment failure and also encourages the isoniazid resistant strains of *Mycobacterium tuberculosis*. It was also observed that after intravenous administration of isoniazid, the peak plasma concentrations remained the same (no significant difference) in rapid and slow acetylators. This aspect prompted the development of

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CR matrix formulations of isoniazid to optimize the blood levels in the rapid acetylators (13).

There are several reports in the literature which substantiated the need for the controlled release formulations of isoniazid (12,14–19). It has been reported that the best results were obtained with the formulation containing 37% free isoniazid and 63% matrix component. A formulation containing 15% free isoniazid and 85% matrix component was designed with an aim to achieve suitable high plasma concentrations in fast acetylators and devoid of any toxic or adverse effects in both fast and slow acetylators (12). However, no literature was found on the use of HPMC polymer as a tablet matrix forming material for the development of controlled release formulations of isoniazid. This is a part of research efforts from author's lab on the development of oral controlled release formulations of anti-tubercular drugs rifampicin and isoniazid. In this regard, authors have reported the oral CR formulations of rifampicin (20–21) and rifampicin and isoniazid combination (22). In light of the above discussion, the objective of this study was to formulate controlled release oral tablet formulations of isoniazid by matrix embedding technique using HPMC polymer of different viscosity grades as a retardant material. The formulated tablets were evaluated for their physical properties and *in vitro* release characteristics. The purpose of the present investigation was also to study the influence of drug/polymer ratio, HPMC viscosity grade, compression force and release media on the release characteristics, and release kinetics of isoniazid from HPMC tablet matrix formulations. Thus, the present study aimed at the design of isoniazid CR formulations by using relatively simple manufacturing technology which can be easily adopted in industrial units on a commercial scale. Further, it was an important aspect of the present investigation to develop an oral CR matrix tablet of isoniazid which could provide both initial release as a free isoniazid (immediate release) portion followed by the controlled release as a matrix component from a single formulation.

MATERIALS AND METHODS

Isoniazid (mean particle size of 120±23 μm) was obtained as a gift sample from Lupin Laboratories, Aurangabad. HPMC K100LV (Methocel) and K15M (Methocel) were received as gift samples from Zydus Cadila Research Center, Ahmedabad. HPMC (Methocel) K4M (2910) was purchased from Sigma Aldrich, Germany. HPMC K100M (Metolose 90SH 100000) was purchased from Sigma Aldrich, Bangalore. All other chemicals and reagents used were of pharmaceutical or analytical grade and were used as received.

Solubility Studies of Isoniazid

Extensive solubility studies for isoniazid were not carried out, as isoniazid was reported to be a class I drug according to biopharmaceutical classification system (BCS) (23). Drugs, which belong to BCS class I category, are reported to have higher solubility throughout the entire gastrointestinal pH conditions (pH 1–7.5). However, for the purpose of this project, solubility studies for isoniazid were carried out only at three pH buffers in simulated gastric fluid (SGF, pH 1.2), pH 5.0 phosphate buffer, and in pH 7.4 phosphate buffer with ionic strength adjusted to 0.2 using sodium chloride. The samples were withdrawn in triplicate and analyzed using in-house developed and validated UV method.

Formulation of CR Matrix Tablets of Isoniazid

Controlled release matrix tablets with HPMC K100LV, HPMC K4M, HPMC K15M, and HPMC K100M were formulated by wet (non-aqueous) granulation method using different proportion of polymers. The drug and polymer (passed through 60# mesh) were mixed uniformly and granulated with isopropyl alcohol (IPA) and dried in a tray drier at 60°C. The final granules were blended with talc (1% *w*/*w*) and magnesium stearate (1% *w*/*w*) and compressed in a single station tablet compression machine (Cadmach) using 13-mm standard concave punches. The compression force, except for the studies on the effect of compression force on the release rate, was kept at a constant level required to produce tablets of about 6.0-kp hardness. Three batches of tablets, 200 tablets for each batch size, were prepared for each formulation, with each tablet containing 300 mg of isoniazid.

The following variations in tablet formulae were done and their effect on *in vitro* release rate, release mechanism (Fickian or non-Fickian), and nature of release (order of release) was studied.

(a) Effect of varying proportions of HPMC: Tablets were made containing 20%, 30%, 40%, 60%, and 80% HPMC (*w*/*w* of the drug) in the case of HPMC K100LV formulations. HPMC K4M, K15M, and K100M ratios studied were, 10%, 20%, 40%, 60%, and 80% (*w*/*w* of the drug).
(b) Effect of viscosity grade of HPMC: Four different viscosity grade HPMCs were used in the present investigation, HPMC K100LV (100 cPs), K4M (4000 cPs), K15M (15,000 cPs), and HPMC K100M (100,000 cPs).
(c) Effect of compression force: For this study, two batches of formulations were selected varying in their viscosity grades (HPMC). The tablet batches containing 60% of HPMC K100LV and HPMC K100M were compressed using three different compression force levels required to produce tablets of about 4.0, 7.0, and 11.0-kp hardness.
(d) Effect of change in the release media: For this study, 40% formulations of HPMC K100LV and HPMC K15M formulations were selected. The release studies were carried out in 0.1 N HCl (pH 1.2) and in 7.4 pH phosphate buffer.

Physical Characterization of the Tablets

Formulated tablets were subjected to the following physical characterization studies. The drug content of each batch of the formulated tablets was determined in triplicate with the in-house developed and validated UV–visible method in pH 5.0 phosphate buffer at 262 nm. The weight variation was determined on 20 tablets using electronic balance (Afcoset). Tablet hardness was determined for a minimum of six tablets of each batch using Monsanto (standard type) tablet hardness tester. Friability was deter-

mined with ten tablets in a Campbell electronic friabilator for 5 min at 25 rpm.

In Vitro Release Studies

Release rate was studied using Electrolab tablet dissolution tester (USP 24, model TDT 06P), type 1 (basket method) in pH 7.4 phosphate buffer at 37±1°C. The volume of the dissolution medium was 900 ml, and the stirring speed was set at 100 rpm. At predetermined time intervals, 10 ml of sample was withdrawn and replaced with fresh dissolution media. After appropriate dilutions, the samples were analyzed by in-house developed and validated UV spectrophotometric method at 262 nm. Cumulative percent of drug released was calculated, and mean of six tablets from three different batches were used in the data analysis.

Analysis of Release Profiles

The release mechanism and kinetics of the release profiles were analyzed by Korsmeyer–Peppas model (Table I).

Korsmeyer–Peppas model (24):

$$\frac{M_t}{M_\infty} = Kt^n \tag{1}$$

where M_t/M_∞ is the fraction of the drug released up to time t, K is a constant incorporating structural and geometric characteristics of the release system, and n is the diffusional exponent indicative of the release mechanism.

Further, the statistical analysis of the drug release profiles was carried out by one-way analysis of variance (ANOVA) and by comparing the drug release profiles using a model-independent method (25). The mean dissolution time (MDT) of the formulations were determined and compared subjecting the MDT values to one-way ANOVA to examine the statistical difference. A confidence limit of $P<0.05$ was fixed, and the theoretical and calculated values of F (F_{crit} and F_{cal}) were compared for the interpretation of results and to examine the statistical difference. The MDT values were calculated using the following equation:

$$\text{MDT} = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \tag{2}$$

where j is the sample number, n is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1} [easily calculated with the expression $(t_j+t_{j-1})/2$], and ΔM_j is the additional amount of drug released between t_j and t_{j-1}.

Batch Reproducibility

Three batches of each formulation were prepared and their quality and respective release characteristics were evaluated under the same conditions as prescribed in previous sections. *In vitro* release data pertaining to reproducibility studies were compared by f_2 metric (similarity factor) values. The statistical analysis of the drug release profiles was carried out by one-way ANOVA.

Stability Test

The selected formulations were subjected to stability studies up to 6 months at different storage conditions. The tablets were sealed in airtight cellophane packets and stored at controlled room temperature condition (25±2°C and 60±5% RH), 40±2°C and 40±2°C/75±5% RH. The *in vitro* release profile was studied as per the specifications enlisted in previous sections and compared with its initial release profile with f_2 factor values. The release profiles were further analyzed by one-way ANOVA to examine the statistical difference.

RESULTS AND DISCUSSIONS

Solubility Studies of Isoniazid

The solubility studies were carried out in three different pH buffer solutions, SGF (pH 1.2), and phosphate buffers pH 5.0 and 7.4 (selected on the basis of physiological pH conditions). In all three media, the solubility was higher; however, it was observed that there was a very slight decrease in the solubility as the pH was increased. The solubility found to be 326±3.96 mg/ml (in SGF), 281±3.52 mg/ml (at pH 5.0), and 274±4.79 mg/ml (at pH 7.4).

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 form Tables II and III. These results indicated that the IPA granulation method is an acceptable method for preparing good quality matrix tablets of isoniazid.

In Vitro Release Studies

Plots of percent cumulative drug released *vs.* time for HPMC K100LV matrix tablet formulations are shown in the Fig. 1. As can be observed from Fig. 1, increase in the polymer ratio resulted in the decrease in the release. Similar trend was observed in the case of HPMC K4M (H6, H7, H8, H9, and H10), HPMC K15M (H11, H12, H13, H14, and H15) and HPMC K100M (H16, H17, H18, H19, and H20) formulations (graphs not shown). The effect of polymer proportion on isoniazid release was further substantiated by the MDT values of formulations studied (Table I). The reason for the decrease in the release with increase in the polymer proportion might be explained as follows (for water-soluble drug isoniazid). An increase in the polymer proportion resulted in the increased viscosity of the tablet matrix gel layer as well as the formation of a gel layer with a longer diffusional path. This phenomenon resulted in the decreased effective diffusion of the drug and therefore a reduction in the drug release rate.

Isoniazid release was found to follow Higuchi's square root kinetics, as the plots of percentage drug released *vs.* square root of time was found to be linear (data not shown) in the case of all the formulations. The reason for initial

Table I. Release Kinetics Parameters and MDT Values for Isoniazid CR Formulations

Formulations	Peppas model parameters				MDT[e] (h)	MDT[f] (6-month stability samples, h)
	n[a]	K[b] (h^{-n})	$t_{50\%}$[c] (h)	r[d]		
H2	0.60	0.438	1.25	0.999	1.48	1.42
H3	0.59	0.396	1.48	0.999	2.24	2.18
H4	0.66	0.321	1.94	0.979	2.62	2.71
H5	0.70	0.282	2.26	0.986	3.31	3.20
H8	0.55	0.361	1.81	0.999	2.62	2.56
H9	0.59	0.301	2.34	0.998	3.79	3.88
H10	0.53	0.266	3.29	0.999	4.24	4.12
H12	0.64	0.368	1.61	0.999	2.07	2.01
H13	0.55	0.370	1.72	0.999	2.73	2.82
H14	0.60	0.296	2.39	0.993	3.95	4.06
H15	0.53	0.262	3.36	0.999	4.25	4.18
H17	0.63	0.359	1.39	0.989	2.25	2.16
H18	0.55	0.345	1.97	0.999	2.80	2.64
H19	0.58	0.287	2.59	0.998	4.18	4.32
H20	0.53	0.256	3.43	0.999	4.22	4.11

[a] Diffusional exponent indicative of the release mechanism
[b] Release rate constant
[c] Time for 50% of the drug release
[d] Correlation coefficient
[e] Mean of six tablets with SD within ±0.13 h
[f] Mean of six tablets with SD within ± 0.16 h

higher release and decrease in the rate of isoniazid with time can be explained as follows. At early times, drug close to matrix surface might be released before the surrounding polymer reached the polymer disentanglement concentration (the concentration of the polymer in a fully hydrated state at which there are no polymer–polymer interactions) because the diffusion coefficients for drug molecules were higher than the polymer. Especially, the high viscosity polymers would take longer time to form a gel layer. Within this time, major amount of the drug might have been released. It has been reported that to get the best results, the controlled release formulations in the case of isoniazid should contain 37% free isoniazid and 63% matrix component (12). The free isoniazid was mentioned probably to achieve initial amount of release required to elicit necessary therapeutic action, and the remaining part (matrix component) was suggested as a controlled release part to compensate for the decreased half-life of the drug (isoniazid) in fast acetylators. Thus, from the present studies, it was observed that the HPMC formulations could provide both the advantages (initial higher release followed by controlled release) in a single controlled release tablet formulation.

The values of K, n, and $t_{50\%}$ (time for 50% of the drug release) are listed in Table I. The n values ranged from 0.53 to 0.70, indicating that the mechanism of release was anomalous non-Fickian diffusion. Although the extension of

Table II. Formula and Physical Properties of Isoniazid Matrix Tablets Prepared with HPMC K100LV and HPMC K4M

Formulations	Components[a]		Physical properties			
	Drug (mg)	HPMC[b] (%)	Drug content (% label claim)[c]	Weight variation (%)[d]	Hardness (kp)[e]	Friability (%)
HPMC K100LV						
H1	300	20	101.5±1.7	±2.3	6.7±0.8	<0.90
H2	300	30	102.0±1.4	±1.9	6.5±0.7	<0.9
H3	300	40	99.1±1.2	±1.8	6.8±0.8	<0.9
H4	300	60	99.8±1.5	±2.8	6.5±0.9	<0.9
H5	300	80	100.7±1.6	±2.5	6.3±0.5	<0.9
HPMC K4M						
H6	300	10	100.3±1.2	±1.9	6.3±0.5	<0.9
H7	300	20	101.5±0.9	±2.3	6.5±0.6	<0.9
H8	300	40	99.8±1.8	±2.4	6.9±0.7	<0.9
H9	300	60	99.8±1.5	±1.8	6.7±0.4	<0.9
H10	300	80	99.6±1.7	±2.9	6.4±0.6	<0.9

[a] Also contains 1% *w*/*w* of talc and 1% *w*/*w* of magnesium stearate as additives
[b] % *w*/*w* of the drug
[c] Mean of triplicate with SD
[d] ±Max % variation from the mean
[e] Mean of six tablets

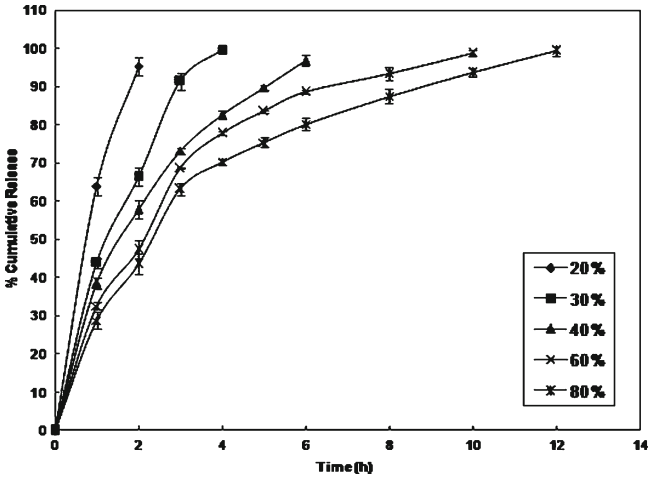

Fig. 1. Comparative release profiles of isoniazid from HPMC K100LV formulations in pH 7.4 PO_4 (each data point represents the average of six tablets from three batches with SD)

release was significantly different among the formulations with different polymer ratios, the K and $t_{50\%}$ values were found to be not that much affected. This might be due to the fact that the K and $t_{50\%}$ values were calculated with the Korsmeyer and Peppas model (24), which could be applied up to 60% release only. It is already discussed that the drug release was higher during initial hours irrespective of the polymer ratio or viscosity. Thus, there were not much differences in the release profiles of the formulations during initial hours (compared to the differences in the later hours of the release studies) and, hence, the K and $t_{50\%}$ values. It has been also reported that the higher K value in the case of the drug release from matrix-embedded CR tablet formulations is an indication of burst release from the formulations (26). Thus, the burst release of highly soluble isoniazid from HPMC formulations might have resulted in the higher K values and lower $t_{50\%}$ values from HPMC matrix tablets.

Effect of HPMC Viscosity

The effect of polymer viscosity, at 40% polymer ratio, is depicted in Fig. 2. It can be observed that as the polymer viscosity increased from 100 cPs (K100LV) to 4000 cPs (K4M), there was a slight decrease in the release. The calculated MDT values (n=6) were found to be 2.24±0.13, 2.62±0.09, 2.73±0.09, and 2.80±0.11, respectively, for the release profiles of K100LV, K4M, K15M, and K100M formulations. A statistically significant difference was observed between the release profiles of K100LV and K4M matrices as indicated by the increased MDT values (P<0.05, F_{crit}=7.7, and F_{cal}=16.1) with increase in polymer viscosity. But there was no significant difference between the release profiles of the formulations made with K4M (4,000 cPs), K15M (15,000 cPs), and K100M (100,000 cPs). The ANOVA of MDT values for K4M and K15M (P<0.05, F_{crit}=7.7, and F_{cal}=1.0), K15M and K100M (P<0.05, F_{crit}=7.7, and F_{cal}=0.2), and K4M and K100M (P<0.05, F_{crit}=6.0, and F_{cal}=3.2) further proved that there is no significant difference in the release profiles of K4M, K15M, and K100M formulations. The release profiles were also analyzed for the similarity factor (f_2) values for assessment of statistical difference or similarity between the release profiles. The f_2 factor value was observed to be 49.67 between K100LV and K4M formulations, indicating the significant difference between the release profiles, whereas the f_2 factor values were found to be 77.83 between K4M and K15M formulations, 84.72 between K15M and K100M formulations, and 69.70 between K4M and K100M formulations, indicating no significant difference between the release profiles of K4M, K15M, and K100M formulations. The statistical analysis (ANOVA) and analysis of the f_2 factor values proved that the effect of HPMC viscosity on release was only significant up to K4M (4,000 cPs), above which, the increase in viscosity (to K15M and K100M) does not have any significant effect on the release profiles.

The reason for such observations would be difficult to explain, but the possible explanation is as follows. It has been already discussed that the polymer viscosity affects the polymer chain disentanglement. At the same polymer con-

Table III. Formula and Physical Properties of Isoniazid Matrix Tablets Prepared with HPMC K15M and HPMC K100M

	Components[a]		Physical properties			
Formulations	Drug (mg)	HPMC[b] (%)	Drug content (% label claim)[c]	Weight variation (%)[d]	Hardness (kp)[e]	Friability (%)
HPMC K15M						
H11	300	10	99.1±1.3	±2.6	6.6±0.6	<0.9
H12	300	20	100.8±1.5	±1.5	6.7±0.8	<0.9
H13	300	40	101.6±1.6	±1.9	6.7±0.8	<0.9
H14	300	60	99.5±1.7	±2.4	6.4±0.6	<0.9
H15	300	80	102.3±1.2	±2.7	6.9±0.7	<0.9
HPMC K100M						
H16	300	10	102.0±1.5	±2.3	6.5±0.7	<0.9
H17	300	20	101.3±1.3	±2.6	6.8±0.4	<0.9
H18	300	40	98.9±1.0	±1.2	6.8±0.4	<0.9
H19	300	60	101.8±1.6	±1.6	6.5±0.5	<0.9
H20	300	80	99.2±1.3	±2.8	6.7±0.8	<0.9

[a] Also contains 1% *w/w* of talc and 1% *w/w* of magnesium stearate as additives
[b] % *w/w* of the drug
[c] Mean of triplicate with SD
[d] ±Max % variation from the mean
[e] Mean of six tablets.

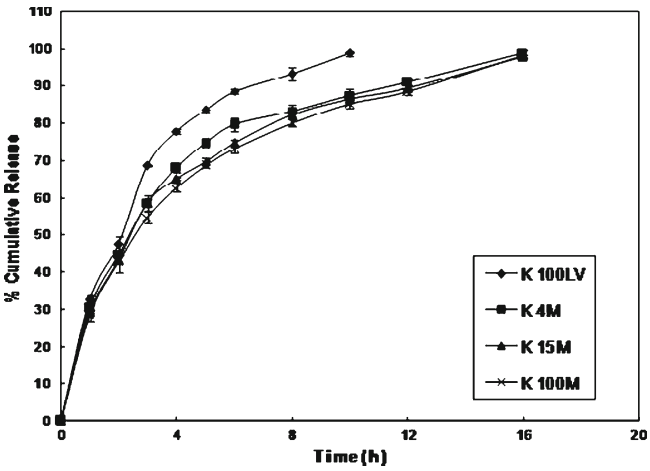

Fig. 2. Effect of HPMC viscosity on isoniazid release profiles from 60% HPMC formulations in pH 7.4 PO_4 (each data point represents the average of six tablets from three batches with SD)

centration, a polymer of higher viscosity induces greater chain entanglement than a polymer of low viscosity. Therefore, it is harder for longer chains to dissolve because of the high energy required for pulling them off the matrix. Thus, higher viscosity polymers induce the formation of a thicker gel layer after hydration. As discussed, the effect of polymer viscosity was mainly due to the differences in their molecular weights. The molecular weights of HPMC K100LV, K4M, K15M, and K100M were reported to be 25, 95, 120, and 250 kDa, respectively (27). There is a strong relationship that exists between the polymer molecular weight (MW) and polymer disentanglement concentration ($C_{p,dis}$) (28):

$$C_{p,dis} = \frac{27,000}{MW}. \quad (3)$$

According to the relationship (equation), the $C_{p,dis}$ decreases with increasing MW and approaches a plateau at high MW. It was, however, reported that the change in the polymer disentanglement concentration between K100LV and other viscosity grades was appreciable leading to a higher release rates for the K100LV matrices. But the change in the $C_{p,dis}$ between K4M, K15M, and K100M was so small that the matrix swelling and drug release profiles for these three HPMC formulations were indistinguishable. Probably, the diffusion coefficient of the highly soluble isoniazid might also have been least affected once the viscosity increased beyond 4,000 cPs (i.e., above K4M), and thus, the release rates remained almost same. Other research groups have reported similar results that the drug release rate decreased with increasing molecular weight for low-molecular-weight HPMCs and became independent of molecular weight for high-molecular-weight HPMCs (29–30).

Effect of Compression Force

It can be observed from Fig. 3 for HPMC K100LV (H4) formulations that the release rate was higher for tablets compressed at lower compression force (to the hardness of 4.0 kp) compared to the tablets compressed to 7.0-kp hardness. The calculated MDT values (n=6) were found to be 1.61±0.08, 2.30±0.12, and 2.51±0.07, respectively, for the release profiles of the formulations compressed to the hardness of 4.0, 7.0, and 11.0 kp. Significant difference in the release profiles of the tablets compressed to the hardness of 4.0 and 7.0 kp was further confirmed by the MDT values (P<0.05, F_{crit}=7.7, and F_{cal}=58.1), whereas there were no significant differences between the release profiles of formulations compressed to 7.0- and 11.0-kp hardness as indicated by the MDT values (P<0.05, F_{crit}=7.7, and F_{cal}=5.6). The release profiles were further analyzed for f_2 factor values. The f_2 factor value was found to be 38.77 between the formulations compressed to 4.0 and 7.0 kp, indicating that the release profiles were significantly affected by the compression force. But the f_2 factor value was found to be 66.29 between the formulations compressed at 7.0 and 11.0 kp, indicating no significant difference between the release profiles. In the case of 60% HPMC K100M formulations (H19) also (data not shown), the release profiles followed similar trend as in the case of H4 (K100LV) formulations.

The reason for the present findings can be explained as follows. At lower applied compression force, there might be insufficient tablet strength and greater level of porosity (void spaces within the matrix) which allowed a greater liquid penetration in to the matrix, causing immediate dissolution of the drug within the matrix that enhanced the diffusivity of the drug out of the matrix. Also, the drug has good solubility in the release medium, and hence, the drug present on the surface might have been released quickly because of the presence of the more pores in the matrix structure. Thus, the matrix became more porous (less tortuous) and allowed quicker release of the drug within a short period of time. But once the required hardness was achieved, i.e., 7.0 kp in the study, further increase in the hardness did not influence the release anymore. This might probably be due to the non-significant influence of initial tablet matrix porosity on the initial release of soluble drug (isoniazid) once the minimum hardness was achieved (7.0 kp). In the later hours also, the release rates remained similar, as initial porosity has no effect on the release from the swollen tablet matrix.

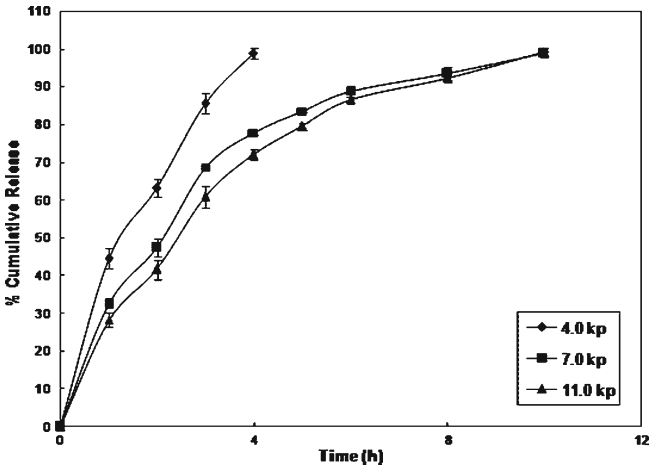

Fig. 3. Effect of compression force on release profiles of isoniazid from HPMC K100LV (60%) formulations in pH 7.4 PO_4 (each data point represents the average of six tablets from three batches with SD)

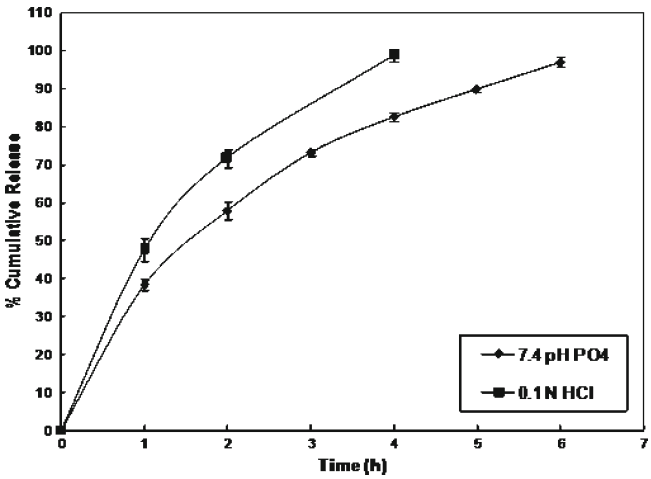

Fig. 4. Effect of release media on release profiles of isoniazid from HPMC K100LV (40%) formulations (each data point represents the average of six tablets from three batches with SD)

Effect of Change in the Release Media

It can be seen from Fig. 4 that the drug release rate was higher in 0.1 N HCl compared to pH 7.4 phosphate buffer for H3 (K1000LV) formulations. The calculated MDT values (n= 6) were found to be 2.02±0.11 and 1.35±0.07 for the release profiles of H3 formulations in pH 7.4 phosphate buffer and 0.1 N HCl, respectively. The difference in the release profiles was statistically confirmed by the MDT values (P<0.05, F_{crit}= 7.7, and F_{cal}=75.5). The f_2 factor value of 43.56 further demonstrated that the drug release was significantly higher in 0.1 N HCl compared to the release in pH 7.4 phosphate buffer. Similarly, the drug release was observed to be higher in 0.1 N HCl than in pH 7.4 phosphate buffer in the case of 40% HPMC K15M (H13) formulations (data not shown).

The observed difference in the release profiles of HPMC formulations (H3 and H13) in 0.1 N HCl and in pH 7.4 phosphate buffer might be explained as follows. It was observed during pre-formulation studies that the solubility of isoniazid was good at all pH values (pH 1.2, 5.0, and 7.4) studied. Thus, at first thought, it appears that there should not be any difference in the release profiles of isoniazid between 0.1 N HCl (pH 1.2) and 7.4 phosphate buffer. However, the release was higher in 0.1 N HCl (pH 1.2) than in 7.4 phosphate buffer in the case of both HPMC formulations (H3 and H13). This might be due to the fact that the HPMC release is reported to be higher in 0.1 N HCl than in 7.4 phosphate buffer or water (31–32). The reason for higher HPMC release in 0.1 N HCl than in 7.4 phosphate buffer might be due to differences in the osmotic pressure between these two media, difference in the solubility of HPMC in these media, and charge effects. The exact analysis of the reason for such observation requires more detailed studies, which are beyond the scope of the present investigation.

Batch Reproducibility

The tablets showed low standard deviation values for the drug content, friability, weight variation, and hardness from three different batches prepared separately (data not shown). The low standard deviation values for all physical properties showed that there was excellent batch-to-batch reproducibility and absence of significant batch-to-batch variations. No significant difference was observed in the release profiles of the formulations between different batches, as indicated by the low standard deviation values of the percent cumulative release data at different time points obtained from the replicate release studies of the samples and by the statistical analysis (ANOVA results of the MDT values; data not shown). The batch reproducibility study indicated that the formulation methodology employed (IPA granulation) was found to be suitable for manufacturing good quality CR matrix tablets of isoniazid.

Stability Test

The isoniazid in matrix-embedded tablets (in the case of all polymer formulations) was found to follow first-order degradation, as the plots of log percent drug content remaining *vs*. time found was to be linear (with "r" value more than 0.971 in all cases and individual plots not given). The K_{deg} for isoniazid in various formulations ranged from 5.05×10^{-3} $month^{-1}$ to 6.64×10^{-3} $month^{-1}$ at CRT, 6.43×10^{-3} $month^{-1}$ to 8.31×10^{-3} $month^{-1}$ at 40±2°C and 8.70×10^{-3} $month^{-1}$ to 12.11×10^{-3} $month^{-1}$ at 40±2°C/75±5% RH. In all polymer formulations, the degradation rate constant increased with increase in the polymer proportion. The $t_{90\%}$ values for isoniazid in various formulations ranged from 15.86 to 20.88 months at CRT, from 12.68 to 16.38 months at 40±2°C, and from 8.70 to 12.11 months at 40±2°C/75±5% RH. Isoniazid was found to be more stable at CRT and less stable at 40±2°C/75±5% RH in all formulations. Also, it was observed that isoniazid was comparatively more stable in HPMC K100M formulations and less stable in formulations with HPMC K100LV. It was observed that with the raise in the temperature, the K_{deg} values increased and $t_{90\%}$ values decreased in the case of all formulations (in all polymer ratios). The K_{deg} values were higher at 40±2°C/75±5% RH compared to 40±2°C in all the cases studied. Thus, from present studies, it was observed that the humidity was one of the most important parameters that affected the stability of isoniazid in all polymer formulations. The increased K_{deg} values found at higher humidity condition supported the fact that avoidance of aqueous granulation technology (use of IPA granulation) in the manufacturing of isoniazid matrix tablets was significantly beneficial in obtaining the stable CR matrix tablets of isoniazid.

The *in vitro* release profiles were studied as per the specifications enlisted in previous sections and compared with their respective initial release profiles. The *in vitro* release profiles of the formulations stored at CRT for 6 months were compared with the initial release profiles (0 time samples at CRT) by ANOVA of the MDT values (Table I). The theoretical and calculated values of F (F_{crit} and F_{cal}) indicated that the isoniazid release profiles were significantly similar for zero time samples and 6 months samples (stored at CRT). Thus, the *in vitro* release characteristics were not significantly affected by the stability studies (storage at CRT) for about 6 months, showing that the formulations were stable in terms of release characteristics.

CONCLUSIONS

The present study showed that the hydrophilic polymer like HPMC could be used as a matrix material to design CR formulations of a water-soluble drug isoniazid with desired quality and release characteristics. The tablet manufacturing method was relatively simple and can be easily adopted in conventional tablet manufacturing units in industries on a commercial scale. In the present investigation, a series of CR formulations of isoniazid were developed with different release rates and duration so that the formulations could further be assessed from the *in vivo* bioavailability studies. From the *in vitro* studies, the formulations were found to be promising and could further be considered for *in vivo* bioavailability studies in suitable animal models or human volunteers to assess *in vivo* performance and bioavailability.

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