The effect of hydrophilic and hydrophobic polymers on release profiles of diclofenac sodium from matrix tablets

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ABSTRACT

Objective: The current study aimed to develop a matrix type sustained release Diclofenac tablet, using hydrophilic hydroxypropyl methylcellulose (HPMC) and hydrophobic polymer cetyl alcohol (CA).

Materials and Methods: Two different polymers, that is, Methocel K15MCR® and CA were used in various proportions as release controlling factor. Matrix tablets were prepared by wet granulation technique. The physicochemical properties of the granules and tablets were evaluated. In vitro dissolution studies of prepared matrix tablet and patent product Voltaren SR® tablet (VSR) were performed at pH 7.4 phosphate buffer at 100 rpm, and at 37 ± 0.5°C, and subjected to in vitro bioequivalence study in terms of similarity and difference factors. Stability studies were conducted for 6 months using optimized formulation for extended period of time, both at room temperature and accelerated conditions. The dissolution data were fit to Zero-order, First-order, Higuchi, and Korsmeyer-Peppas’ equations.

Results: The formulated tablets showed acceptable weight variation, hardness, drug content uniformity with sustained release matrix characteristics. Hydrophilic Methocel K15 MCR® matrices-based tablets showed zero-order and hydrophobic CA matrices-based tablets followed first-order kinetics except for formulation six (F6 showed zero-order profile). It was found that formulations containing CA showed better dissolution properties with respect to formulations containing Methocel K15 MCR® in terms of similarity and difference factor. Furthermore, the formulations F4, F5, and F6 exhibited similar drug release profile as compared with VSR tablet, which indicated that these formulations could be bioequivalent with VSR tablet in vitro. Tablets were stable both at room temperature and as well as at accelerated conditions.

Conclusion: The present study demonstrated that Diclofenac could be successfully prepared using an appropriate amount of Methocel K15 MCR® and CA in the form of matrix tablets with similar dissolution profile of patent product Voltaren SR®. The type of polymers used was found to induce a profound effect on release rate and mechanism.

INTRODUCTION

Diclofenac sodium (DS), a potent nonsteroidal antiinflammatory drug (NSAID), possesses antiinflammatory, analgesic and antipyretic effects. It is widely used in the treatment of rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.\(^1\) It is an
inhibitor of prostaglandin synthetase and effective in relief of pain and inflammation in conditions such as acute gout, surgical procedures.[3] Furthermore, DS is a cyclooxygenase COX-inhibitor whose potential for the treatment of Alzheimer’s disease has been postulated.[3] DS, a phenylacetic acid derivative, having the pKₐ value of 4.0, is practically insoluble in acidic solution but dissolves in intestinal fluid and water. Generally DS gets into blood within 30 min and reaches the maximum blood concentration (C_max) within 1.5-2.5 h following oral administration of an enteric coated tablet. However, it undergoes extensive hepatic metabolism.[4] The oral bioavailability is around 60%,[5] and this compound exhibits a terminal half-life of 1-2 h, volume of distribution 0.171/l/kg, and 99% protein binding.[6]

Sustained-release (SR) systems are the methods that can achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance. Oral SR dosage forms are commonly prepared by incorporating the drug into a hydrophilic polymeric matrix. The hydrophilic matrix consists of a mixture of one or more active ingredients with one or more gel forming agents. The mixture is usually compressed into tablets.[7] Among various types of swellable water-soluble polymers, cellulose ethers are widely used in pharmaceutical literature as matrices for drug delivery system.[7] The most commonly used cellulose ethers include the following: Hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (Na-CMC), and methylcellulose (MC). These polymers possess advantages, for example, nontoxic in nature, ease of compression, ability to accommodate a large percent of drug and negligible influence of the processing variables on drug release rates.[8,9]

Several retarding substances have been used in the controlled release formulation of DS including Eudragit® RS100,[10] ethyl cellulose,[4,11] HPC,[12] HPMC,[13] hydrogenated vegetable oil and carboxypolymethylene,[14] methacrylic acid copolymer and camauba wax,[15] ionexchange resins, cetostearyl alcohol, and cetyl alcohol (CA).[13]

However, the current study evaluates HPMC, a hydrophilic polymer, for the preparation of oral controlled release drug delivery systems. One of the most important characteristics of HPMC is the high swell ability, which has a considerable effect on the release kinetics of the incorporated drug.[16] Drug release from HPMC matrices is controlled by the rapid formation of viscous gel layer as a resultant of hydration in HPMC. Drug diffuses through this gelatinous barrier layer at the surface of the matrix. Moreover, viscosity grade of HPMC influences the resistance of such a gel layer to erosion. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, while poorly water-soluble drugs are released predominately by erosion mechanisms.[17] Thus, in vitro drug release of water-soluble drugs, such as DS, are controlled by diffusing out of the gel layer, which is produced by hydration of polymer in the presence of biological fluids. Moreover, the current study investigates the hydrophobic polymer, CA, as SR matrix former. This is due to the better matrix erosion by the CA resulting from higher water penetration in the matrix.[18]

DS is used at the daily dosage of 75-150 mg given in two to four divided administrations this drug is a suitable candidate to be formulated as SR dosage forms.[2] Moreover, it has an unpleasant taste and causes gastric irritation.[3] Due to its elimination and posology, and in order to minimize the incidence of gastric mucosal damage resulting from the administration of DS, and to provide an effective blood level for a reasonably long period, DS has been formulated as SR tablets.[19] Thus, the current study investigated the development of a matrix type sustain release diclofenac tablet, using hydrophilic HPMC and hydrophobic polymer CA. The physicochemical properties of the developed formulations such as hardness, thickness, friability, and in vitro drug release study were evaluated and compared with patented market product Voltaren SR® tablet for in vitro bioequivalence study.

MATERIALS AND METHODS

Materials

DS BP was obtained from (Abbott Logistics B.V.), HPMC-Methocel K15 MCR® and CA was obtained from Colorcon Asia Pvt. Ltd. Microcrystalline cellulose (Avicel® PH-101) (Comprecel101, Mingtai Chemical Co. Ltd., Taiwan), polyvinylpyrrolidone (Povidone® K-30) (BASF, Southeast Asia Pvt. Ltd.), colloidal silicon dioxide (Aerosil® 200) (Degussa AG, Germany), magnesium stearate (Chemical Management Co., Germany), lactose and sucrose crushed (The Lactose Co. New Zealand). All other chemicals were of analytical grade and were used without further purification.
Methods

Preparation of matrix tablets

DS tablets 100 mg were prepared by the process of wet granulation in a lab-scale wet granulator (Shakti Engineering, India). The active ingredient, release retardants polymer, diluents were mixed together, granulated, and sieved. After sieving through 30 mesh, granules were formed. The loss on drying (LOD) of the granules were maintained within 2.5-3.5%. In all cases, the amount of the active ingredient (DS) is 100 mg/tablet. Materials were blended in a laboratory blender for 10 min. Extra precaution was taken to ensure thorough mixing. The appropriate amounts of the mixture were then taken and compressed to tablets. Six different formulations were prepared of different compositions of Methocel K15 MCR® (24%, 20%, and 16%) and CA (13.8%, 17.25%, and 20.70%) to evaluate the drug release according to polymer type and the different compositions of polymers. The formulation perspective parameters are illustrated in Table 1a and b.

Determination of granules properties

Angle of repose (θ)

Angle of repose of the granules was determined by the funnel method. The diameter and height of the powder cone were measured and θ was calculated using the following equation:

\[
\tan \theta = \frac{h}{r}
\]

Where, \( h \) and \( r \) are the height and radius of the powder cone, respectively.

Density

Bulk density and tapped density determination:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. LBD and TBD were calculated using the equations:

- Bulk density = Weight of powder/Bulk volume
- LBD = Weight of the powder/Volume of the packing
- TBD = Weight of the powder/Tapped volume.

Carr’s index

The compressibility index of the granules was determined by Carr’s index using the equation:

\[
\text{Carr’s index} = \left( \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \right) \times 100
\]

Total Porosity was determined by measuring the volume occupied by a selected weight of powder \( V_{\text{bulk}} \) and the true volume of the granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, \( V \)):

\[
\% \text{ Porosity} = \frac{V_{\text{bulk}} - V}{V_{\text{bulk}}} \times 100.
\]

Determination of tablet parameters

Hardness and thickness

Ten matrix tablets were sampled and individually subjected to test for hardness using the hardness tester (Erweka, Germany). The mean and standard deviation of the tablet hardness were calculated and the value of the hardness was expressed in kilopascal (Kp). The thickness of the matrix tablets was determined using a vernier caliper (E-Base Measuring Tools Co., Taiwan). The results were expressed as mean values of ten determinations.

Friability

Ten tablets from each formulation were weighed, and taken into the rotating disk of a Friability Tester (Pharma test, Germany). It was allowed to rotate at 25 rpm for 4 min. At the end of the rotation, tablets were collected, dedusted, and reweighed. The friability was calculated as the percent of weight loss.

Drug content assay

Ten tablets of each formulation were taken, weighed, and then placed in a mortar and pestle and powdered. Equivalent amount of 100 mg of DS powder was dissolved in 80 ml of methanol (50%) and shaken for 30 min, added sufficient mobile phase to produce 100 ml. After proper mixing, an aliquot of the solution was centrifuged and filtered through 0.45 mm syringe
filter, 5 ml of the filtrate was diluted in 100 ml volumetric flask and volume adjusted with mobile phase.

Study of release kinetics
To understand the mechanism of drug release from these formulations, the data were fitted to zero-order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs. time), Higuchi’s (cumulative percentage of drug released vs. time), and the Korsmeyer’s (log cumulative percentage of drug released vs. log time) equations. [20]

Zero-order kinetics
\[ Q = K_0 t \]
Where \( Q \) is the fraction dissolved at time \( t \) and \( K_0 \) is the apparent dissolution rate constant or zero-order rate constant.

First-order kinetics
\[ \log Q_t = \log Q_0 - K_t t / 2.303 \]
Where \( Q_t \) is the amount released at time \( t \), \( Q_0 \) is the initial amount of drug in solution and \( K_t \) is the first-order rate constant.

Higuchi’s equation
\[ \frac{dM}{dh} = C_0 dh - C_s / 2 \]
Where, \( dM \), change in the amount of drug release per unit area \( dh \), change in the thickness of the zone of matrix that been depleted of the drug \( C_0 \), total amount of drug in a unit volume of the matrix \( C_s \), Sustained concentration of the drug within the matrix. [21]

Korsmeyer’s equation
\[ \frac{Q}{Q_\infty} = K t^n \]
Where, \( Q \) is the amount of drug released at time \( t \), \( Q_\infty \) is the amount of drug released after infinite time (total drug in a dosage form), \( K \) is the kinetic constant, and \( n \) is the diffusional exponent indicating the type of drug release mechanism. An \( n \) value of 0.5 is consistent with diffusion-controlled release, whereas if \( n \) approaches to 1.0, release mechanism can be zero-order. If \( 0.5 < n < 1 \) non-Fickian transport could be obtained. [22]

In vitro drug release studies
Dissolution studies were carried out in USP Dissolution apparatus (Apparatus 2). A total of 900 ml of phosphate buffer (pH 7.4) was used as the dissolution medium with the rotation speed of the paddle at 100 rpm. The temperature of the medium was maintained at 37 ± 0.5°C. A total of 5 ml of the sample was taken at the interval of 2, 4, 6, and 8 h with the continuous replacement of the fresh medium. The content in the samples were determined using UV-VIS spectrophotometer at the wavelength of 274 nm. All these experiment were performed taking six tablets (n = 6) for each formulation.

In vitro Bioequivalence studies
In vitro release profile of the reference DS SR tablets (Voltaren SR® [VSR], Novartis) were performed under similar conditions as described earlier. The difference and similarity factors between the formulations were determined using the data obtained from the drug release studies. The data were analyzed by the following equations: [23]

\[ f_1 = \frac{\sum [R_t - T_t]}{\sum R_t} \times 100 \]

\( R_t \) and \( T_t \) = dissolution of reference and test products at time \( t \), respectively.

\( f_1 \) = difference factor.

For similarity factor (\( f_2 \)):
\[ f_2 = 50 \log[1 + 1 / n \sum W_i (R_t - T_t)^2]^{0.5} \times 100 \]

If \( f_1 \) is less than 15 and \( f_2 \) is greater than 50 it is considered that two products share similar drug release behaviors.

Stability studies
The stability studies were carried out at 30 ± 2°C and 65 ± 5% RH for long-term condition and 40 ± 2°C and 75 ± 5% RH for accelerated condition in Alu–PVC blister pack according to ICH guide line using the stability chamber (Hanbaek ST Co., Korea). The samples were tested initially and the stability test has been completed up to 6 months at accelerated condition.

Statistical analysis
The statistical significance of the difference in the parameters was determined using the analysis of variance (ANOVA). A \( P \) value < 0.05 was deemed to be statistically significant using a Student t-test between the two means for the unpaired data. All data are expressed as mean ± SD.

RESULTS AND DISCUSSION
Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs.
contained in a heterogeneous formulation\textsuperscript{[24]} The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, and total porosity. Results are summarized in Table 2. The results of angles of repose ranged from 20.55 ± 0.02 to 23.15 ± 0.03, which indicates good flow properties of granules.\textsuperscript{[25]} The results of LBD and TBD ranged from 0.41 ± 0.01 to 0.50 ± 0.03 and 0.55 ± 0.03 to 0.69 ± 0.05, respectively. The results of compressibility index (%) ranged from 19.25 ± 0.01 to 27.00 ± 0.04. The percentage porosity values of the granules ranged from 23.21 ± 0.12% to 26.98 ± 0.05% indicating that the packing of the granules may range from close to loose packing and also further confirming that the particles are not of different sizes.\textsuperscript{[25]} All these results indicated that the granules possess satisfactory flow properties and compressibility index.

Methocel K15 MCR\textsuperscript{®} and CA were used as the representative of hydrophilic and hydrophobic polymers, respectively, for the development of DS SR dosage form. Out of the six formulations, F1 to F3 were developed by using Methocel K15 MCR\textsuperscript{®} in the proportion of 24%, 20%, and 16% of the total weight of tablet; whereas F4 to F6 were developed by using CA in the proportion of 13.8%, 17.25%, and 20.70% of the total tablet weight.

The tablets of the proposed formulations (F1 to F6) were subjected to various evaluation tests like thickness, hardness, weight variation test, content analysis, and friability test. The results are summarized in Table 3. The hardness and percentage of friability of the tablets of all formulations ranged from 11.50 ± 0.02 to 13.50 ± 0.04 KP and 0.50 ± 0.01%, respectively. The average percentage of deviation of 20 tablets of each formulation was less than 6%. Drug content among different batches of tablets ranged from 99.09 ± 0.01% to 100.77 ± 0.10%. In this study, the percentage friability for all the formulations was below 1%, indicating that the friability was within the official limits. All the tablet formulation showed acceptable properties and complied with the specifications for weight variation, drug content, hardness, and friability.

The effect of different concentrations of Methocel K15 MCR\textsuperscript{®} and CA on the release profile of DS SR tablet was assessed. Comparing the release profile for a particular polymer system from Figure 1, it can be

![Figure 1: Zero-order plot of release kinetics of proposed formulations (F1 to F6) Diclofenac Sodium SR tablets containing Methocel K15 MCR\textsuperscript{®} (F1 to F3) and Cetyl alcohol (F4 to F6). Each point represents the mean value ± S.D. (n = 3)](image-url)
observed that drug release is inversely proportional to the level of rate retarding polymer present in the matrix systems for formulation F1 to F3, that is, the rate and extent of drug release increases with decrease in total polymeric content of the matrix. A linear relationship exists between the Methocel K15 MCR content and rate of drug release as characterized by higher values of correlation coefficient as illustrated in Table 4.[26,27]

However, although CA content increases in formulation F5 and F6, the increase in percent drug release may be explained by the effect of trapped sugar content in these proposed formulations.

The effect of sucrose content inside the granule on fractional release profile of DS is reported.[28] Drug release was higher from the matrices containing Methocel K15 MCR® compared with CA. Methocel K15 MCR® is reported to form a viscous gel in contact with water and release the drug by swelling in aqueous media.[17] On the contrary, CA, as hydrophobic in nature, potentially erodible and controls the release of drug through pore diffusion and erosion.[18] Thus the drug release rate from CA containing the matrix tablet is lower than the HPMC containing formulations. Moreover, the amount of drug retarding polymer was replaced by lactose (F1 to F3) and sucrose (F4 to F6). Lactose amount was highest in F3 and showed highest dissolution comparing with F1 and F2. This is due to the fact that lactose caused a decrease in the tortuosity of the diffusion path of the drug[20] and enhanced the release rate of the drug. Analogous result was also demonstrated by earlier investigators.[30]

To evaluate the release kinetics of DS from different formulations, obtained drug release data were extrapolated by zero-order, first-order, and the Higuchi equation.[20,21] The results are summarized in Table 4 and Figures 1-3. It was observed that, in case of proposed formulations F1, F2, and F3, zero-order kinetics were predominant. While, formulations F4 and F5 followed first-order release kinetics, however, formulation F6 followed zero-order release kinetics. This shows that by increasing the proportion of CA in the tablet tends the release pattern toward the zero-order kinetics.

The effect of sucrose content inside the granule on fractional release profile of DS was also reported.[28] Since sucrose outside the granule acts as a disintegrator, the increase in the sucrose content outside the granule, the fractional release increases. However, when sucrose is trapped inside the granule, it is encapsulated by CA, a hydrophobic material, the sucrose absorbs water by means of osmosis through the surrounding polymer. Therefore, sucrose inside the granule of CA cannot act as a disintegrator. In contrast, as the sucrose content in

| Table 4: Release kinetics of the various formulations by mathematical processing |
|---------------------------------|-----------------|---------------------|-----------------|-----------------|
| Formulation | Multiple coefficient of determination ($r^2$) | Korsmeyer–Peppas | |
| | Zero-order | First-order | Higuchi | N | r^2 |
| F1 | 0.9755* | 0.951 | 0.899 | 0.961 | 0.9609 |
| F2 | 0.9872* | 0.9556 | 0.9628 | 0.819 | 0.996 |
| F3 | 0.979* | 0.9421 | 0.9694 | 0.7946 | 0.9936 |
| F4 | 0.9552 | 0.9939* | 0.9883* | 0.6534 | 0.9894 |
| F5 | 0.9576 | 0.9983* | 0.9867* | 0.6789 | 0.9924 |
| F6 | 0.9934* | 0.8886 | 0.9365 | 0.824 | 0.9903 |

* P = 0.05.
a tablet increases, compressibility and hardness of the tablet also increases and consequently the fractional release decreases.\cite{33}

Figure 1 shows the effects of sucrose on the fractional release of DS. Formulation F4 contains the highest concentration of sucrose inside the granules and consequently showed the lowest fractional release of the drug, although the CA content is the minimum in this formulation among the three formulations (F4 to F6). However, although CA content increases in formulation F5 and F6, the increase in the percent drug release might be due to decreased amount of the trapped sucrose content than formulation F4.

For further study, the data were plotted in the Korsmeyer–Peppas equation to know the confirmed diffusion mechanism [Table 4 and Figure 4]. The formulations F1 to F3 showed good linearity ($r^2$: 0.9609-0.996) with slope ($n$) values ranging from 0.7946 to 0.961. Kinetic study of formulation F1 showed aberrant type of release exponent ($n$) >0.89 indicating a super case II type of release. It is difficult to make clear inference regarding the kinetics of drug release from this formulation (F1) and this formulation showed very poor fitting with the Korsmeyer–Peppas model. The release exponent ($n$) of the other two formulations (F2 and F3) containing Methocel K15 MCR® 0.819 and 0.7946 indicating a so-called anomalous transport (non-Fickian), that is, F2 and F3 showed both diffusion and dissolution controlled drug release. This finding was reported earlier by Kabir et al.\cite{30}. In contrast, formulations containing CA F4 to F6 showed release exponent ranging from 0.6534 to 0.824 indicating anomalous transport (non-Fickian) as that of F2 and F3.

The release rate of formulations F1 to F6 were compared with the innovator’s drug VRS tablet in terms of difference factor ($f_1$) and similarity factor ($f_2$). The results are summarized in Table 5. It is revealed that formulations F1 to F3 were not bioequivalent with the innovator’s drug compared with the difference factor ($f_1$) and similarity factor $f_2$. The difference factors for this group of formulations ranged from 13.66 to 43.64. Although formulation F2 shows less than 15 but the similarity factor is less than 50. The similarity factor ($f_2$) was more than 50% ranging from 69.41% to 96.52%, and the difference factor was less than 15% ranging from 0.89 to 6.75 for formulation F4, F5, and F6. According to 21 CFR, if difference factor is less than 15 and similarity factor is more than 50 with innovator drugs, the test drug can be claimed as bioequivalent with the innovator drugs. Thus, formulation F4 to F6 showed satisfactory similarity factor and difference factor with the innovators’ drug VRS tablet, that is, these formulations are bioequivalent with the innovator’s drugs.

Therefore, from this comparative study, it may be concluded that formulation F4 to F6, containing CA, showed better release pattern and was suitable for bioequivalence study, which will avoid expensive clinical trial and hence reduced cost. Overall, it will offer cost effective treatment. Wet granulation method may increase high production, enhance performance, save time, and there will be less involvement of labor too.

Furthermore, F6 was evaluated for stability study for a 6-month period both in room and accelerated condition. No significant change in appearance of the tablet at accelerated condition was observed. The potency of the active ingredient was within limit both in controlled room temperature (CRT) and accelerated condition. At CRT, the assay percent was 96.83 and 96.74 for 3 and 6 months, respectively [Table 6]. At accelerated conditions, the assay percent was 97.57 and 95.37 for 3 and 6 months, respectively [Table 7]. Dissolution profile of the tested formulation (F6) at various stability conditions is shown in Figure 5 and

<table>
<thead>
<tr>
<th>Table 5: Summary of in vitro bioequivalence analysis</th>
<th>Formulation</th>
<th>Difference factor ($f_1$)</th>
<th>Specification</th>
<th>Similarity factor ($f_2$)</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>15.54</td>
<td>NMT 15</td>
<td>42.40</td>
<td>NLT 50</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>13.66</td>
<td>44.92</td>
<td></td>
<td></td>
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<tr>
<td>F3</td>
<td>43.64</td>
<td>38.27</td>
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<tr>
<td>F4</td>
<td>3.49</td>
<td>81.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F5</td>
<td>6.75</td>
<td>69.41</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>F6</td>
<td>0.89</td>
<td>96.52</td>
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</tbody>
</table>

NMT = Not more than, NLT = Not less than
were within the limit at long-term condition and as well as at accelerated condition.

Significance of the study
Formulation F4 and F6 containing CA showed comparable release pattern and suitable for bioequivalence study, which will circumvent the affluent clinical trial and hence compact the cost. Overall, it will offer cost effective treatment. Wet granulation method may increase high production, enhance performance, and save valuable time in manufacturing plan, which ultimately leads to minimize labor cost and generate revenue.

CONCLUSION
The study reveals that, the mechanism of release changed with the nature and contents of polymers in the matrix. The type of polymers used was found to induce a conspicuous effect on release rate and mechanism. The data obtained in this study also showed that, the drug release from Methocel K15 MCR\textsuperscript{\textregistered} (hydrophilic polymer) was higher than that from CA (hydrophobic polymer). The wide range of polymers available for controlling the release rate of drug from dosage form endows the formulators with higher degree of flexibility and the present study reinforces the necessity of using different classes of polymers to get an acceptable pharmacokinetic profile in the fluctuating in vivo environment.

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