Formulation and Evaluation of Ethyl Cellulose-Coated Diclofenac Sodium Microcapsules: Influence of Solvents

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The influence of three solvents for the polymer (chloroform, dichloromethane and ethyl acetate) employed in the preparation on the drug release from ethyl cellulose microcapsules was studied. Diclofenac sodium was used as core and microcapsules were prepared by an emulsion solvent evaporation method. All the three solvents gave discrete, large sized, free flowing spherical microcapsules. The microcapsules were evaluated for size analysis, drug content, microencapsulation efficiency, wall thickness, drug release characteristics, influence of solvent employed on diclofenac sodium release from microcapsules, surface characteristics. Diclofenac release from the microcapsules was, followed first order kinetics and influenced by the size of the microcapsules and the solvent employed in their preparation. Among the solvents employed chloroform was found to be more suitable for slow release of diclofenac from ethyl cellulose microcapsules.

Though ethyl cellulose microcapsules have been extensively studied for controlled release, no attempts were made to study the influence of solvents on drug release from the microcapsules. In a few reports the permeability coefficient of ethyl cellulose microcapsules prepared by different coacervation methods and relation ship between physical properties such as size and density on the permeability and drug release from the microcapsules was studied. The solvent employed in the preparation of microcapsules is likely to influence both the permeability and drug release from the microcapsules. In the present study the influence of three solvents employed in the preparation on drug release from the ethyl cellulose microcapsules was studied. Diclofenac sodium, which requires oral controlled release because of its short biological half-life of 2.0 h and gastrointestinal irritation if present in larger concentration was used as core in the microencapsulation.

MATERIALS AND METHODS

Ethyl cellulose with a viscosity of 14 CPS (5% w/w solution in 80:20 toluene:ethanol by weight at 25°) and containing not less than 46.5 % ethoxyl groups was provided by S. D. Fine Chemicals, Mumbai. Diclofenac sodium IP was provided by Natco Pharmaceuticals, Hyderabad. All solvents and reagents were of AR grade and procured from commercial sources. The spectrophotometer used was an Elico UV/Vis model.

Preparation of microcapsules:

Ethyl cellulose microcapsules of diclofenac sodium were prepared by an emulsion solvent evaporation method employing three solvents, chloroform, dichloromethane and ethyl acetate with coat:core ratio 3:7. The polymer (1.5 g) was dissolved in the polymer solvent (25 ml) to form a homogeneous polymer solution. Core material, diclofenac sodium (1.4 g) was added to the polymer solution (10 ml) and mixed thoroughly. The resulting mixture was then added in a thin stream to 100 ml of 0.1N HCl containing sodium CMC (0.5% w/v) contained in a 450 ml beaker while stirring at 200 rpm to emulsify the added droplets. A Remi medium
TABLE 1: DICLOFENAC CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE RATE CONSTANT OF EC MICROCAPSULES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chloroform</th>
<th>Solvent employed</th>
<th>Solvent employed</th>
<th>Solvent employed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10/16 size</td>
<td>22/44 size</td>
<td>10/16 size</td>
</tr>
<tr>
<td>Percent drug content</td>
<td>66.8</td>
<td>66.37</td>
<td>66.0</td>
<td>66.48</td>
</tr>
<tr>
<td>(1.07)*</td>
<td>(0.5)</td>
<td>(1.94)</td>
<td>(1.19)</td>
<td>(0.58)</td>
</tr>
<tr>
<td>Microencapsulation efficiency (%)</td>
<td>95.43</td>
<td>94.94</td>
<td>94.13</td>
<td>93.24</td>
</tr>
<tr>
<td></td>
<td>(1.16)</td>
<td>(1.23)</td>
<td>(0.72)</td>
<td>(1.02)</td>
</tr>
<tr>
<td>Wall thickness (μ)</td>
<td>169.4</td>
<td>67.62</td>
<td>173.19</td>
<td>67.41</td>
</tr>
<tr>
<td></td>
<td>(3.9)</td>
<td>(3.48)</td>
<td>(1.7)</td>
<td>(4.47)</td>
</tr>
<tr>
<td>Release rate constant</td>
<td>0.141</td>
<td>0.235</td>
<td>0.204</td>
<td>0.31</td>
</tr>
<tr>
<td>(k_r/h)</td>
<td>(3.6)</td>
<td>(3.48)</td>
<td>(1.7)</td>
<td>(4.47)</td>
</tr>
</tbody>
</table>

*Figures in parentheses are coefficient of variation (CV) values.

duty stirrer with speedometer (Model RQT 124) was used for stirring. Stirring was continued for 5 min to disperse the added mixture as fine droplets. The dispersion was transferred to a Buchner flask and stirring was continued with magnetic stirrer. The solvent was then removed by evaporation at RT (28°C) under reduced pressure (8 in. Hg Abs) to produce spherical microcapsules. The microcapsules were collected by decantation and washed with water. The product was then dried at 40°C for 4 h to obtain discrete microcapsules.

Characterization of microcapsules:

For size distribution analysis, different sizes in a batch were separated by sieving, using a range of standard sieves. The amount retained on different sieves were weighed. Microencapsulation efficiency was calculated using the formula, microencapsulation efficiency = (estimated percent drug content/theoretical percent drug content)X100. The microencapsulation efficiency values are reported in Table 1. Wall thickness of microcapsules was determined by the method of Luu et al using the equation, h = r(1-P)d_1/3[Pd_2 + (1-P)d_1], where h is the wall thickness; r is the arithmetic mean radius of the microcapsules; d_1 is the density of the core material; d_2 is the density of the coat material; P is the proportion of medicament in the microcapsules. The wall thickness of different microcapsules is reported in Table 1. The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S430, UK). For SEM, the microcapsules were mounted directly on to the SEM sample stab, using double - sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr). The SEM photograph of microcapsules is represented in fig. 1.

Estimation of diclofenac sodium:

Diclofenac sodium content in the microcapsules was calculated by an UV spectrophotometric method based on the measurement of absorbance at 285 nm. The method was validated for linearity, accuracy and precision. The method obeyed Beer’s law in the concentration range 0-10 μg/ml. When a standard drug solution assayed repeatedly (n=6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.8% and 1.2%, respectively. A sample of microcapsules equivalent to 100 mg of diclofenac sodium were dissolved in 25 ml ethyl alcohol and the volume was adjusted to 100 ml using buffer of pH 7.4. The solution was suitably diluted and the absorbance was measured at 285 nm. The amount of diclofenac sodium estimated from different samples and sizes are depicted in Table 1.

Drug release studies:

Release of diclofenac sodium from the microcapsules of size 10/16 and 22/44 was studied in phosphate buffer of pH 7.4 (900 ml) using an USP XXXIII dissolution rate test apparatus (M/s. Campbell Electronics, Mumbai) with a paddle stirrer at 100 rpm and at 37±0.5°C. A sample of microcapsules equivalent to 100 mg of diclofenac sodium were used in each test. Samples were withdrawn through a filter (0.45 μ) at different time intervals and were assayed at 285 nm for diclofenac sodium using an Elico double beam UV spectrophotometer. The drug release experiments were
Fig. 1: SEM Photographs of EC microcapsules.
The microcapsules formulated with chloroform (a), dichloromethane (b) and ethyl acetate (c). The microcapsules are spherical with smooth surface.

conducted in triplicate. The dissolution profiles are shown in fig. 2.

RESULTS AND DISCUSSION

Ethyl cellulose microcapsules containing diclofenac sodium were prepared by an emulsion solvent evaporation method employing three solvents for the polymer namely chloroform, dichloro methane, ethyl acetate. All the microcapsules prepared were found to be discrete, spherical and free flowing. The sizes could be separated and a more uniform size of microcapsules could readily be obtained. The size analysis of different microcapsules showed that generally about 17%, 30% and 40% were in the size
range of $-10+16$ (1350), $-16+22$ (855) and $-22+44$ (32.5) mesh size respectively. A lognormal size distribution of the microcapsules was observed in all the batches prepared. Low CV (<2.0) in the percent drug content indicated uniformity of drug content in each batch of microcapsules (Table 1). Drug content of the microcapsules was found to be the same in different sieve fractions. As the microcapsules are spherical the wall thickness of the microcapsules was calculated as per Luu et al. SEM photographs (fig. 1) indicated that the microcapsules are discrete, nearly spherical and covered with continuous coating of the polymer.

Diclofenac release from the pure drug and from the microcapsules was studied in phosphate buffer of pH 7.4 for a period of 12 h. Diclofenac release from the pure drug was found to be with in 5 minutes where as diclofenac release from the microcapsules was slow and spread over an extended period of time. Release followed first order kinetics with r' greater than 0.956 and the corresponding release rates ($k_r$) are given in Table 1. To analyze the mechanism of release of drug from these microcapsules the equation, $Q=kt^n$ was used, where $Q$ is the percentage of drug released; $t$ is the release time; $k$ is a constant incorporating structural and geometric characteristics of the release device, and $n$ is the release exponent indicative of the mechanism of release. When $n$ approximates to 0.5, a fickian/diffusion control release is implied, where $0.5<n<1$ non fickian transport and $n=1$ for zero order release. The drug release mechanism from these microcapsules was diffusion controlled as $n$ value approaches to 0.5. The drug release depended on size of the microcapsules and the solvent employed for the polymer in their preparation (fig. 2).

The solvent employed has significant influence on diclofenac release from the microcapsules in both the sizes studied. Microcapsules prepared employing ethyl acetate gave relatively fast release and those prepared employing chloroform gave slow release spread over 12 h. Large sized spherical microcapsules of ethyl cellulose containing diclofenac sodium as core could be prepared by an emulsion solvent evaporation method. Drug release from the microcapsules can be controlled by the size of the microcapsules and the solvent employed in the preparation of microcapsules. Chloroform was found to be a promising solvent for preparing ethyl cellulose microcapsules for controlled release as slow, controlled and complete release of diclofenac over a period of 12 h was observed with these microcapsules.

REFERENCES: