Development and Evaluation of Carbomer Based Matrices for the Controlled Delivery of Diclofenac Sodium

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Abstract.

Diclofenac Sodium (DS) is a potent non-steroidal anti-inflammatory drug used in treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. An investigation was carried out to develop sustained and controlled release carbomer matrices of DS using Carbopol 974P alone as well as in combinations with Hydroxypropylmethylcellulose (HPMC) and Carboxymethylcellulose (CMC) and to evaluate them for physical characteristics like thickness, weight variation, hardness, drug content uniformity and drug delivery performance. The in vitro study was carried out in pH 7.4 buffer medium (Simulated Intestinal Fluid) using USP XXI dissolution apparatus II. The kinetics of release data were evaluated using regression coefficient analysis and mechanism of release by Peppas exponential equation, \( M_t / M_\infty = K t^n \). The observation of results clearly indicated that carbomer matrices of DS provided greater control over drug delivery for longer duration and followed non-Fickian diffusion mechanism, with zero order release kinetics.

Key words: Diclofenac sodium; NSAID, oral drug delivery, zero-order drug delivery, carbomer based matrices.

Introduction

Sustained (SR) and controlled release (CR) delivery systems for oral drug dosing are effective in achieving improved therapy of drugs having a narrow therapeutic range of blood concentration or rapid elimination (Hosny et al., 1997; Nishihata, 1987). Diclofenac sodium (DS) is a potent non-steroidal anti-inflammatory drug (NSAID), used in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis (Gohel and Amin, 1999). But due to its short biological half life of 1-2 hrs (Todd and Sorkin, 1988) and associated gastrointestinal side effects, it is considered to be an ideal candidate for controlled drug delivery. Several studies had been done (Hosny et al., 1997; Nokhodchi et al., 1997; Malamataris and Ganderton, 1991; Hasan et al., 1992; Mishra et al. 1999a & 1999b) on various types of SR formulations of DS. However, in our investigation involving evaluation of drug delivery performance of five Indian marketed SR tablets of DS, we observed a large variation in the rate and extent of DS release from these five products that may result into variable therapeutic performance. This indicates that still there is need to develop more optimized and controlled SR formulations of DS with constant delivery rate and improved therapeutic performance.

Carbopol® belong to a family of polymers, known generically as the carbomers. They are high molecular weight, non-linear synthetic polymers of acrylic acid, cross-linked with polyalkenylpolyether and are currently being used as polymeric matrices for controlling drug release in pharmaceutical tablets affording zero to near zero-order release kinetics (Ahuja et al., *Corresponding author*)
Carbopol 934P, 971P and 974P are the pharmaceutical grades for internal use as a tablet binder in SR formulations (Matharu and Sanghavi, 1992). Therefore, in present study an effort has been made to develop carbomer based matrices of DS using Carbopol 974P alone and also in combinations (Traconis et al., 1997; Fassihi and Parker, 1986) with HPMC and CMC possessing numerous potential advantages (Ranga Rao et al., 1990) and to evaluate their drug delivery characteristics. The in vitro data were analysed using regression coefficient analysis (Sankar et al., 2001) for determining zero order, first order and Higuchi release kinetics and Peppas exponential equation (Peppas and Franson, 1983) \( M_t / M_\infty = Kt^n \), for determining drug delivery mechanism, where \( M_t / M_\infty \) is fractional drug release into the dissolution medium, \( K \) is a constant which incorporates the properties of the macromolecular polymeric system and the drug and \( n \) is the diffusional exponent which characterizes the drug transport mechanism. Different values of \( n \) indicates different drug release mechanisms. As \( n \leq 0.5 \) indicates quasi-Fickian diffusion, \( n > 0.5 \) anomalous non-Fickian diffusion, \( n \approx 1 \), zero-order kinetics and \( n > 1 \) Pseudo-case-II transport mechanism (Durrani et al., 1994).

Material and Methods

Five commercial SR tablets of DS (Batches C1, C2, C3, C4 and C5, each containing 100 mg drug) manufactured by five different companies in India were purchased from the market. DS was obtained as gift sample from Win Medicare Ltd., Modipuram (India). Carbopol 974P, CMC and HPMC were purchased from BF Goodrich Company (USA), GSC, Mumbai (India) and S.D. Fine Chemicals Ltd., Mumbai (India), respectively. All other chemicals used were of analytical grade.

Preparation of matrix tablets of DS: Five different batches (F1, F2, F3, F4 and F5) of matrix tablets of DS were prepared by direct compression technique using 100 mg of DS, 200 mg of polymer and 1% w/w of magnesium stearate as a lubricant, in each tablet. The different batches contained different polymers as variable factor. For example, batch F1 contained Carbopol 974P only, batches F2 and F3 contained mixture of HPMC and Carbopol 974P in 50:50 and 75:25 ratio, and batches F4 and F5 contained mixture of CMC and Carbopol 974P in 50:50 and 75:25 ratio, respectively. Each batch size of tablets was 200. All the ingredients were passed through sieve No. 85, blended uniformly and compressed on a Manesty E2 tabletting machine using 10 mm standard flat surface punches to obtain tablets of hardness 8 kg/cm².

All the fabricated tablets were evaluated for thickness, weight variation, hardness, drug content uniformity and in vitro drug release characteristics as per USP XXI monograph.

In vitro Drug Release Study: All the commercial and fabricated tablets were evaluated in vitro (5 runs for each batch) on an USP XXI dissolution apparatus II for 8 hours using 900 ml of pH 7.4 phosphate buffer maintained at 37 ± 0.1°C and stirred at 100 rpm. 5 ml of samples withdrawn at different time intervals were analysed on a Jasco UV/VIS Spectrophotometer (model 7800) at 275 nm after suitable dilution. Same volume of the withdrawn samples were replaced in the dissolution medium with prewarmed (37 ± 0.1°C) fresh buffer of pH 7.4. The actual drug content in the samples were read from a calibration curve prepared from pure DS in pH 7.4 phosphate buffer.

Results and Discussion

The variation in the thickness, weight, hardness and drug content uniformity values for all the batches of commercial and fabricated tablets, in reference to average values of each parameter, were found within the official limits (U.S.P., 1985).

The in vitro drug release profiles for commercial and fabricated tablets are shown in Figs. 1 and 2, respectively and the time for 30% \( (t_{30\%}) \), 60% \( (t_{60\%}) \) and 90% \( (t_{90\%}) \) DS release are presented in Table 1. Out of 5 commercial SR tablets tested, C1, C2 and C3 performed like fast release conventional dosage forms (Fig. 1), as they delivered 90% or more of the drug within one or
two hours of the study. Tablet C4 however delivered almost all the drug (≈ 100%) in 4 hours while tablet C5 delivered 100% drug in 7 hours, indicating slower delivery of drug from C5 than from C4. The results clearly exhibited large variation in the rate and extent of DS release from five commercial tablets and thus indicate towards possibility of variable therapeutic performance of such formulations. Further, since they contain 100 mg of DS in SR tablets (prescribed as one tablet a day) as compared to 50 mg in conventional tablets (prescribed as one tablet twice a day), C1, C2, C3 and C4 SR tablets may result into dose-dumping due to fast drug release and may thus produce severe gastrointestinal and other complications and also may not be therapeutically effective after 12-15 hrs of dosing due to faster clearance of the dumped dose. To avoid these problems, SR product of DS with an optimum slow, controlled and consistent drug delivery rate is essentially required to be developed and an effort was made in the same direction with following results.

![Fig. 1.](image1) **In vitro** release profiles of DS from commercial tablets. Crossbars indicates ± S.D. (n = 5).

![Fig. 2.](image2) **In vitro** release profiles of DS fabricated tablets. Crossbars indicates ± S.D. (n = 5).
The *in vitro* results (Table 1, Fig. 2) for the fabricated tablets showed that all tablets (F1 to F5) provided significantly more sustained and controlled drug release profiles as compared to commercial tablets. Tablets prepared with HPMC and Carbopol 974P combinations (F2 and F3) slowed down the delivery rate maximum followed by tablets F4 and F5 having CMC and Carbopol 974P combinations. Tablet F1 fabricated with Carbopol 974P only gave faster drug release than the other fabricated tablets. This clearly indicate that the admixed polymers offer more sustaining effect on drug delivery than the single polymer.

Table 1. Kinetics of *in vitro* DS release (using regression analysis) and time to release 30% (t₃₀%), 60% (t₆₀%) and 90% (t₉₀%) DS from different tablets.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Batches</th>
<th>r values</th>
<th>t₃₀% (h) (mean ±SD)</th>
<th>t₆₀% (h) (mean ±SD)</th>
<th>t₉₀% (h) (mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Zero order</td>
<td>First order</td>
<td>Higuchi</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>C1</td>
<td>0.9080</td>
<td>0.8861</td>
<td>0.9806</td>
<td>0.33* ± 0.06</td>
</tr>
<tr>
<td>2.</td>
<td>C2</td>
<td>0.9652</td>
<td>0.8184</td>
<td>0.9375</td>
<td>0.25* ± 0.03</td>
</tr>
<tr>
<td>3.</td>
<td>C3</td>
<td>0.9222</td>
<td>0.8176</td>
<td>0.9907</td>
<td>0.50* ± 0.04</td>
</tr>
<tr>
<td>4.</td>
<td>C4</td>
<td>0.9927</td>
<td>0.8379</td>
<td>0.9835</td>
<td>0.83* ± 0.05</td>
</tr>
<tr>
<td>5.</td>
<td>C5</td>
<td>0.9976</td>
<td>0.8220</td>
<td>0.9651</td>
<td>1.85 ± 0.10</td>
</tr>
<tr>
<td>6.</td>
<td>F1</td>
<td>0.9988</td>
<td>0.8771</td>
<td>0.9553</td>
<td>3.15* ± 0.2</td>
</tr>
<tr>
<td>7.</td>
<td>F2</td>
<td>0.9940</td>
<td>0.9700</td>
<td>0.9236</td>
<td>-</td>
</tr>
<tr>
<td>8.</td>
<td>F3</td>
<td>0.9994</td>
<td>0.9498</td>
<td>0.9543</td>
<td>-</td>
</tr>
<tr>
<td>9.</td>
<td>F4</td>
<td>0.9915</td>
<td>0.9379</td>
<td>0.9174</td>
<td>4.30* ± 0.23</td>
</tr>
<tr>
<td>10.</td>
<td>F5</td>
<td>0.9946</td>
<td>0.9243</td>
<td>0.9427</td>
<td>5.00* ± 0.28</td>
</tr>
</tbody>
</table>

r = coefficient of correlation

* p < 0.01 in reference to tablet C5 (considered as standard marketed SR tablet).

Evaluation of *in vitro* data by regression analysis (Table 1) indicated that all the fabricated tablets exhibited zero-order drug release kinetics. Commercial tablets C2, C4 and C5 also exhibited zero-order drug release kinetics while C1 and C3 followed Higuchi kinetics. Further, treatment of data using Peppas equation showed (Table 2) that all the fabricated tablets delivered drug with anomalous non-Fickian diffusion mechanism as values of n for all the tablets were greater than 0.5. *In vitro* data for tablets C1, C2 and C3 were not evaluated by Peppas equation, as they delivered drug very fast and behaved like a conventional tablet. However, n values for tablets C4 and C5 were 1.28 and 1.15 respectively, indicating Pseudo-case-II transport mechanism (Durrani *et al.*, 1974).

Table 2. Drug release kinetics for different tablets using Peppas exponential equation

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Batches</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>K</td>
</tr>
<tr>
<td>1.</td>
<td>F1</td>
<td>0.158</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>0.931</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>0.467</td>
</tr>
<tr>
<td>4.</td>
<td>F4</td>
<td>0.488</td>
</tr>
<tr>
<td>5.</td>
<td>F5</td>
<td>0.420</td>
</tr>
</tbody>
</table>

K is a constant which incorporates the properties of the macromolecular polymeric system and the drug.

n is the diffusional exponent.

r² is the correlation coefficient.
The drug release mechanism for the fabricated tablets containing Carbopol 974P or its combinations with HPMC and CMC may be described as "swelling-controlled". It's due to macromolecular relaxation of the polymer(s) from a glassy to rubbery state and due to constant velocity of the glassy/rubbery interface, a quasi or zero-order drug release is obtained from such pharmaceutical tablets (Durrani et al., 1994).

The present investigation, thus established the usefulness of evaluating existing commercial SR formulations of DS and points towards the need of design and development of more optimized SR formulations for DS. It was concluded that a potential SR and CR matrix tablets of DS could be prepared by incorporating polymers like Carbopol 974P and its combinations with HPMC and CMC in an optimized ratio.

References


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