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Bio-fluid uptake and release of Indomethacin of direct-compressed HPMC tablets

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ABSTRACT

Tablets of three different grades of hydroxypropyl methyl cellulose (HPMC), having different viscosity, were prepared using the direct-compression technique with no additive or binder. The fluid uptake behavior of these HPMC tablets was studied in three types of bio-media – water, simulated gastric fluid (SGF), and simulated intestinal fluid (SIF). The amount of fluid uptake by the tablets followed a power law relationship with time for all three media. Variants such as pH value, type of salts and salt concentration in the media were found to have little influence on the swelling process for the tablet. On the contrary, viscosity and molecular weight of HPMC were the controlling parameters for the swelling process. Subsequently, Indomethacin was added in certain percentage to the tablets as a model drug. It was to examine and elucidate drug releasing properties of the HPMC tablets. The possible mechanisms involved in the process of drug dispersion are proposed and discussed.

1. Introduction

Among various dosage forms in medicine, tablets still account for 80% of the drug delivery systems administered to human due to ease of manufacture, convenience of dosing and stability compared with liquid and semi-solid dosage patterns (Jivarij, Martini, & Thomson, 2000). For the dosage of an active ingredient under 30%, the direct compression to form tablets is used widely in pharmaceutical industry for ease of fabrication and robustness to handling environment (Armstrong, 1997).

Cellulose and its derivates in the form of agglomerated porous particles are regarded as the most useful filler for direct-compression tablets (Shangraw & Demarest, 1993). They are physically stable under normal conditions. They are chemically inert to the active ingredients, compatible with packing components and easily available (Armstrong, 1986). In order to enhance water solubility and affinity of cellulose, methyl and hydroxypropyl groups are introduced to glucose units of cellulose leading to derivatives such as HPMC. By disrupting interactions within the network of hydrogen bonds, these groups grant HPMC the various properties depending upon the different substitution ratios (Li, 2002). Due to its high swellability and thermal gelation properties, until now HPMC has been the most important carrier material for the drug release systems (Colombo, 1993; Pham & Lee, 1994). HPMC is also widely studied for relaxation and rearrangement of the polymer chains under certain conditions that lead to swelling and gelation.

Various parameters influence the drug releasing profile of HPMC tablets. Porosity of the formed tablets, different particle size and distribution of HPMC powder and physicochemical properties of various grades of HPMC are some of the critical factors that influence behavior of a drug-loaded HPMC tablet in body fluids (Lim & Lin, 1996; Lim & Lin, 1998; Nahano et al., 1983; Varma, Kaushal, Grag, & Grag, 2004). Many studies have been focused on swelling process for cellulose-based materials in various media. Water was the most common medium for in-vitro release profile study. Some artificial bio-fluids like SGF and SIF were chosen to simulate the human body environment for studying the swelling and gelation processes (Liu, Joshi, Lam, & Tam, 2008). Some focused on kinetics of the swelling process and drug release profile. Kinetic studies often described the cumulative drug releasing profile as a power function of time (Ford, Rubinstein, McCcaul, Hogan, & Edgar, 1987; Korsmeyer, Gurny, Doelker, Buri, & Peppas, 1983). The power law model, however, is too simple to express the detailed drug release profile of HPMC (Siepmann, Podual, Sriwongjanya, Peppas, & Bodmeier, 1999). With further developments, more detailed models were proposed with consideration for diffusion of water and drug, and the moving boundary and swelling of HPMC system (Siepmann, Kranz, Bodmeier, & Peppas, 1999a; Siepmann, Kranz, Bodmeier, & Peppas, 1999b; Siepmann & Peppas, 2000). However, there is no comprehensive study on the bio-fluid uptake and disintegration of HMPC tablets with time in those fluid media. It is important to study the behavior of HPMC tablets in water as well as in simulated bio-media to find out the key factors and mechanisms that drive and control the tablet swelling as well as the drug release processes.

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In this study, tablets of three grades of HPMC with different properties were fabricated using the direct-compression technique. The swelling behavior was monitored in water, SGF and SIF without and with an active drug ingredient. Indomethacin was adopted as the active drug for studying the release properties of the three grades of HPMC tablets. The role played by salts present in the media and the properties of HPMC matrix in these processes was assessed. The possible mechanisms behind the observed behavior were proposed and discussed.

2. Materials and methods

2.1. Materials

Three different grades of HMPC powders were procured from Sigma–Aldrich. The 2 wt% aqueous solution of these powders have 6, 40–60, 4000 mPa.s viscosity, respectively, at 20 °C and referred in these studies as HPMC-A, -B, and -C, respectively. Salts such as sodium chloride, sodium hydroxide, monobasic potassium phosphate required for preparing the buffer solutions and hydrochloric acid (37%) were purchased from Fluka. Deionized water was produced using Milli-Q system. Indomethacin was the product of Aldrich.

2.2. Preparation of tablets

To begin with, HPMC-A, -B, and -C in their powder form were dehydrated in vacuum at 60 °C for 24 h. The tablets were prepared using the direct-compression method without any extra additives or binders. The forming condition was set to 1-min compression under 400 kg/cm^2 pressure at room temperature using Carver Laboratory Press (2158 series, USA). The average weight of the formed tablets was 1.3 g. The tablets were of cylindrical shape with their average diameter measuring 18 mm, and height measuring 5–8 mm. The tablets were stored all the time in a dry box before use.

2.3. T_g measurement

Upon taking 10 mg of pre-dried HPMC powders A, B, C each time and sealing the sample in the standard aluminum sample pan, T_g of the three samples was measured using the TA modulated DSC 2920 in the range 20–220 °C with the ramp rate of 10 °C/min under N_2 environment maintained at flow rate of 50 ml/min.

2.4. Preparation of simulated gastric and intestinal fluids

SGF without pepsin and SIF without pancreatin were prepared using the procedure from pages 1788–1789 of US pharmacopoeia (*XXII* edition), which is briefly given below.

For SGF, dissolved 2.0 g sodium chloride in 7.0 ml of hydrochloride acid and added sufficient deionized water to make it 1000 ml. The final pH of the solution was 1.2. In order to prepare SIF, dissolved 6.8 g monobasic potassium phosphate in 250 ml of deionized water, then added 190 ml of 0.2 mol/l sodium hydroxide with 400 ml water. Finally the resulting solution was adjusted with 0.2 mol/l sodium hydroxide solution to the pH of 7.5 ± 0.1 and diluted to 1000 ml.

2.5. Fluid uptake and swelling measurements in various media

Three full-sized tablets of each of HMPC- A, -B and -C were weighed accurately before placing them individually in a porous paper bag. The bag was used to facilitate handling of the tablets as and when required and simultaneously ensure that the solvent could diffuse without any obstruction during the swelling process. A 50 ml of deionized water, SGF, and SIF were loaded in separate plastic tubes with a properly marked scale line. One set of media was used to soak one grade of HPMC tablets. Three rounds of experiments were carried out for each of HPMC-A, -B and -C tablets. All solutions were maintained at body temperature of 37 °C. In order to assess the water uptake at various time intervals, the swollen tablets were taken out quickly, had their surfaces wiped using a tissue paper and weighed immediately. The swelling ratios were calculated using Eq. (1) as below:

$$\alpha = \frac{W_t - W_{t0}}{W_{t0}} \times 100\% \quad (1)$$

where α represents the swelling ratio, W_t and W_{t0} represent weights of the tablet at a certain time and its the original dry weight. The values of α were averaged over three weight readings for each tablet for minimizing measurement errors.

2.6. Drug release profile of Indomethacin-loaded tablets

Indomethacin in a powder form was mixed with each of the three types of pre-dried HPMC powders in 1:20 proportion, respectively. Each mixture was then compressed under 400 kg/cm^2 pressure for 1 min at room temperature in tablet maker.

The ready tablets were soaked in a 50 ml SIF solution maintained at 37 °C adopting the same procedure as described in Section 2.5. Starting from the first half an hour until the 60th hour, a 0.25 ml of drug-mixed solution was taken out every 30 min and diluted to 3 ml aqueous for UV measurements. The UV measurements were carried out using HP UV–vis spectrometer (2820) at 265 nm wavelength to determine the concentration of Indomethacin in the fluid media derived from the immersed tablets.

A series of aqueous solution samples with different concentration of Indomethacin were prepared separately and tested for UV absorption at 265 nm wavelength, and the relationship between the UV readings versus the drug concentration was gotten as a standard curve.

By comparing the results of UV tests on the collected samples with the standard curve, the release profiles for Indomethacin-loaded HPMC tablets were obtained.

3. Results and discussion

3.1. Swelling behavior of HPMC tablets

HPMC is a derivative of cellulose obtained by adding hydroxypropyl and methyl groups to substitute primary and secondary hydroxyl groups. Its typical structure is shown in Fig. 1, where R represents either methyl or hydroxypropyl group. The count for R varies with the grade of HPMC. Properties of HPMC are controlled by the ratio and distribution of the methyl and hydroxypropyl substitution. Thus, three factors, namely, methyl content, hydroxypro-

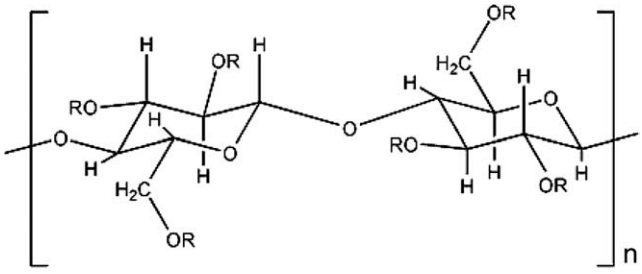

Fig. 1. Chemical structure of HPMC (R represents either methyl [CH_3] or hydroxypropyl [$CH_2CH(CH_3)OH$] group).

pyl content, and molecular weight control the final properties and behavior of HPMC (Siepmann & Peppas, 2001).

As summarized in Table 1, the three grades of HPMC namely, HPMC-A, -B and -C have different viscosity, different ratio of methyl/hydroxypropyl groups substitution and different molecular weight. Although average molecular weight determines viscosity in an aqueous media, the physicochemical structures and distribution of substitution groups have a great influence on the final properties of HPMC. Comparing the parameters for HPMC-A and HPMC-C, it can be seen that both HPMC have similar substitution ratio of methyl and hydroxypropyl groups. Viscosity of C is 667 times higher than that of A whereas the molecular weight of C is 8.6 times higher than that of A. This confirms that the molecular weight of HPMC play a dominant role in changing the viscosity when the polymers have similar chemical structures. When parameters for A and B, which have different percentage of methyl substitution, are compared, viscosity of B is found to be 7–10 times higher than that of A. The methyl substitution ratio for B is approximately half that of A, while the average molecular weight of B is slightly over two times of A.

Thus, variations in methyl substitution and molecular weight lead to different viscosity. The possible explanation is that viscosity of HPMC is influenced by the hydrophobic interactions introduced by methyl groups onto HPMC backbone in different ratios. It seems that hydrophobic associations caused by the methyl groups' substitution enhance viscosity of HMPC with the increasing molecular weight.

Due to methyl (hydrophobic) and hydroxypropyl (hydrophilic to some extent) substitution, the network of hydrogen bonding (H-bond) in cellulose is disrupted. The hydrophobic interactions between methyl groups and water can lead to self-aggregation of HPMC chains. The aggregation is accelerated with aid of interactions with water (H-bonding) at elevated temperature or in a highly plasticized state, which leads to gelation of HPMC in most cases. It was mentioned in the previous studies that the methyl modified cellulose chain can be aggregated in to a network under the driving force from hydrophobic methyl groups associations and inter-chain clusters thereof (Joshi & Lam, 2006; Joshi, Su, Liang, & Lam, 2008; Kobayashi, Huang, & Lodge, 1999). When hydroxypropyl groups are introduced into cellulose systems, HPMC shows more affinity to water molecules, and lead to higher water solubility of the polymer. Opposing effects of the hydrophobic methyl groups and hydrophilic hydroxypropyl groups grant HPMC the swellability in the aqueous media. By adjusting the hydrophobic –hydrophilic balance with the suitable ratio of hydroxypropyl and methyl groups, the swellability of HPMC in the aqueous media can be modulated.

In Table 1, it is seen that T_g of the three grades of HPMC are between 160 and 190 °C. These results indicate that the polymer chains are almost immobile at 37 °C, the temperature used in the current experimental studies. Therefore it is impossible to have the formation of systematic aggregation taking place spontaneously except the inherent presence of H-bond network.

When HPMC tablets are soaked in aqueous media, a large amount of water is absorbed into the porous polymeric matrix. The absorbed water acts as a plasticizing reagent and reduces the H-bond inter-/intra-chains interactions. As an effect, T_g of HPMC is reduced drastically. This results in reducing energy barriers that restrict the mobility of the functional groups, side chains and polymer main chains. This allows the polymer chains to change the conformation with greater freedom.

As depicted in Fig. 2, water, SGF, and SIF have been chosen as media to study the fluid uptake behavior of the different grades of HPMC tablets. In all three media, HPMC-A tablet could absorb the fluid equal to its original weight. Finally the tablet disintegrated into various portions after 9 h. HPMC-B absorbed a significant amount of water that weighed 3–4 times the weight of the tablet. These tablets kept their shape for 15 h before disintegration. Tablets made of HPMC-C could remain integrated even up to 45 h after absorbing the fluid 6–7 times of their original weight.

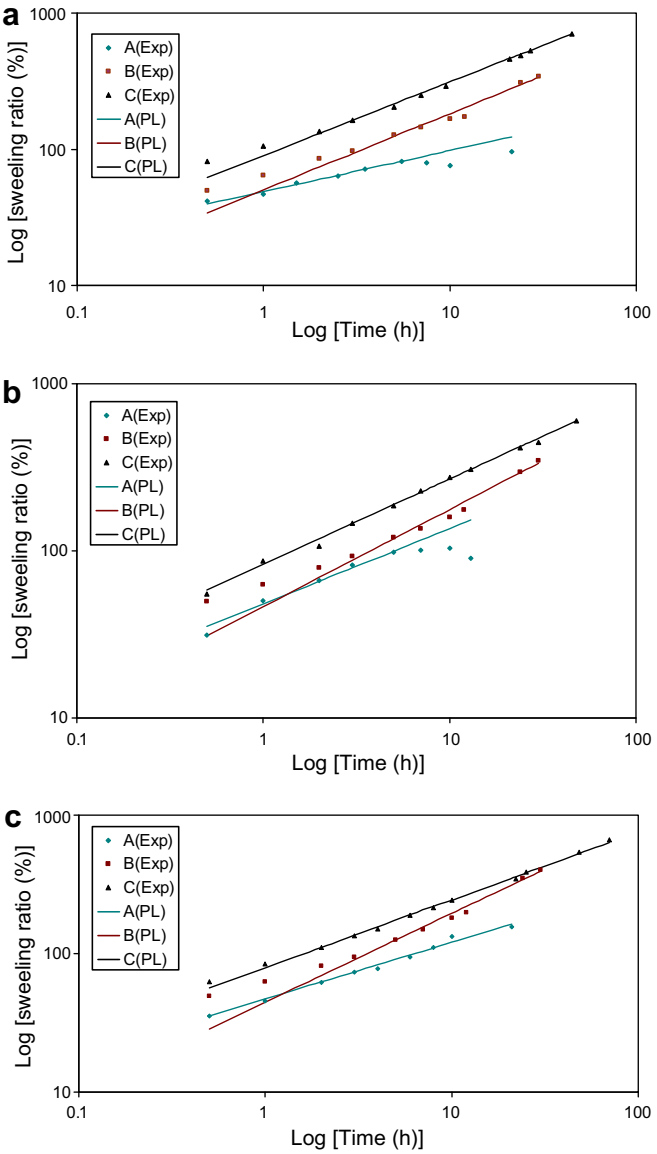

Fig. 2. Experimental data (Exp) and power law profiles (PL) of fluid uptake and swelling ratio for HPMC tablets in (a) water; (b) SGF; (c) SIF at 37 °C.

Table 1
Specific parameters for different grades of HPMC

HPMC	Viscosity (2 wt%)	Methyl content	Hydroxypropyl content	Molecular weight (M_n)	Glass transition T_g (°C)
A	6 cps	60–67%	7–10%	10,000	176
B	40–60 cps	28–30%	7–12%	22,000	188
C	4000 cps	60–67%	7–12%	86,000	163

3.2. Swelling behavior of HPMC tablets: power law simulation

It is known that the swelling process is governed by a power law (Peppas, 1985) as shown in Eq. (2):

$$S_r = a * t^b \quad (2)$$

where S_r represents the swelling ratio, t means the soaking time and, a and b are the process related constant parameters. Eq. (2) may be expressed as a linear curve by $\mathrm{Log}(S_r) = \mathrm{Log}(a) + b * \mathrm{Log}(t)$.

The experimental data is represented using Eq. (2) by obtaining necessary parameters for the best-fit curves. The obtained parameters are listed in Table 2 and the experimental data along with the best-fit lines on log–log scale are shown in Fig. 2. HPMC-A, -B and -C show similar trends irrespective of the type of media they are soaked in. The swelling patterns in the three media also show a similar trend with similar swelling rate and the final swelling ratio. These results testify that the variants like pH and ionic strength of media have little effect on the swelling behavior in the adopted time scale (Fukui, Uemura, & Kobayashi, 2000). The difference in the parameters signals to the fact that water uptake and swelling processes are primarily controlled by the nature of the polymer.

3.3. Swelling behavior of HPMC tablets: mechanism

Many factors including particle size and distribution of powder, porosity of the formed tablets, interaction between polymer and solvent, influence the rate at which the fluid media is absorbed into HPMC tablets. However, the determining factors should be the physicochemical properties of HPMC especially when a large amount fluid media is absorbed in the swollen state. Hydrophobic interactions between methyl groups and water are the main drivers for the spontaneous swelling process. The self-aggregation behavior of different grades of HPMC is linked to their different chain structures. The ordered network formed is determined by the density of methyl groups in the polymer-fluid system at the swollen state. The possible mechanism involved in the fluid uptake and swelling processes is shown in Fig. 3.

HPMC-A has the lowest average molecular weight and relatively higher methyl substitution ratio in all three grades of HPMC. Therefore the physical cross-linking sites formed by the clustering of methyl groups in the swollen state are limited, and the formed network is composed of multiple shorter polymer chains in the medium aggregation scale. The density of physical cross-linking sites is limited by the shorter length of the polymer chains and the fewer total number of methyl groups. Thus, it is believed that the cells in the gelation network are of a small size. HPMC-B has the lowest substitution ratio of methyl groups, but in a higher molecular weight range (longer polymer chains). The formed network for this type of HPMC is seemed to compose of longer polymer chains with fewer cross-linking sites, resulting in a loosely formed network. HPMC-C has the longest polymer chains, and the highest ratio of methyl group substitution. This induces the formed network with the highest density of physical cross-linking sites.

Table 2
Parameters for power law simulation of swelling processes for HPMC

Equation	Media	Parameters					
		HPMC-A		HPMC-B		HPMC-C	
		a	*b*	*a*	*b*	*a*	*b*
$S_r = a * T^b$	Water	49.04	0.30	50.21	0.56	89.75	0.54
	SGF	48.19	0.45	46.46	0.58	83.31	0.51
	SIF	46.96	0.41	44.72	0.64	79.15	0.49

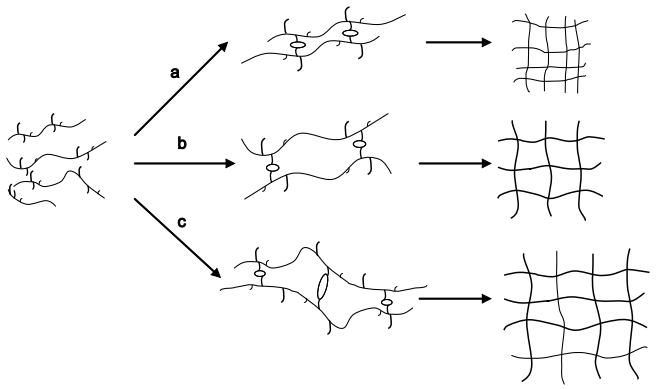

Fig. 3. Aggregation patterns for various grades of HPMC having different substitution ratio and molecular weight as (a) network of HPMC-A with small cells; (b) network of HPMC-B with larger cells at lower cross-linking density; (c) network of HPMC-C with large cells at the highest cross-linking density.

Size of the formed network cells and density of the physical cross-linking sites determine the strength of the gel layers and also control the disintegration behavior of the direct-compressed tablets with time in the fluid media. Obviously, HPMC-A had the weakest network that disintegrated much earlier than HPMC-B. HPMC-C exhibited the strongest network and stable shape even after absorbing considerable amount of the fluid media.

3.4. Release profile for Indomethacin-loaded HPMC tablets

From the release profile in SIF shown in Fig. 4, it can be seen that the accumulated amount of Indomethacin in the media increased fast at the initial stages (within the first 10 h) for all the three grades of HPMC tablets. The drug release rate became approximately constant after 30 h for the tablets made of HPMC-B and HPMC-C, and the same trend was maintained for the remaining time scale. Due to direct-compression technique used for forming the tablets, any variations in the release patterns for the three grades of the HPMC tablets are believed to be linked directly to the changes in the fluid uptake and the swelling process. It may be observed that in Fig. 4, the sequence of drug release rate follows the order as for HPMC-A > HPMC-B > HPMC-C, which is the reverse of the trend for the swelling and disintegration of HPMC tablets in SIF discussed in the earlier sections.

It is known that the gel barrier is the determining factor of translocation of drug transportation from HPMC matrix (Colombo, Bettini, & Peppas, 1999). The faster the formation of gelation barrier, the thicker is the gel layer, leading to the slower drug release in the early stages. In the latter stage, the thickness of the gel layer and the integration of the HPMC network in the swollen tablets are

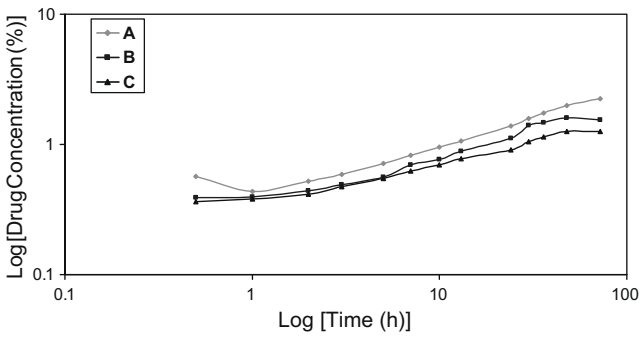

Fig. 4. Indomethacin release profiles of HMPC tablets in SIF at 37 °C.

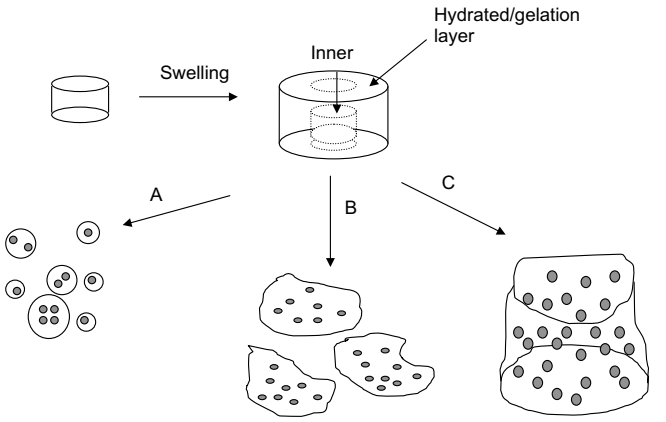

Fig. 5. Water uptake process and subsequent disintegration of tablets in the drug release process (A stands for 6 mPa.s HPMC; B for 40–60 mPa.s HPMC and C for 4000 mPa.s HPMC).

the key factors in determining the drug release profile in the related time scale.

3.5. Mechanism involved in the drug release profile

Based on the drug release profile, a detail description of the possible mechanism of the process can be depicted as shown in Fig. 5. In the early stage, the drug-loaded tablets absorb a large amount of fluid media into the porous matrix. This causes the outer layer to hydrate and convert the part into gel with the assistance of water molecules as plasticizing agents. As time progresses, the outermost layer dissolves either partially or fully into the media allowing more water molecules to diffuse into the inner core region, which is intact so far, by forming a new gel front. The drug that remains trapped within the disintegrated part is released faster than that from those separated portions of the HPMC gel. The thickness of the gelation layer is rather thin at the early swelling stage, which is also the reason for the faster drug release.

As more and more aqueous media is absorbed into the tablets, the gelation layer gets thicker and thicker until it reaches the fully swollen stage, which is the fully saturated and expanded state of the gel. With more water coming in, the fully swollen tablets show different routes in the later stage of drug releasing process. In the case of HPMC-A, the tablets disintegrate into various microgel particles containing drug in small amount at a rather early stage (10 h or so). Due to the smaller size of the microgel particles floating in the media in large numbers, the loaded drug is able to easily pass through the thin gel layer and dissolve into the media around. This has resulted into the fastest release rate among the three grades of HPMC. As far as HPMC-B is concerned, after achieving the fully swollen state, the tablets disintegrate into much larger pieces compared to HPMC-A. The much thicker gel layer and smaller specific surface area, led to a slower drug release rate after 25 h. During the whole time scale, HPMC-C tablets kept its content integrated; the tablets became fully gelated with a small residual core. The thickest gel barrier hindered the diffusion of the drug trapped within the matrix into the media freely, resulting in the slowest drug release rate.

4. Conclusion

The swelling behavior of tablets of all three grades of HPMC in water, SGF, and SIF showed similar trends. It was observed that the percentage substitution of methyl side groups and molecular weight of the polymer determine and control the various patterns of the fluid uptake and the swelling process for the tablets. The drug release profiles for the Indomethacin-loaded tablets showed a reverse trend as compared to the fluid uptake process. However, similar to the fluid uptake process, drug release was also controlled by the size and density of the gel network.

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