ABSTRACT

The objective of the study is to evaluate olibanum resin, a natural lipophilic polymer for its application as microencapsulating agent and to prepare and evaluate olibanum resin-coated microcapsules of carbamazepine for controlled release. Controlled release formulations are needed for carbamazepine to avoid erratic absorption, fluctuating plasma concentrations and associated toxicity and patient compliance. Olibanum resin coated microcapsules of carbamazepine were prepared by emulsification-solvent evaporation method and the microcapsules were evaluated for controlled release. The resin coated microcapsules prepared are spherical, discrete, free flowing and were of multinucleate and monolithic type. Microencapsulation efficiency was in the range 99.0-102.5 %. Carbamazepine release from the microcapsules was slow over 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules. The drug release was by non-fickian diffusion when the drug release was slower as in the case of all microcapsules.
Good linear relationship was observed between wall thickness of the microcapsules and release rate. Olibanum resin was found suitable as a new microencapsulating agent and the resin coated microcapsules exhibited good controlled release characteristics. Carbamazepine release from the olibanum resin coated microcapsules, OMC3 (size 20/35) was similar to that from Trigretal CR tablets, a commercial controlled release formulation of carbamazepine.

**Key Words:** Olibanum resin, Carbamazepine, Microencapsulation, Controlled release.

**INTRODUCTION:**
Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of the activity and targeting the delivery of the drug to the tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Microencapsulation and microcapsules are widely accepted for controlled release. Polymers and release retarding materials used as coat plays vital role in controlling the drug release from the microcapsules. Microencapsulation by various polymers and their applications are described in various standard text books\(^1\), \(^2\). Though a variety of polymeric materials are available to serve as release retarding coat materials, there is a continued need to develop new, safe and effective release retarding coat materials for microencapsulation.

Carbamazepine is a widely used anticonvulsant drug belonging to the chemical category of iminostilbenes. It is used in doses of 100, 200, 300 and 400 mg, 3 to 4 times a day. It is absorbed slowly and erratically after oral administration\(^3\). This erratic absorption may lead to fluctuations in plasma concentrations, which are responsible for its side effects and neurotoxicity\(^4\). Hence controlled release formulations are needed for carbamazepine to avoid erratic absorption, fluctuating plasma concentrations and associated toxicity. Controlled release formulations also improve patient compliance in the long-term therapy with carbamazepine.

Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists\(^6\) chiefly an acid resin (50-60 %), gum (30-36 %) and volatile oil (3-8 %). The resin consists\(^7\) mainly a resin acid
(boswellic acid) and a resene (olibanoresene) in equal proportions. Ether soluble resin extracted from olibanum exhibited excellent release retarding properties in microcapsules for controlled release due to its hydrophobic water repellent properties. Preliminary studies indicated that the resin has good film forming property when dried from chloroform solution. The objective of the present work is to evaluate the resin extracted from the olibanum as coating material in microencapsulation for obtaining controlled release of carbamazepine. Studies were carried out on microencapsulation of carbamazepine by the olibanum resin and evaluation of the resin-coated microcapsules of carbamazepine for controlled drug release.

EXPERIMENTAL

Carbamazepine was a gift sample from M/s Ranbaxy Research Labs, Gurgaon, India. Sodium carboxy methyl cellulose (high viscosity grade 1500-3000 cps) and chloroform AR (Merck) were procured from commercial sources. Olibanum gum (Boswellia serrata, Roxburgh) was procured from M/s Girijan Co-operative Corporation, Visakhapatnam, India. All other materials used were of pharmacopoeial grade.

Preparation of olibanum resin:
Olibanum resin used as coat material was extracted from olibanum gum in the laboratory as follows: Powdered olibanum (10 g) was extracted repeatedly with 4 × 50 mL of ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40 °C. The dried mass obtained was powdered and passed through mesh no. 120.

Preparation of microcapsules:
An emulsification-solvent evaporation method was tried to prepare olibanum resin-coated microcapsules containing carbamazepine. Olibanum resin (2 g) was dissolved in chloroform (100 mL) to form a homogenous polymer solution. Core material, carbamazepine (0.8 g) was added to the polymer solution (10 mL) and mixed thoroughly. The resulting mixture was then added in a thin stream to 200 mL of an aqueous mucilage of sodium CMC (0.5 %) contained in a 500 mL beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A
medium duty stirrer with speed meter (Remi, model RQT 124) was used for stirring. The solvent was then removed by continuous stirring at room temperature (28°C) for 3 h to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules. Different proportions of core to coat materials namely 1:19 (OMC1), 1:9 (OMC2), 2:8 (OMC3) and 7:3 (OMC4) were used to prepare microcapsules with varying coat thickness.

**Estimation of carbamazepine:**
Carbamazepine content of the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance at 284 nm in water. The method was validated for linearity, precision and accuracy. The method obeyed Beer's law in the concentration range 1-10 μg/mL. When a standard drug solution was assayed repeatedly (n = 6), the mean error (accuracy) and relative standard deviation precision) were found to be 0.6 and 0.4 %, respectively. No interference from the excipients used was observed.

**Characterization of microcapsules**

**Size analysis:**
For size distribution analysis, different sizes in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed.

**Microencapsulation efficiency:**
Microencapsulation efficiency was calculated using the equation:

\[
\text{Microencapsulation Efficiency} = \frac{\text{Estimated percent drug content in microcapsules}}{\text{Theoretical percent drug content in microcapsules}} \times 100
\]

**Scanning electron microscopy:**
The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S340, UK). Microcapsules were mounted directly on to the SEM sample stub, using double sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

**Wall thickness:**
Assuming the microcapsules to be uniform and spherical, wall thickness of the microcapsules was determined by the method of Luu et al.\textsuperscript{9} using the equation:

\[
h = \frac{\bar{r}(1-p)d_1}{3[pd_2 + (1-p)d_1]}
\]
Where $h =$ wall thickness, $r =$ arithmetic mean radius of the microcapsules, $d_1 =$ density of the core material, $d_2 =$ density of the coat material and ‘$p$’ = proportion of the medicament in the microcapsules. Mean radius of the microcapsules was determined by sieving. Densities were measured using petroleum ether as a displacement fluid at room temperature (28ºC).

**Drug release study:**

Drug release from the microcapsules was studied using 8-Station Dissolution Rate Test Apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at a temperature of 37 ± 1 ºC. Water (900 mL) was used as dissolution fluid.

A sample of microcapsules equivalent to 100 mg of carbamazepine were used in each test. A 5 mL aliquot of dissolution medium was withdrawn through a filter (0.45 μ) at different time intervals and assayed spectrophotometrically by measuring absorbance at 284 nm. All drug release experiments were conducted in triplicate.

**RESULTS AND DISCUSSION**

An emulsification-solvent evaporation method was developed for microencapsulation of carbamazepine by the olibanum resin. The method involves emulsification of the polymer (resin) solution in chloroform containing the dispersed drug particles in an immiscible liquid medium (0.5 % w/v solution of sodium CMC) as microdroplets, followed by removal of solvent chloroform by continuous stirring to form rigid microcapsules. Resin-coated microcapsules of carbamazepine could be prepared by emulsification-solvent evaporation method. The microcapsules were found to be discrete, spherical and free flowing. The nature of the method of preparation indicated that the microcapsules were of multinucleate and monolithic type. SEM (Fig. 1) indicated that the microcapsules were spherical with smooth surface and completely covered with the polymer (resin) coat. The sizes could be separated by sieving and a more uniform size range of microcapsules could readily be obtained. The sieve analysis of different microcapsules showed that a large proportion of microcapsules were in the size range 20/35 (63.76 %) mesh. Low
coefficient of variation in per cent drug content (< 1.0 %) indicated uniformity of drug content in each batch of microcapsules (Table 2). The microencapsulation efficiency was in the range 99.0-102.5%. Drug content of the microcapsules was found to be the same in different sieve fractions. As the microcapsules are spherical, the theoretical mean thickness of the wall that surrounds the core particles in the microcapsules was calculated as described by Luu et al. Microcapsules prepared with various ratios of core:coat were found to have different wall thickness. Smaller microcapsules have thinner walls.

Carbamazepine release from the microcapsules was studied in water (900 mL). Carbamazepine release from the microcapsules was slow and spread over a period of more than 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules. The release data were analyzed as per zero order, first order, Higuchi and Peppas equation models. The correlation coefficient ($r^2$) values observed in fitting the release data to various kinetic models are given in Table 3.

The analysis of release data as per zero and first order kinetics models indicated that carbamazepine release from the microcapsules of size 20/35 followed zero order kinetics. Correlation coefficient ($r^2$) values were higher in the zero order model than those in the first order model with these microcapsules (Table 3). When the release data were analysed as per the Peppas equation, the release exponent (n) was in the range of 0.530 - 0.705 in the case of all microcapsules of size 20/35 indicating that the release mechanism from these microcapsules was by non- Fickian diffusion. Plots of percent released vs square root of time were found to be linear ( $r^2 > 0.964$) indicating that the drug release from the microcapsules was diffusion controlled.

As the proportion of the coat was increased, carbamazepine release rate was decreased. Smaller microcapsules gave higher release rates due to increased surface area. A good linear relationship was observed between wall thickness of the microcapsules and release rate ($K_0$ or $K_1$) and $T_{50}$ shown in Fig. 3,4 and 5. For comparison, carbamazepine release from Trigrital CR
tablets, a commercial controlled release formulation of carbamazepine was also studied. Olibanum resin-coated microcapsules, OMC3 (size 20/35) gave a release profile similar to that of the commercial controlled release product tested.

Hence, carbamazepine extended release tablets are official in USP30 for which a release of 10-35% in 3 h; 35-65% in 6 h; 65-90% in 12 h and not less than 75% in 24 h is prescribed. A comparison of drug release profiles of various olibanum resin coated microcapsules prepared with the official release specification indicated that the microcapsules OMC3 and OMC4 of size 20/35 gave drug release profiles fulfilling the official specification. Hence, olibanum resin coated microcapsules are considered as good sustained release formulations to provide extended release of carbamazepine over 24 h.

**Conclusion**

(i) Spherical olibanum resin coated microcapsules of carbamazepine could be prepared by the emulsification-solvent evaporation method developed. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely. (ii) Microencapsulation efficiency was in the range of 99.0-102.5%. (iii) Carbamazepine release from the olibanum resin-coated microcapsules was slow and extended over 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was by non-fickian diffusion mechanism. (iv) A good linear relationship was observed between wall thickness of the microcapsules and release rate. (v) Carbamazepine release from olibanum resin coated microcapsules (size 20/35) was similar to that from Trigrital CR tablets, a commercial controlled release formulation of carbamazepine. (vi) Olibanum resin was found suitable as a new microencapsulating agent and the olibanum resin coated microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of carbamazepine. (vii) Olibanum is reported as non-toxic\(^1\) and since it is of natural origin, it is biocompatible and cheaper.
Table 1: List of Olibanum Microcapsules Prepared

<table>
<thead>
<tr>
<th>S.No</th>
<th>Core</th>
<th>Core: Coat ratio</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbamazepine</td>
<td>19:1</td>
<td>OMC1</td>
</tr>
<tr>
<td>2</td>
<td>Carbamazepine</td>
<td>9:1</td>
<td>OMC2</td>
</tr>
<tr>
<td>3</td>
<td>Carbamazepine</td>
<td>8:2</td>
<td>OMC3</td>
</tr>
<tr>
<td>4</td>
<td>Carbamazepine</td>
<td>7:3</td>
<td>OMC4</td>
</tr>
</tbody>
</table>

Table 2: Drug content, Microencapsulation efficiency, Wall Thickness and Release Characteristics of Carbamazepine Microcapsules Prepared Employing Various Polymers

<table>
<thead>
<tr>
<th>Microcapsule (Coat : Core)</th>
<th>Drug content (%)</th>
<th>Wall Thickness (µm)</th>
<th>Microencapsulation efficiency (%)</th>
<th>T_{50} (h)</th>
<th>T_{90} (h)</th>
<th>K_{0} (mg/h)</th>
<th>K_{1} (h^{-1})</th>
<th>‘n’ in Peppas equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMC1(1:19)</td>
<td>95.07 (0.19)*</td>
<td>10.5</td>
<td>100.0</td>
<td>4.0</td>
<td>11.2</td>
<td>6.999</td>
<td>0.2346</td>
<td>0.563</td>
</tr>
<tr>
<td>OMC2(2:9)</td>
<td>90.60 (0.57)</td>
<td>16.2</td>
<td>100.6</td>
<td>4.2</td>
<td>11.7</td>
<td>6.042</td>
<td>0.1841</td>
<td>0.566</td>
</tr>
<tr>
<td>OMC3(2:8)</td>
<td>82.00 (1.0)</td>
<td>18.5</td>
<td>102.5</td>
<td>6.3</td>
<td>15.4</td>
<td>5.652</td>
<td>0.1473</td>
<td>0.585</td>
</tr>
<tr>
<td>OMC4(3:7)</td>
<td>69.30 (0.43)</td>
<td>24.5</td>
<td>99.0</td>
<td>9.2</td>
<td>20.2</td>
<td>4.590</td>
<td>0.1036</td>
<td>0.705</td>
</tr>
</tbody>
</table>

*Figures in parentheses are Coefficient Variation values

Table 3: Correlation Coefficient (r^2) Values in the Analysis of Release Data Olibanum Resin Coated Microcapsules of Carbamazepine as per Various Kinetic Models

<table>
<thead>
<tr>
<th>Microcapsules</th>
<th>Size</th>
<th>Correlation coefficient (r^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Zero order</td>
</tr>
<tr>
<td>OMC 1</td>
<td>20/35</td>
<td>0.956</td>
</tr>
<tr>
<td>OMC 2</td>
<td></td>
<td>0.942</td>
</tr>
<tr>
<td>OMC 3</td>
<td></td>
<td>0.973</td>
</tr>
<tr>
<td>OMC 4</td>
<td></td>
<td>0.976</td>
</tr>
</tbody>
</table>
Fig. 1. SEM of olibanum microcapsules, OMC2 (size 20/35) of carbamazepine

Fig 2: Release Profiles of Olibanum Resin Coated Microcapsules of Carbamazepine

Fig 3: Relationship between Wall thickness and Release Rate (K_o) for Olibanum Resin Coated Microcapsules of Carbamazepine (Size 20/35)
**Fig 4.** Relationship between Wall thickness and Release Rate ($K_1$) for Olibanum Resin Coated Microcapsules of Carbamazepine (Size 20/35)

**Fig 5:** Relationship between Wall thickness and $T_{50}$ for Olibanum Resin Coated Microcapsules of Carbamazepine (Size 20/35/)

**REFERENCES**


