Research Article

Controlled Release Imatinib Mesylate Tablet Formulation: Using Hydrophilic Matrix System

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A B S T R A C T

Background: Imatinib mesylat as an oral anticancer agent need a controlled released formulation to get steady and stable plasma concentration. The aim of the present study was to develop controlled release matrix tablet formulations of Imatinib using hydroxy propyl methyl Cellulose as a hydrophilic release retardant polymer and to study the effects of different formulation features like polymer viscosity grade, ratio of the polymer, compression force, and release medium on the in vitro release properties. *Methods*: The in vitro release studies were performed using US Pharmacopoeia type I apparatus. The release kinetics was analyzed by Korsmeyer–Peppas model and were also analyzed using statistical method and f_2 metric values. The release profiles look like Higuchi's square root kinetics model irrespective of the viscosity grade and polymer proportion. *Results:* The results showed that the release rate of the drug is greatly affected by the drug/polymer ratio and viscosity grade. Also, the effect of release medium and compression force was showed to be significant on the release profiles. The release mechanism was found to be anomalous non-Fickian diffusion in all formulations. *Conclusions:* The formulations were found to be reproducible and stable. Controlled release formulations were developed with different release rates and profiles so that these formulations could be evaluated for more in vivo studies.

Introduction

Imatinib is one the first-line treatments of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST).[1] One of the major drawbacks in taking conventional Imatinib tablets by patients is the severe toxic/adverse effects associated with.[2] The severe adverse effects lead to discontinuation of the therapy because of the lack of patient compliance and these side effects associated with higher than therapeutic plasma concentration of Imatinib. The variation in pharmacokinetic of Imatinib results in sub-therapeutic concentrations of the drug, which leads to treatment failure and also encourages the drug resistant.[3-4] There are several reports in the literature which substantiated the need for the controlled release formulations of Imatinib.[5-7] This aspect prompted the development of controlled release formulations of Imatinib to optimize the plasma levels in the patients.[8-9]

Among oral controlled drug delivery systems, matrix systems are the most accepted because of their simplicity, reproducibility, stability of dosage form and ease of scale-up and validation. This is shown by the large number of patents and commercial success of novel drug delivery systems that based on this technology.[10] In matrix systems, the drug is homogeneously dispersed in either a hydrophobic or hydrophilic polymer matrix. The drug release rate from matrix systems remains unaffected by complications such as thin spots, pinholes, crashes and other similar defects, which can be a serious problem with reservoir systems.[11]

Hydroxy Propyl Methyl Cellulose (HPMC), a semi-synthetic derivative of cellulose, has its popularity as a swellable and hydrophilic polymer for formulation of matrix controlled release (CR) dosage forms.[12-14] Its safety, compressibility, compatibility, accommodation of large amount of active ingredients and relatively simple process of manufacturing make it an excellent delivery system.[15] Various formulation factors influence the drug release form HPMC matrices such as polymer viscosity and particle size, drug/polymer ratio, drug solubility, drug particle size, drug loading, compression force, tablet shape, formulation excipients, as well as the testing medium.[16]

The objective of present study was to formulate controlled release oral tablet formulations of Imatinib by matrix embedding technique using HPMC polymer of different viscosity grades as a retardant materials by using relatively simple manufacturing technology and study the influence of drug/polymer ratio, HPMC viscosity grade and compression force of pressing on the release characteristics.

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Materials and Methods

Imatinib manufactured by Cipla, India was obtained from Osveh pharmaceutical company, Tehran, Iran. All HPMC (Methocel®) was obtained from Sigma-Aldrich Co, Germany. All other materials were of pharmaceutical and analytical grade and used as received.

Solubility studies of Imatinib

As Imatinib Mesylate was reported to be a class I according to biopharmaceutical classification system (BCS)[17] which has high solubility throughout the gastrointestinal pH conditions (pH 1–7.5). The solubility study for Imatinib was carried out only at three pH which are 1.2, 5.0 and 7.4. The samples were withdrawn in triplicate and analyzed using a sensitive UV-spectrophotometric analytical method (Maximum absorbance wavelength of 285nm). The developed spectroscopic method was validated for selectivity, linearity, precision, accuracy and sensitivity. The developed method demonstrated consistent high recoveries (99–102%) and low relative standard deviation (< 5%) at 285 nm. Moreover, the method was found to be highly sensitive with low limit of detection (0.50 mg/mL) and limit of quantitation (1.75 mg/mL).[18-20]

Formulation of controlled release matrix

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 40 # mesh) were mixed uniformly and then granulated with isopropyl alcohol (IPA) and dried at 50 °C. The final granules were fully blended with talc powder (1% w/w) and magnesium stearate (1% w/w) and compressed in the compression machine using 13-mm concave punches and dies. The compression force, except for the studies on the compression force effect on release rate, was kept at a constant level required to produce tablets of about 6.0 kp hardness. Three batches of tablets, 100 tablets for each batch size, were prepared for each formulation, with each tablet containing 478 mg of Imatinib Mesylate equivalent to 400 mg Imatinib base. 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. At first the effect of varying proportions of different HPMC were investigated. Tablets were made containing different concentration of HPMC K100LV (20%, 30%, 40%, 60% and 80%), HPMC K4M, K15M, and K100M (10%, 20%, 40%, 60%, and 80%). At second the effect of viscosity grade of different HPMC polymer (K100LV (100 cPs), K4M (4000 cPs), K15M (15,000 cPs), and K100M (100,000 cPs) was investigated. Then the effect of compression force on formulation (60% of K100LV and K100M) were assessed using three different force level (final

tablets hardness of 4.0, 7.0, and 11.0 kp).

Physical characterization of the tablets

Tablets were subjected to the following physical characterization studies. The drug content of each batch of the formulated tablets was determined in triplicate in pH 5.0 phosphate buffer. The weight variation was determined on 20 tablets using electronic balance. Tablet hardness was determined for a minimum of six tablets of each batch using Erweka tablet hardness tester. Friability was determined with ten tablets in a friabilator for 5 min at 25 rpm.

In Vitro release studies

Release rate was studied using standard tablet dissolution tester, type I (rotating basket method) in different medium 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. Cumulative percent of drug released was calculated, and mean of six tablets from three batches were used in the data analysis.

Analysis of release profiles

The release mechanism and its kinetics were analyzed by Korsmeyer–Peppas model. 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.[21] 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:

$$MDT = \frac{\sum_j^n \hat{t}_j \Delta M_j}{\sum_j^n \Delta M_j} \qquad \text{Eq.(1)}$$

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} 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 (similarity factor) metric 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 25±2°C and 60±5 %RH, 30±2°C/60±5 %RH 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

Solubility studies of Imatinib

The solubility studies were carried out in three different pH solutions, pH 1.2, and phosphate buffers pH 5.0 and 7.4 (selected on the basis of gastrointestinal physiological pH conditions). In all three media, the solubility was high; however, it was observed that there was a decrease in the solubility as the pH was increased. The solubility found to be 756.4±3.9 mg/ml (in 1.2 pH), 221.8±3.5 mg/ml (at pH 5.0), and 64.3±4.7 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 acceptable, as can be observed form Tables 1 and 2. These results indicated that the method of granulation is a suitable for preparing high quality matrix tablets of Imatinib.

Table 1. Formulation and Physical Properties of Imatinib Matrix Tablets Prepared with HPMC K100LV and HPMC K4M (Mean ± SD (n=3)).

Formulations	Main components			Physical Properties		
	Drug (mg)	HPMC (% w/w)	Drug Content (%)	Weight Variation (%)	Hardness (Kp)	Friability (%)
HPMC K100LV						
H1	300	20	101.2±3.1	±2.4	6.5±0.2	<0.9
H2	300	30	102.0±1.4	±1.7	6.2±0.5	<0.9
H3	300	40	99.2±1.4	±1.0	6.5±0.4	<0.9
H4	300	60	100.3±0.9	±1.4	7.0±0.2	<0.9
H5	300	80	99.0±1.3	±1.9	6.2±0.3	<0.9
HPMC K4M						
H6	300	10	100.0±1.0	±1.3	6.0±0.4	<0.9
H7	300	20	99.0±0.8	±2.2	6.2±0.3	<0.9
H8	300	40	100.0±0.4	±1.5	6.6±0.4	<0.9
H9	300	60	102.0±1.9	±2.5	6.4±0.7	<0.9
H10	300	80	99.2±1.2	±1.3	6.3±0.5	<0.9

Table 2. Formulation and Physical Properties of Imatinib Matrix Tablets Prepared with HPMC K15M and HPMC K100M (Mean ± SD (n=3)).

| Formulations	Main components			Physical Properties		
	Drug (mg)	HPMC (% w/w)	Drug Content (%)	Weight Variation (%)	Hardness (Kp)	Friability (%)
HPMC K15M						
H11	300	10	100.1±1.2	±2.2	6.8±0.3	<0.9
H12	300	20	99.1±1.5	±1.5	6.3±0.5	<0.9
H13	300	40	102.2±0.7	±2.0	6.2±0.8	<0.9
H14	300	60	100.4±2.1	±1.5	6.9±0.3	<0.9
H15	300	80	98.5±1.6	±2.5	6.5±0.1	<0.9
HPMC K100M						
H16	300	10	101.1±0.2	±2.4	6.5±0.2	<0.9
H17	300	20	98.1±1.7	±1.6	6.4±0.4	<0.9
H18	300	40	100.5±0.2	±2.2	6.2±0.6	<0.9
H19	300	60	103.0±1.8	±1.6	6.8±0.3	<0.9
H20	300	80	99.9±1.3	±2.3	6.4±0.2	<0.9

In Vitro release studies

Plots of percent cumulative drug released vs. time of HPMC K100LV matrix tablet formulations (H1, H2, H3, H4, and H5) are shown in the Figure 1. As can be observed, 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. The effect of polymer proportion on Imatinib release was further verified by the MDT values of formulations (Table 3). Imatinib release in the

case of all the formulations 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 (Figure 2). The values of K, n, and $t_{50\%}$ (time for half of Imatinib release) are listed in Table 3. The n values ranged from 0.53 to 0.70, indicating that the mechanism of release was anomalous non Fickian diffusion.
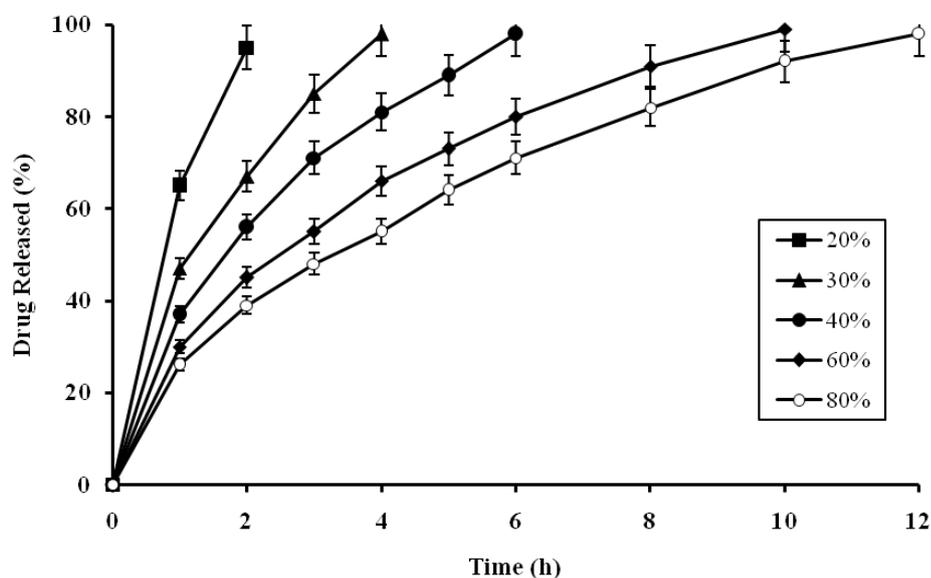
Figure 1. Comparative release profiles of Imatinib from HPMC K100LV formulations in pH 7.4 PO4 (each data point represents the average of six tablets from three batches with SD).
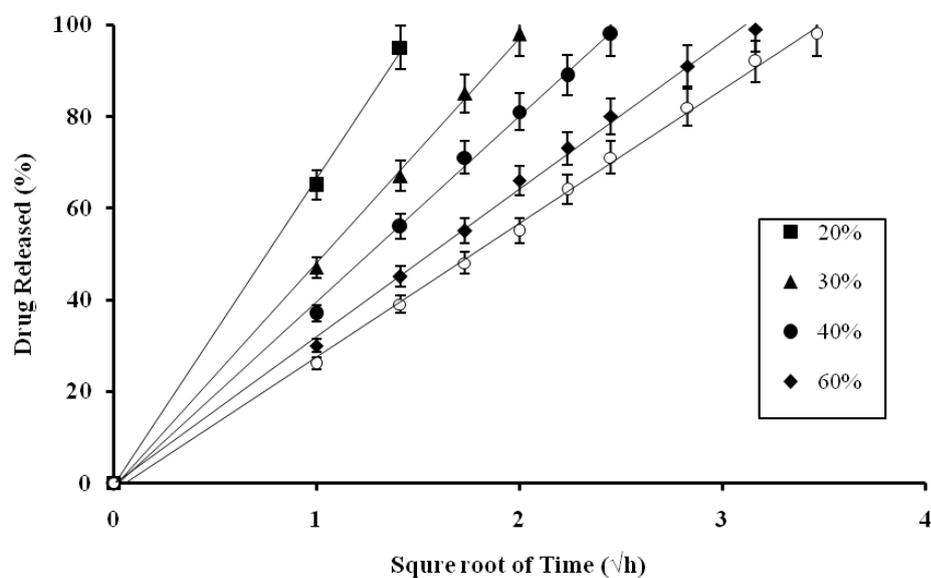
Figure 2. Plot of percent of Imatinib released from HPMC K100LV matrix as a function of square root of time according to Higuchi's release model.

Table 3. Release Kinetics Parameters and MDT Values for Imatinib CR Formulations.

Formulations	Model Parameter (Peppas)			Physical Properties	
	Diffusional exponent (n)	Release rate constant	$t_{50\%}$	Correlation coefficient	MDT (h)
H2	0.63	0.423	1.25	0.992	2.23
H3	0.60	0.388	1.45	0.993	2.45
H4	0.58	0.334	1.78	0.979	3.78
H5	0.62	0.285	1.65	0.988	4.24
H8	0.54	0.366	2.23	0.962	3.22

Table 3 Continued.

H9	0.65	0.277	2.44	0.992	4.12
H10	0.55	0.377	3.11	0.995	3.85
H12	0.55	0.299	2.29	0.988	2.69
H13	0.57	0.276	1.23	0.979	3.99
H14	0.60	0.358	3.45	0.955	4.18
H15	0.62	0.340	2.21	0.998	4.21
H17	0.53	0.287	1.98	0.999	2.75
H18	0.61	0.256	2.73	0.988	3.89
H19	0.55	0.288	2.11	0.945	4.29
H20	0.62	0.290	2.84	0.982	3.95

Effect of HPMC polymer viscosity

The effect of polymer viscosity, at 40% polymer ratio, is depicted in Figure 3. 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 hour, 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 and considerable difference in the release profiles of K4M, K15M, and K100M formulations. The release profiles were also analyzed for the similarity factor 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 considerable 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.
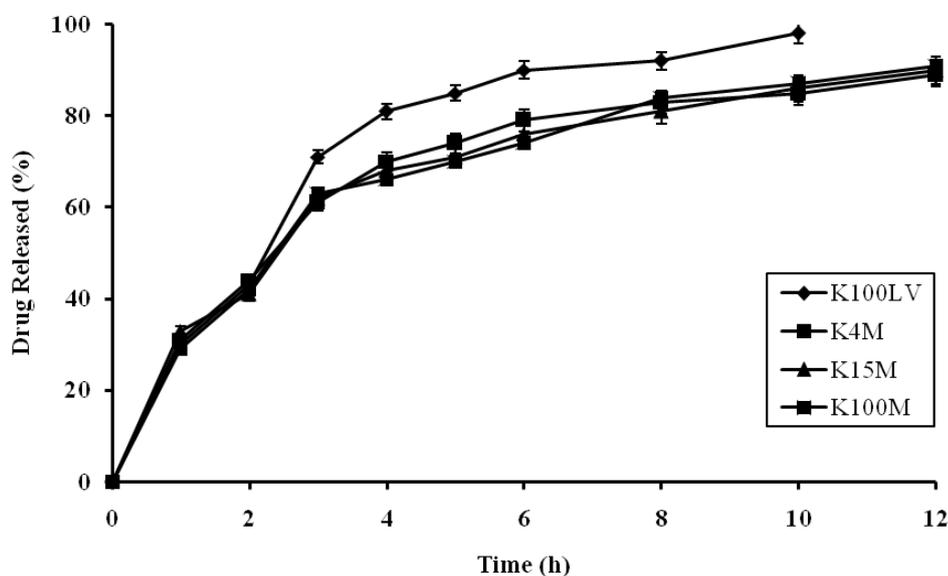
Figure 3. Effect of HPMC viscosity on Imatinib release profiles from 60% HPMC formulations in pH 7.4 PO4 (each data point represents the average of six tablets from three batches with SD).
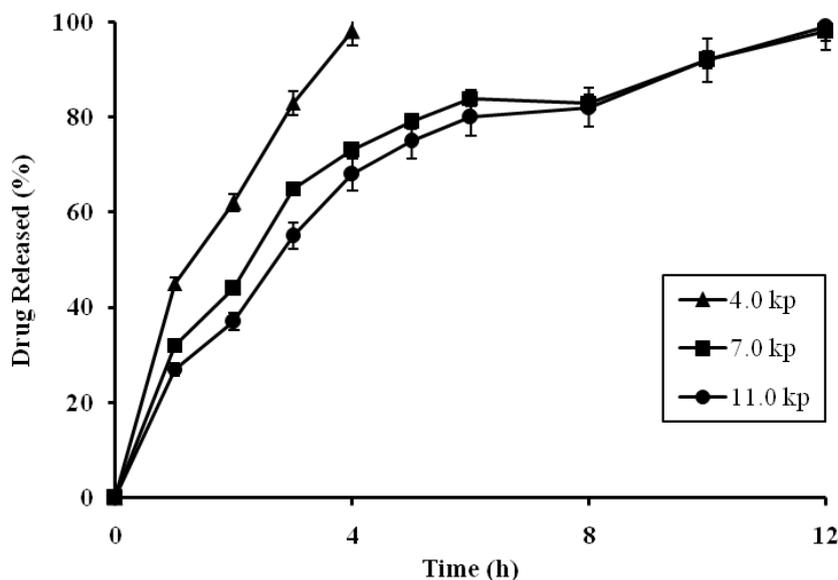
Effect of compression force

It can be observed on Figure 4 for HPMC K100LV 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 with of 4.0, 7.0, and 11.0 kp compression hardness.

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.
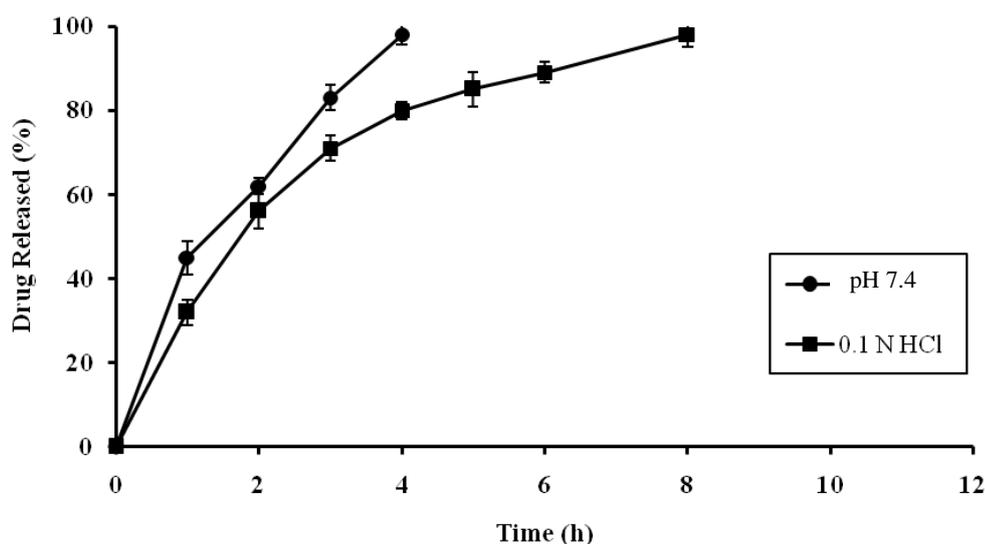

Figure 4: Effect of compression force on release profiles of Imatinib from HPMC K100LV (60%) formulations in pH 7.4 PO4 (each data point represents the average of six tablets from three batches with SD).

Effect of change in the release media

It can be seen from Figure 5 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, Fcrit=7.7, and Fcal=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).

Figure 5. Effect of release media on release profiles of Imatinib from HPMC K100LV (40%) formulations (each data point represents the average of six tablets from three batches with SD).

Batch reproducibility

The tablets showed little deviation from standard values for the drug content, weight variation, hardness, and friability from all different batches prepared separately and that show there were excellent batch-to-batch reproducibility and absence of significant batch-to-batch variations.

No considerable difference was observed in the release profiles between different batches, as indicated by the lower standard deviation values of the cumulative release data at different time points obtained from the replicate 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 Imatinib.

Stability test

The Imatinib 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 nearly linear (with "r" value more than 0.971 in all cases). The K_{deg} for Imatinib in various formulations ranged from 5.05×10^{-3}/month to 6.64×10^{-3}/month at $25 \pm 2°C$, 6.43×10^{-3}/month to 8.31×10^{-3}/month at $30 \pm 2°C$ and 8.70×10^{-3}/month to 12.11×10^{-3}/month at $40 \pm 2°C$. In all polymer formulations, the degradation rate constant increased with increase in the polymer proportion. The $t_{90\%}$ values for Imatinib in various formulations ranged from 15.86 to 20.88 months at $25 \pm 2°C$, from 12.68 to 16.38 months at $30 \pm 2°C$, and from 8.70 to 12.11 months at $40 \pm 2°C$. Imatinib was found to be more stable at $25 \pm 2°C$ and less stable at $40 \pm 2°C$ in all formulations. Also, it was observed that Imatinib was fairly 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 $40 \pm 2°C$ compared to $30 \pm 2°C$ in all the cases studied.

Discussions

As shown in In Vitro release study the reason for the decrease in the release with enhance in the polymer proportion may be explained that the increase in the polymer ratio resulted in the increased viscosity of the tablet matrix layer gel as well as the development of a gel layer with a longer diffusion path. This event resulted in the decreased effective diffusion of the drug and so a decrease in the drug release rate. The reason for initial higher release and reduce in the rate of Imatinib with time can be due to that, at early times, drug near to the matrix surface may be released before the contiguous polymer reached the polymer disentanglement concentration (mean the concentration of the polymer in a hydrated state at which there are no

polymer to 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 seems that to get the best results, the controlled release formulations in the case of Imatinib should contain about 30% Imatinib and 70% matrix component. The free Imatinib was mentioned probably to achieve initial amount of release required to elicit necessary therapeutic concentration, and the remaining part (matrix component) was suggested as a controlled release part to compensate for the decreased level of Imatinib during dose intervals. Thus, 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.

Although the extension of release was significantly different among the formulations with different polymer ratios, the $t_{50\%}$ and K 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,[22] 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) 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. Thus, the burst release of Imatinib from HPMC formulations might have resulted in the higher K values and lower $t_{50\%}$ values from HPMC matrix tablets.[23-24]

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 (4000 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 concentration, a polymer of higher viscosity induces better chain entanglement than a low viscosity polymer. Therefore, it is not easily possible for longer chains to dissolve because of the high force required for pulling them off. Thus, higher viscosity polymers bring the formation of a thicker layer gel after hydration. As discussed, the effect of polymer viscosity was mostly due to the differences in the molecular weights. The molecular weights of HPMC K100LV, K4M, K15M, and K100M were reported to be 25, 95, 120, and 250 kDa, respectively.[25] There is a relationship between the

polymer molecular weight and polymer disentanglement concentration ($C_{p,dis}$):[26]

$$C_{p,dis} = \frac{27000}{MW} \qquad \text{Eq.(2)}$$

According to the equation, the $C_{p,dis}$ decreases with growing MW and get a plateau at higher MW. It was, however, reported that the change in the polymer disentanglement concentration between K100LV and other viscosity grades was considerable leading to a higher release rates for the K100LV matrices. But the change in the $C_{p,dis}$ between K4M, K15M, and K100M was little that the matrix swelling and drug release profiles for these three HPMC formulations were indistinguishable. Almost certainly, the diffusion coefficient of Imatinib might have been least affected once the viscosity increased beyond 4000 cPs, and thus, the release rates remained almost same. Other studies 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.[27-28]

In the case of 60% HPMC K100M formulations (H19) also, 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 force and more porosity which permit 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 nonsignificant influence of initial tablet matrix porosity on the initial release of soluble drug 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.

The 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 Imatinib 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 Imatinib 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.[29-30] 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.

It was shown that the humidity was one of the most important parameters that affected the stability of Imatinib formulations. The increased K_{deg} values found at higher humidity condition bring the fact that use of IPA granulation (avoidance of aqueous granulation) in the manufacturing of Imatinib matrix tablets was significantly beneficial in obtaining the steady CR matrix tablets of Imatinib. The in-vitro release profiles were studied as per the condition enlisted in earlier 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 1). The theoretical and calculated values of F (F_{crit} and F_{cal}) indicated that the Imatinib 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 investigation confirmed that the hydrophilic polymer could be applied as a suitable matrix to design controlled release tablet formulations of Imatinib with expected properties and release characteristics. The process of tablet manufacturing was quite uncomplicated and may be implemented in on a commercial industry scale in conventional tablet manufacturing units. In this investigation, a series of controlled release tablet formulations of Imatinib were developed with different release profiles so that the formulations could be assessed more rapidly than the in-vivo bioavailability studies. From the in-vitro studies, the formulations were found to be promising and should further be considered for bioavailability studies in human volunteers to assess in-vivo characteristics.

Acknowledgments

Conflict of Interest
The authors report no conflicts of interest.

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