Sustained Release of Diclofenac Sodium from Tabletted Ethyl Cellulose Microcapsules

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Abstract

This study aims at preparation of once-daily sustained release tablets of Diclofenac Sodium (DFS). Using Ethyl Cellulose (EC) as coat material, DFS was microencapsulated by a non-aqueous phase-separation technique induced by nonsolvent addition and the resulting microcapsules were studied. The microcapsules were tabletted with an intention of extending the drug release profile. All the tablets prepared were of good quality, when tested for hardness, friability and drug content. In vitro Dissolution studies indicated that drug release from tablets followed zero order kinetics; the release could be extended up to 24 hours, and non-fickian diffusion was involved.

Keywords: Diclofenac Sodium, Ethyl cellulose, Coacervation, Phase separation, Microencapsulation.

1. Introduction

Microencapsulation provides a simple and cost-effective way to enclose bioactive materials, such as drugs and cells, within a semi-permeable polymeric membrane for the purpose of protecting the bioactive materials and releasing the enclosed substances or their products in a controlled fashion. The rate of drug release from microcapsules may be manipulated by changing coat: core ratio, the polymer used as coating material and the method of microencapsulation. Diclofenac Sodium (DFS) is one of the most effective non-steroidal anti-inflammatory drugs for clinical treatment of both inflammation and pain. Because of its relative short biological half-life, the hazards of adverse gastrointestinal reactions and chronic nature of treatment and to improve patient compliance, sustained release dosage forms of DFS are needed. Ethyl cellulose (EC) is an inert, hydrophobic polymer and is essentially tasteless, odorless, colorless, non-caloric and physiologically inert. It has been widely used in microencapsulation. Microencapsulation of DFS has been reported by many researchers. In the present work, DFS was microencapsulated with EC by non-aqueous phase separation induced by non solvent addition. Different coat: core ratios were tried and the resulting microcapsules were studied for micromeritic properties, drug content, microencapsulation efficiency, yield percentage and in-vitro release characteristics. Further, the microcapsules were tabletted with a view to obtain sustained release up to 24 hours.

Materials

Diclofenac Sodium (gift sample from Amoli Organics, Ahmadabad), Ethyl Cellulose (BDH) (having an ethoxyl content of 47.5% weight and a viscosity of 22 cp in a 5% concentration, by weight, in a 80:20 toluene-ethanol solution at 25°C), Toluene (BDH) (109°-112°C), Petroleum ether (Glaxo) (60°-80°C), Starch I.P. and Magnesium stearate I.P.

2. Experimental

Preparation of Microcapsules and their Tablets:

DFS was microencapsulated with EC by a process of coacervation-phase separation by the addition of non-solvent. Microcapsules with three ratios of EC and DFS (2:3 (ECMC-1), 3:2 (ECMC-2), and 3:1 (ECMC-3) were prepared.

Sustained release non-disintegrating tablets of DFS (T-ECMC-1, T-ECMC-2 and T-ECMC-3) were prepared by direct compression of respective microcapsules separately. Each tablet contained microcapsules equivalent to 100 mg of DFS. The microcapsules were blended with 1% talc and 0.5% magnesium stearate and compressed into tablets on a rotary multi-station tableting machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) using 9 mm round and flat punches.

Measurement of Micromeritic Properties of Microcapsules:

Angle of Repose: The angle of repose of microcapsules was determined by the fixed-funnel and free-standing cone method. A funnel was secured with its tip at a given height (h); above a flat horizontal surface to which a graph paper was attached. The microcapsules were carefully poured.
through the funnel until the apex of the heap of microcapsules just touched the tip of the funnel. The diameter of the microcapsule cone formed (_r_) was measured and angle of repose _θ_ was calculated using the following equation:

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

(1)

Bulk Density: Both loose bulk density (\( \rho_l \)) and tapped bulk density (\( \rho_t \)) were determined. An accurately weighed quantity of microcapsules from each batch was introduced into 50ml tared graduated cylinder with the aid of funnel. After the initial volume was observed, the cylinder was tapped until no further reduction in volume was noted. \( \rho_l \) and \( \rho_t \) were calculated using the following formulae:

\[
\rho_l = \frac{\text{weight of the microcapsules}}{\text{volume of the packing}}
\]

(2)

\[
\rho_t = \frac{\text{weight of the microcapsules}}{\text{tapped volume of the packing}}
\]

(3)

These density parameters were used to calculate Hausner’s ratio and Carr’s index.

Hausner’s Ratio: The Hausner Ratio was calculated by the following equation:

\[
\text{Hausner Ratio} = \left( \frac{\rho_t}{\rho_l} \right) \times 100
\]

(4)

Carr’s Index: The Carr’s Index of the microcapsules was determined by the following equation:

\[
\text{Carr’s Index (\%)} = \left( \frac{\rho_t - \rho_l}{\rho_t} \right) \times 100
\]

(5)

Characterization of Microcapsules:

Drug Content: The accurately weighed microcapsules were taken into 100 ml volumetric flask; 5 ml of methanol was added and mixed thoroughly to dissolve the coat. To this 15 ml of distilled water was added and the resulting solution was heated on water bath to evaporate the methanol. The solution was made up to volume and suitably diluted with distilled water, and assayed at 276 nm.

Measurement of Microencapsulation Efficiency:

Microencapsulation efficiency was calculated using the following formula:

\[
\text{Microencapsulation efficiency} = \left( \frac{\text{estimated percentage drug content}}{\text{theoretical percentage drug content}} \right) \times 100.
\]

(6)

Yield: The percentage yield of microcapsules was calculated using the following formula:

\[
\% \text{ yield} = \frac{\text{weight of microcapsules (g)}}{\text{initial weight of DFS (g)}} + \frac{\text{initial weight of EC (g)}}{100}
\]

(7)

The initial amount of raw material corresponds to the amount of drug plus polymer.

Evaluation of Tablets:

Hardness and friability were evaluated using a Monsanto hardness tester and a Roche friabilator respectively. DFS content of the tablets was estimated at 276 nm by UV spectrophotometer.

Evaluation of Dissolution of Diclofenac Sodium: Release of DFS from microcapsules (equivalent to 100 mg of medicament) and from tablets was studied using USP Dissolution Type 2 apparatus. Distilled water was used as dissolution medium. The stirring speed was set at 50 rpm and at 37±0.1°C. During dissolution experiments of tablets, both dissolution vessel and the water bath used to warm the dissolution medium were covered, for the entire period of study, to minimize losses due to evaporation. A 2 ml sample of dissolution medium was withdrawn at different time intervals, suitably diluted and assayed at 276 nm for DFS. The percent of drug released at various was calculated and plotted against time. The dissolution studies were conducted in triplicate.

Fitting of Dissolution Data: The kinetics and mechanism of drug release from microcapsule based tablets was fitted to the following equations:

\[
Q = Q_o + k_0 t \quad \text{Zero order kinetics equation (8)}
\]

\[
\ln Q = \ln Q_o - k_1 t \quad \text{First order kinetics equation (9)}
\]

\[
Q = k_H t^{1/2} \quad \text{Higuchi equation (10)}
\]

\[
M_t/M_{\infty} = k_p t^n \quad \text{Peppas Equation (11)}
\]

Where, _Q_ represents percentage of drug released at time _t_. In equations (8) and (9) _k_0 and _k_1 represent respective release rate constants. In Higuchi equation (10), _k_H_ stands for diffusion rate constant. In Peppas equation (11), _M_t/M_{\infty_} is the fractional release of the drug _k_p_ is a constant incorporating structural and geometric characteristics of the release device, and _n_ is the release exponent indicative of mechanism of release. If the _n_ value is 0.5 or less, the release mechanism follows Fickian diffusion, and the values 0.5 < _n_ < 1 indicate a non-Fickian release (anomalous/zero order release). The drug release follows zero-order and case-II transport if the _n_ value is 1. For the values of _n_ higher than 1, the mechanism of drug release is regarded as super case-II transport. The value of 'n' is estimated from linear regression of _ln M_t/M_{\infty_} vs. _ln t_.

3. Results and Discussion:

For microencapsulation with ethyl cellulose a non-aqueous phase separation method was employed. Three ratios of EC and DFS namely, 2:3 (ECMC-1), 3:2 (ECMC-2), and 3:1 (ECMC-3) were used to prepare microcapsules. The microcapsules were white, free flowing and spherical in shape.
A good flow of microcapsules to be compressed is necessary to assure efficient mixing and acceptable pharmaco technical properties of compressed tablets. Therefore, flow characteristics of the microcapsules should be studied. The value of angle of repose less than 30° generally indicate a free flowing material and angles greater than 40° suggest a poorly flowing material. Hausner ratios below 1.25 indicate good flow and values above 1.25 indicate poor flowing nature of the material. The values of Carr’s Index between 5-15% indicate excellent flow. The results of micromeritic studies (Table-1) indicate good flow of the microcapsules. This indicates that the microcapsules can be easily handled during processing.

To characterize the microcapsules, three parameters were calculated: the drug content, the microencapsulation efficiency and the weight yield. These parameters are helpful to ascertain whether the preparation procedure adopted for incorporating a drug into polymeric particles is efficient. Low s.d. values in the mean percent drug content ensured uniformity of drug content in each batch of microcapsules. Also, microencapsulation efficiency and yield % are satisfactory (Table-1). Overall, the results indicate that the microcapsules possessed satisfactory flow properties, compressibility and drug content.

The tablets prepared were evaluated for hardness, friability and drug content. Tablet hardness varied between 6.0-7.0 kg/cm² and friability less than 0.4%. Good uniformity in drug content was found among different batches of tablets and the percentage of drug content was more than 95%. Thus, all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content. This could be attributed to uniform coating or spherical nature of the microcapsules, leading to good flow and uniform mixing.

DFS release from various microcapsules was found to be spread over varying periods of time (Fig.1). The drug release depended on the proportion of EC in microcapsules. Drug release decreased when the proportion of EC increased. However, drug release from microcapsules was rapid, perhaps due to hydrolysis of DFS and subsequent raise in pH. The microcapsules didn’t disintegrate during dissolution experiments, suggesting diffusion controlled process in drug release. Plots of percent DFS released vs. square root of time were linear (r=0.9690) confirming that the drug release from the microcapsules was diffusion controlled.

In vitro dissolution studies are valuable tools to judge quality and stability of sustained release dosage forms and are often used to predict in vivo performance. Tableting microcapsules resulted in the extension of release profile of the drug (Fig.2). Drug release depended on the proportion of EC and there was a decrease in drug release and k₀ with increase in EC proportion. The greatly reduced porosity and surface area, formation of a non-disintegrating matrix or an increase in tortuosity might be responsible for prolongation of the release of DFS from tablets compared to the original microcapsules. The tablets retained their shape and structure throughout the dissolution study period with very marginal erosion of the tablet matrix.

The dissolution data of tablets were fitted to various mathematical models (zero order, first order, Higuchi’s square root and Peppas equations) to evaluate the kinetics and mechanism of drug release from the tablets using MS-Excel 2007 software. Coefficient of correlation (r) values were used to select the best fit for the data. The results given in Table-2 indicated that the drug release from the tablets followed zero order kinetics and k₀ decreased as the proportion of EC increased.

Kinetic models which fit zero order and Higuchi are more suitable for controlled release formulations; while first order model is more appropriate for conventional tablets. When the release data were analyzed as per Peppas equation, the “n” values were between 0.6065 and 0.8552, indicating that non-fickian diffusion was involved in drug release from tablets.

4. Conclusion

DFS could be microencapsulated by non-aqueous phase separation method using ethyl cellulose - toluene - petroleum ether system. The microcapsules could be compressed into tablets. Tableting the microcapsules not only retarded drug release but also resulted in zero-order release. The mechanism of drug release was of non-fickian diffusion. Among the tablet formulations prepared, T-ECMC-3 was found suitable for achieving sustained release up to 24 hours. However, pharmacokinetic studies are required to confirm its in vivo performance.
Fig. 1 Dissolution Profile of DFS from EC microcapsules

Fig. 2 Dissolution Profile of DFS from Tabletted EC microcapsules

**Table 1**
Flow Properties, Drug Content, Microencapsulation Efficiency and % Yield of Microcapsules

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of Repose (°)</th>
<th>Carr's Index</th>
<th>Hausner Ratio</th>
<th>Drug Content (%)</th>
<th>Microencapsulation Efficiency (%)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMC-1</td>
<td>29.34</td>
<td>13.9</td>
<td>1.16</td>
<td>48.46 (0.58)</td>
<td>80.77 (0.23)</td>
<td>80.56</td>
</tr>
<tr>
<td>ECMC-2</td>
<td>26.56</td>
<td>13.2</td>
<td>1.15</td>
<td>35.45 (0.65)</td>
<td>88.63 (0.54)</td>
<td>72.49</td>
</tr>
<tr>
<td>ECMC-3</td>
<td>25.78</td>
<td>12.8</td>
<td>1.14</td>
<td>24.21 (0.43)</td>
<td>96.84 (0.46)</td>
<td>65.53</td>
</tr>
</tbody>
</table>

**Table 2** Analysis of DFS Release Data of Tablet Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Coefficient of Correlation (r)</th>
<th>n value in Peppas Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero order</td>
<td>First order</td>
</tr>
<tr>
<td>T-ECMC-1</td>
<td>0.9946</td>
<td>0.6731</td>
</tr>
<tr>
<td>T-ECMC-2</td>
<td>0.9966</td>
<td>0.6285</td>
</tr>
<tr>
<td>T-ECMC-3</td>
<td>0.9955</td>
<td>0.5457</td>
</tr>
</tbody>
</table>

References


