Formulation and Physico-Chemical Evaluation of Ethylcellulose Microspheres Containing Etodolac

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Abstract—The ethylcellulose microspheres containing etodolac was prepared by emulsion solvent evaporation technique. The effect of increase in polymer concentration in various parameters like particle size, drug content, percentage yield, entrapment efficiency and in vitro release profile were studied. The entrapment efficiency and the mean particle size of the microspheres were found to be proportionately increasing with the polymer ratio. The in vitro release profile of the formulation with drug polymer ratio of 1:2 (F3) was found to be ideal as the release was consistent and complete. It released about 98.03% of the drug from the microspheres at the end of 12 hours. Thus the ethylcellulose microspheres of etodolac (F3) was capable of producing controlled release of drug over 12 hrs is expected to reduces the frequency of dosing and total drug required for the treatment.

Keywords— Etodolac, microspheres, ethylcellulose, controlled release.

I. INTRODUCTION

ETODOLAC is a non-steroidal anti-inflammatory drug (NSAID) with potent analgesic and anti-arthritis properties. It is widely used in the treatment of osteoarthritis, rheumatoid arthritis, ankylosis, and spondylitis and in the alleviation of postoperative pain. It is a racemic mixture of (+)S and (-)R-enantiomers belonging to pyranocarboxylic acid group of NSAIDs [1]. The inhibition of the enzyme cyclooxygenase, that synthesizes prostaglandins results in low concentrations of prostaglandins and thus the conditions like inflammation, pain and fever are reduced [2]. The antipyretic effect may occur by central action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat loss [3]. The total daily dose of this drug for acute pain is up to 1000 mg, given as 200-400 mg every 6 to 8 hours. Thus, development of a consistent controlled release system of etodolac, will logically help to reduce the dosing frequency and thereby reducing the adverse effects.

Microspheres are small particles with 1-1000 micrometer size range commonly used as carriers for drugs and other therapeutic agents. The term microspheres describe a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles [4]. A wide range of polymers are used, natural or semi-synthetic polysaccharides, such as cellulose derivatives, play an important role in microencapsulation processes [4]. Ethylcellulose (EC) a biocompatible and water insoluble polymer that has been frequently used in the preparation of micro and nano capsules [5, 6]. Thus, the main aim of the present study is to develop microsphere delivery system of Etodolac with ethylcellulose and to explore the effect of concentration of polymer on the production yield, drug loading, encapsulation efficacy, particle size, surface morphology and in-vitro drug release characteristics.

II. MATERIALS AND METHODS

Materials

Etodolac was received as a gift sample from Kreative Organics (Pvt) Ltd., Hyderabad, India. Ethylcellulose was purchased from Indian Research Chemicals, Chennai, India. All other chemicals and solvents were of analytical grade and were used without any purification.

Methods

A. Preparation Of Microspheres

Ethylcellulose microspheres containing etodolac (EMEC) were prepared by emulsion solvent evaporation technique [7]. The method involves the preparation of o/w primary emulsion of drug and polymer. The resulting organic phase was added to pre heated external phase (aqueous phase 100ml) consisting of 500mg of PVA. The primary emulsion was prepared by dissolving accurately weighed quantity of polymer in dichloromethane and the drug was separately dissolve in an organic solvent Ethanol with required quantity, then the organic phase was added slowly to the external phase with
constant stirring using propeller at 1500 rpm. The formed microspheres were collected by filtering and washed with distilled water, and dried at room temperature. Four formulations designated as F1, F2, F3 and F4 with drug: polymer concentrations of 1:1, 1:1.5, 1:2 and 1:3 respectively, were prepared.

**B. Morphological studies and particle size analysis**

To study the external morphology, air dried microspheres were subjected for scanning electron microscopy (SEM) [8] operating at 20kv. The samples are mounted on a metal stub with double adhesive type and coated with platinum under vacuum.

The particle size of the microspheres is determined by optical microscopy method [9]. The eye piece is calibrated using the stage piece. The minute quantity of microspheres was suspended in the glycerin and the particle size of the 100 microspheres was determined.

**C. Percentage Yield**

Microspheres were dried at room temperature and then weighed. The percentage yield [10] of microspheres prepared is calculated using formula (1)

\[
\text{Yield(%) = \frac{\text{Weight of microparticles}}{\text{Total expected weight of drug and polymer}} \times 100} \quad (1)
\]

**D. Determination of drug content in microspheres**

Accurately weighed quantity of microspheres was added to 10 ml pH 6.8 phosphate buffer. The resultant mixture were kept in ultrasonic bath for 15 min. The solution was then filtered and the drug content was measured at 276 nm spectrophotometer (Shimadzu UV: VIS spectrophotometer) after suitable dilutions.

**E. Determination of drug loading capacity and entrapment efficiency of microspheres**

The loading capacity [10] of EMEC was estimated by using the formula (2)

\[
\text{Drug loading capacity (\%) = \frac{Q_m}{W_m} \times 100} \quad (2)
\]

Where, \(L\) = percentage of drug loading in the microspheres
\(Q_m\) = Quantity of drug present in weighed grams of microspheres
\(W_m\) = Weight of microspheres in grams

The amount of the drug entrapped in various formulations of microspheres were determined by using the formula (3)

\[
\text{Drug entrapment efficiency E (\%) = \frac{Q_m}{Q_t} \times 100} \quad (3)
\]

Where, \(E\) = percentage of entrapment of microspheres
\(Q_p\) = Percentage of drug loaded in the microspheres
\(Q_t\) = Quantity of drug added.

**F. In vitro drug release studies**

The in-vitro dissolution studies were carried out using Dissolution apparatus [LABINDIA DISSO 2000] in pH 6.8 up to 12 hours. A sample of microspheres equivalent to 50 mg of etodolac was placed in the dissolution medium. The dissolution medium was maintained at 37 ± 2°C. The shaft of the apparatus to which the basket is fixed was rotated at a speed of 100rpm. 5ml samples were withdrawn at predetermined time intervals and same volume of fresh medium was replaced into the basket. The dissolution was carried out for a period of 12 hours. The concentration of drug released was estimated by using UV spectrophotometer at 276nm. The percent of drug released at various time intervals was calculated and plotted against time.

**III. RESULTS AND DISCUSSION**

Four formulation of EMEC were prepared by emulsion solvent evaporation method. The dried microspheres were free flowing dull white in colour. The dried microspheres were stored in airtight containers and subjected for various physico-chemical evaluations.

**A. Morphological studies and particle size analysis**

The SEM analysis of various batches of EMEC was carried out. The study indicated that the surface of the microspheres were smooth and rigid. Few drug crystals were also observed in the field, which is an indicative of the presence of the unloaded free drug (Figure 1.(b)).

The microspheres were viewed under the optical microscope to study their properties and to perform the particle size analysis. In all the batches of formulations (F1-F4) the microspheres were found to be spherical and discrete. Mean particle size was determined by optical microscopy and the average particle size were calculated for each formulation in triplicate and the results are shown in figure 2. The mean particle size of the formulations F1, F2, F3 and F4 were 16.12±4.3, 19.28±6.8, 24.53±8.4 and 29.9±9.3µm, respectively. Increase of mean particle size with increase in polymer concentration was observed, which may be due to the fact that the increase in polymer concentration leads to a significant increase in the viscosity in a fixed volume of solvent, thus leading to an increase of the emulsion droplet size and finally a higher microsphere size.

**B. Percentage Yield and Percentage of Entrapment Efficiency**

The increase in concentration of EC had increased the entrapment efficiency of the drug and the results are shown in figure 3. The formulations F1, F2, F3 and F4 exhibited 67.2, 75.5, 83.7 and 92%, respectively. A significant increase in percentage yield was also observed with increase in the polymer ratio. The percentage yield of the EMEC formulations F1, F2, F3 and F4 were 45, 52, 56 and 60%, respectively. The increase in percentage yield and entrapment efficiency can be related to the increase in the particle size and this indicates drug is embedded in the matrix of EC.
Figure 1. Ethylcellulose microspheres containing etodolac (a) under light microscope (magnification 45x) and (b) under scanning electron microscope.

Figure 2. Mean particle size of etodolac loaded microspheres with varying concentrations of EC.

Figure 3. Increase in entrapment of etodolac in various formulations with increase in concentration of EC.

C. In vitro Release Studies

The in vitro release studies of the prepared microspheres were carried out by using dissolution test apparatus in phosphate buffer pH 6.8 for 12hrs and the results are represented graphically in figure 5. The formulations F1, F2, F3, and F4 released 79.16%, 65.07%, 48.35%, and 38.1% of drug at the end of 6th hour. Maximum drug release of 98.03% was indicated by the formulation F3 at the end of 12 hrs where as about 75.75% was only released by F4. This may be due to increased encapsulation of ethyl cellulose on the surface of microspheres which hinders the release of drug. The formulation F1 and F2 released about 98.19% and 98.88% at the end of 8 and 9 hours, respectively. Thus the release studies data suggests that the formulation F3 posses the controlled release characters.

This investigation indicates that EMEC can serve as a potential drug delivery system for controlled release of etodolac, but also for many other NSAIDs. However, further research is required to find out efficacy of EMEC in vivo.

IN VITRO DRUG RELEASE

Figure 4. In vitro release of etodolac from EC microspheres.
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REFERENCES


