Formulation and *In Vitro* Evaluation of Polymers Blend Based Diclofenac Sodium Microparticles for Sustained Release Drug Delivery

Mukarram Anees1,*, Farzana Chowdhary1, Muhammad Irfan Masood1, Aqeel Javeed2, Mahwish Ilyas1

1 Institute of Pharmaceutical Sciences, University of Veterinary and Animal Sciences, Lahore, Pakistan
2 Department of Pharmacology and Toxicology, University of Veterinary and Animal Sciences, Lahore, Pakistan

**ABSTRACT**

**Purpose:** The purpose of research was to formulate polymeric blend based Diclofenac sodium microparticles for sustained release drug delivery.

**Method:** The diclofenac sodium microparticles were formulated by emulsification and solvent evaporation method. The diclofenac loaded microparticles were evaluated or characterized for different parameters such as, micrometric properties, particle size, particle shape measurement, encapsulation and loading efficiency, FTIR, dissolution and drug release kinetics studies.

**Results:** Compact white spherical shaped microparticles of Diclofenac sodium microparticles were observed under optical microscope with a size of 169 - 552 µm. All formulation showed good percentage yield (96-100%). There was no effect of either increased or decreased concentration of polymers observed. Concentration of polymers and sustained release behavior of drug was directly proportional. *In Vitro* drug release study was performed in 0.2M HCl (pH 1.2) for first 2 hours, then followed by 0.2 M phosphate buffer solution (pH 6.8) for next 6 hours. The drug release from microparticles was irregular diffusion process.

**Conclusion:** From the study, it was evident that a suitable combination of polymers is necessary to achieve desired effects. Diclofenac Sodium microparticles can be used to reduce adverse effects and increase the patient compliance.

**Keywords:** Diclofenac sodium, microparticles, polymers blend, sustained release drug delivery.

**INTRODUCTION**

Conventional oral solid dosage forms create irregular plasma drug levels, which result in toxic and sub-therapeutic effects [1]. The controlled delivery system can minimize the problems related to conventional oral dosage forms by controlling the rate of drug release, which ultimately results in the optimum therapeutic level of drug and minimization of the side effects of the drug [2]. Fundamentally, the oral controlled drug delivery system consists of drug reservoir, in which drug is slowly released in a controlled manner to achieve a constant drug absorption level [3].

Different approaches are being used for dosage forms. One of them is microparticle [1, 4]. Microparticles are sphere-shaped molecules with breadth in the micro-meter range ordinarily from 1 µm-1000 µm [5, 6]. The benefits of using microparticles as drug delivery system include controlling or prolonging the drug release, masking of taste and odour of many drugs, minimization of GI irritation, achieving alteration in site of absorption, improving patient compliance and comforting by reducing dosing frequency [7, 8]. A formulation with...
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encapsulating ability, and prolonged release of the encapsulated drug with restrained structural purity is an ideal microparticle preparation [6]. Modified release drugs, such as enteric coated tablets or twofold film coated tablets releases the drug slowly for 12-24 hours. This drug release rate results in insufficient delivery of drug in systemic circulation and also shows potential irritation of GIT. For minimizing such problems, drug loaded microparticles is considered as one of the best approach as drug carrier [9].

Diclofenac sodium (DS) is a nonsteroidal anti-inflammatory drug (NSAID). It shows pharmacological activity by inhibiting the synthesis of prostaglandins (PGs), specifically either non selectively inhibiting cyclooxygenase-I and cyclooxygenase-II or selectively inhibiting Cyclooxygenase-II [10]. DS is a derivative of phenyl acetic acid having an acid dissociation constant value of 4.00. DS exits in acidic form in digestive fluid. Its solubility in water is very low, but in intestinal fluid, its solubility is very high. When given through oral route, it absorbs instantly [11]. It is used as anti-inflammatory and analgesic in joint pain, ankylosing spondylitis and osteoarthritis for a long duration of time. The plasma half-life (t1/2) of diclofenac is 1-2 hour. Bleeding, ulceration and intestinal wall perforation are most commonly seen adverse effects by diclofenac. Because of short plasma t1/2 and side effects, it can be formulated by sustaining drug release in the form of microparticles [12]. Sustained and controlled release oral drug delivery systems increase safe profile of NSAIDs [13]. One approach to minimize these problems is polymeric microparticles formulations [9, 14]. In view of these problems, the main purpose of the study is to formulate the sustained release natural and synthetic polymeric blend based Diclofenac Sodium microparticles for reducing side effects and improving patient compliance and to evaluate the Diclofenac sodium microparticles with respect to particle size, flow properties, percentage loading efficiency, drug polymer interaction studies and in-vitro drug release kinetic studies.

**MATERIALS AND METHODS**

**Materials**

Diclofenac sodium and Acetone (manufactured by Merck, England), Ethyl cellulose, Starch, Liquid-paraffin (manufactured by BDH Chemicals, England), Span-80, and Petroleum ether of 40-60°C (manufactured by Sigma-Aldrich, USA) were procured from commercial sources of local market and were used as such.

**Formulation of Diclofenac Sodium Microparticles**

Diclofenac sodium (DS) microparticles were formulated according to the Table 1. An external phase was prepared by taking 50gm of Liquid-paraffin containing 0.75gm of Span-80 in a 100ml beaker. The internal phase was prepared in solution form by adding accurately weighed amount of polymers (as per formulations composition) and organic solvent (polymer: acetone is 1:5) in a separate beaker. Accurately weighed quantity of the drug DS was added in the internal phase under stirring at high revolution i.e. 2000 rpm, using stirrer (IKA Eurostar 20 Digital, Germany). After preparation of both phases, the internal phase was added into external phase under continuous stirring at 2,000 rpm for 2 hours and then rigid spherical microparticles were separated by filtration. The prepared microparticles were rinsed by using petroleum ether and then dried in an oven to get freely flowing microparticles.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Diclofenac Sodium gm</th>
<th>Ethyl Cellulose gm</th>
<th>Starch gm</th>
<th>EC Starch Ratio %</th>
<th>Liquid Paraffin gm</th>
<th>Acetone ml</th>
<th>Span 80 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>2.50</td>
<td>0.625</td>
<td>1.875</td>
<td>25:75</td>
<td>50</td>
<td>12.5</td>
<td>0.75</td>
</tr>
<tr>
<td>D2</td>
<td>2.50</td>
<td>1.250</td>
<td>1.250</td>
<td>50:50</td>
<td>50</td>
<td>12.5</td>
<td>0.75</td>
</tr>
<tr>
<td>D3</td>
<td>2.50</td>
<td>1.875</td>
<td>0.625</td>
<td>75:25</td>
<td>50</td>
<td>12.5</td>
<td>0.75</td>
</tr>
</tbody>
</table>
The Percentage (%age) Yield
The %age yield of diclofenac sodium microparticles was estimated by dividing the weight of microparticles obtained from each formulation with the total weight of drug (diclofenac sodium) and the polymers for each formulation and multiplied by 100.

Particle Shape and Size Measurement
Particle shape of Diclofenac Sodium microparticles was estimated using a microscopic method [15]. Labomed iVu 3000 optical microscope was used for shape and size measurement. The size of Diclofenac sodium microparticles was calculated by using software ProgRes® CapturePro 2.7.7 - Jenoptik AG.

Micromeritic Studies
The Angle of repose (θ) was estimated by funnel method. All granules were passed through the funnel to obtain granule’s cone. Then radius and granule’s cone height were determined. Angle of repose (θ) was determined by using equation 1 [16].

\[ \theta = \tan^{-1} \frac{1}{r} \]  

Tapped density was determined by tapping the graduated cylinder 100 times. Tapped density was determined by using equation 2 [17].

\[ d_t = \frac{\text{weight}}{\text{tapped volume}} \]  

Car’s index was calculated by using the equation 3 [17].

\[ \text{Car’s Index} = \frac{[(\text{Initial volume} - \text{Final volume})/\text{Initial volume}] \times 100}{\%} \]  

Hauser’s ratio was calculated by equation 4 [18].

\[ \text{H.R.} = \frac{\text{Tapped density}}{\text{Bulk density}} \]  

Encapsulation and Loading Efficiency
10 mg powdered microparticles were extracted by sonication with 100 ml of phosphate buffer having molarity 0.2M and pH 6.8. The drug contents were assayed by UV-visible spectrophotometer at 276nm. It was then calculated by using a regression equation derived from the standard curve of Diclofenac Sodium (R² =0.992). Each test was carried out three times. The %age loading efficiency was determined as theoretical content percentage. Microparticles without diclofenac sodium were used as a reference. The encapsulation efficiency (%) was estimated by using equation 5.

\[ \text{Loading efficiency} (\%) = \left( \frac{D_a}{D_t} \right) \times 100 \]  

Where \( D_a = \) actual drug loading and \( D_t = \) theoretical drug loading.

Fourier Transform Infrared Spectroscopy Measurement
The drug polymer interactions among Diclofenac sodium, polymers (ethyl cellulose and starch) and Diclofenac Sodium microparticles were studied by using Fourier Transform Infrared Spectrophotometer [11, 19].

In-Vitro Drug Release Studies
Dissolution Type-II (Paddle) Apparatus were used for in-vitro dissolution studies of formulations D1, D2 and D3. Dissolution was performed at 37±0.50°C in 0.9 L of 0.2M HCl having pH 1.2 for 2 hours at 50rpm, followed by 0.9L of 0.2M phosphate buffer having pH 6.8 for 6 hours at 50 rpm. 5ml sample of each formulation were taken at 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0 and 8.0 h intervals. The sample was replaced with the equal volume of dissolution medium already maintained at the test temperature. 0.45 µm filters were used for filtration of samples. The filtrate was assayed for drug concentration at 276nm after further 10 times dilutions with phosphate buffer. Percentage drug release was then calculated [12].

Drug Release Kinetics
In the model dependent approaches, various kinetic models were used for analysis of drug release, as shown in equations 6-10.

Zero order model \[ Q_0 - Q_t = K_0 t \]  

First order model \[ \log Q_t = \log Q_0 + \log K_1 t / 2.303 \]  

Higuchi model \[ Q = K_M t^{1/2} \]  

Hixson-Crowell model \[ W_0^{1/3} - W_t^{1/3} = K_s t \]  

Korsmeyer-Peppas model \[ \frac{Mt}{M_\infty} = K t^n \]  

Where, \( Q_0, Q_t, K_0, K_1, K_M, M_t, M_\infty, K_s, W_0, W_t \) and \( K_s \) are quantity of drug at time \( t \), initial drug concentration in mixture, zero order, first order rate constant, Higuchi dissolution constant, fraction of drug release at \( t \) time and at \( \infty \) time, release rate constant, release exponent which depends on mechanism of drug release, initial drug concentration, remaining drug concentration and surface volume relation respectively [20].
RESULTS

Evaluation/ Characterization of Microparticles
Image of prepared white rigid spherical Diclofenac Sodium microparticles is shown in Figure 1.

![Figure 1. Diclofenac Sodium Microparticles.](image)

All formulation showed good percentage yield (96-100%). There was no effect of either increased or decreased concentration of polymers observed.

Compact spherical shaped microparticles were observed under optical microscope as shown in Figure 2, while Table 2 shows mean particle size of all three formulations.

![Figure 2. Compact spherical shaped Diclofenac Sodium microparticles.](image)

Table 2. Characterization of different parameters of diclofenac sodium microparticles.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Particle Size (µm)</th>
<th>Angle of Repose</th>
<th>Mean Bulk Density</th>
<th>Mean Tapped Density</th>
<th>Mean Carr’s Index</th>
<th>Mean Hausner’s Ratio</th>
<th>Loading Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>552±27</td>
<td>35.67±1.53</td>
<td>0.40±0.05</td>
<td>0.49±0.0</td>
<td>19.6±0.70</td>
<td>1.24±0.01</td>
<td>30.74±9.00</td>
</tr>
<tr>
<td>D2</td>
<td>416±39</td>
<td>36.4±1.00</td>
<td>0.33±0.01</td>
<td>0.41±0.0</td>
<td>19.6±1.98</td>
<td>1.24±0.30</td>
<td>81.47±0.81</td>
</tr>
<tr>
<td>D3</td>
<td>169±14</td>
<td>31.47±0.50</td>
<td>0.44±0.57</td>
<td>0.50±0.0</td>
<td>13.2±1.08</td>
<td>1.15±0.01</td>
<td>98.07±5.11</td>
</tr>
</tbody>
</table>

Micromeritic Studies
The Micromeritic studies like, bulk density, tapped density, angle of repose, Carr’s index and Hauser’s ratio are also given in Table 2. Formulation D3 showed excellent flow property as compare to other two formulations.

Encapsulation and Loading Efficiency
The mean %age loading efficiency of each formulation is given in Table 2. Formulation D3 showed maximum loading efficiency.

Fourier Transform Infrared Spectroscopy Measurement
The FT-IR spectra showed no drug, polymers and microparticles interaction as shown in Figure 3.

![Figure 3. FT-IR of pure diclofenac sodium, ethylcellulose, starch and DS microparticles.](image)
**In-Vitro Drug Release Studies**

*In-vitro* drug release data of all formulations of diclofenac sodium microparticles are shown in Figure 4.

![Drug Release Graph](image)

**Figure 4. In-vitro drug release of microparticles.**

**Drug Release Kinetics**

Different drug release kinetic models were applied for determining drug release pattern of each formulation of Diclofenac Sodium microparticles. The best model was selected on the basis of goodness of fit.

**DISCUSSION**

**Preparation of Diclofenac Sodium Microparticles**

All formulations of Diclofenac Sodium microparticles (D1, D2 and D3) were formulated with combination of ethyl cellulose (synthetic polymer) and starch (natural polymer) by emulsification and solvent evaporation method. All the formulations showed good percentage yields between the ranges of 96 to 100%. There was no any significant difference noted between the percentage yields of different formulations of the present study. In a previous study, microparticles showed good percentage yield with the ratio of 1:1 of drug and polymers [21].

**Particle Size Measurement**

The decreasing order of particle size is D3<D2<D1 as shown in Table 2. Polymeric blend used for formulating Diclofenac Sodium microparticles resulted in a smaller particle size as compared to the previous study in which nimesulide microparticles were prepared in 1:1 ratio of drug and polymer [11]. Significant effect was shown by Eurostar mixer on the particle size distribution, it produced microparticles of smaller size. Increased concentration of starch and decreased concentration of ethyl cellulose in a formulation resulted in an increased microparticles size [22]. The particle size of formulation D1 was more larger as compared to formulation D3, because formulation D1 contained more starch and less ethylcellulose.

**Micromeritic Studies**

All formulations of Diclofenac Sodium microparticles (D1, D2 and D3) showed good flow properties as shown in Table 2. The greater concentration of ethyl cellulose increased the flow properties of microparticles [23]. Micromeritic studies determined that formulation D3 showed excellent flow properties as it contained more concentration of ethyl cellulose. The increasing order of flow properties of all formulations is D3>D2>D1.

**Encapsulation and Loading Efficiency**

The increased loading efficiency of microparticles was due to incorporation of starch and ethyl cellulose blend. It was also reported that the microparticles having increased concentration of ethyl cellulose resulted in an increased loading efficiency. The percentage loading efficiency of D2 and D3 was found to be increased as compared to previously reported studies [11, 21].

**FT-IR Spectroscopy Measurement**

FT-IR spectra in Figure 3 showed no degradation of drug during microencapsulation. The characteristic peaks at 3388.1 cm⁻¹, 3066 cm⁻¹, 1507-1555 cm⁻¹, 1573 cm⁻¹, 1453 cm⁻¹, 1399 cm⁻¹, 1343-1367 cm⁻¹ and 747.45-766.74 cm⁻¹ represented N-H stretching, C-H (aromatic hydrogen), N-H bending, C=O stretching, CH2, CH3, O-H bending and C-Cl stretching respectively. FT-IR spectra, during formulation, did not show any significant interaction between diclofenac sodium drug and polymers. All characteristic peaks were present.

**In-Vitro Drug Release Studies**

Figure 4 shows the *in-vitro* release results for DS microparticle formulations. Polymer concentration affected the drug release from the microparticles. With increase in ethyl cellulose concentration, percentage drug release of Diclofenac Sodium was found decreased significantly [12]. After 8 hours of dissolution, all formulations D1, D2 and D3 gave drug release 68.5%, 49.5% and 51.25% respectively, thus it was indicated that microparticle formulations showed sustained release behavior of the drug.
Drug Release Kinetics

All the data obtained from *in-vitro* drug release study of various formulations of Diclofenac Sodium microparticles were analyzed by using different kinetic models.

The Higuchi and Korsmeyer Peppas model best explained the drug release pattern from formulation D3, i.e., release of drug is directly proportional to the square root of time with R2 value of 0.9957. The diffusion was main release mechanism as the concentration of ethylcellulose (non-biodegradable polymer) increased in D3 formulation as compared to D1 and D2, ultimately showed more controlled release profile. D3 showed best release profile in 8 hours.

The Korsmeyer Peppas model best explained the drug release pattern from formulations D1 and D2, i.e., release of drug is directly proportional to the square root of time with R2 value of 0.9813 and 0.9904 respectively. It was observed that drug release from D2 followed both diffusion and erosion [24]. It was due to swelling of polymeric microparticles by taking fluid, the diffusion pathway was generated that controlled the release profile of the drug.

**CONCLUSION**

This study demonstrates that emulsification and solvent evaporation method can be a best method for formulating microparticles of diclofenac sodium with ethylcellulose and starch blend for sustained release. Characterization studies indicate that there was no significant chemical interaction between the drug and excipients. However, a suitable combination of polymers (75:25 ratio of EC: Starch) is necessary to achieve desired effects. Diclofenac Sodium microparticles can be used to reduce adverse effects and to increase the patient compliance.

**REFERENCES**

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