**ABSTRACT**
The main objective of the present work was to prepare ibuprofen loaded ethyl cellulose microspheres by means of solvent evaporation technique to attain the sustained release of the drug. Three formulations were prepared (F1, F2, and F3) by altering drug to polymer ratio. The effect of polymer concentration upon product yield, entrapment efficiency, particle size and stability was studied. In vitro drug release studies were performed and compared for the sustained release nature of the formulation. Best results were obtained for F3 formulation with mean particle diameter of 1.4μm, entrapment efficiency of 50%, drug content of 93%. It was able to sustain the drug release up to 12 hours with a drug release rate of 94.8%.

**Keywords:** Ibuprofen, Ethyl Cellulose, Solvent Evaporation Method, Microspheres

**INTRODUCTION**
The concept of advanced drug delivery has been revolutionized. The studies have been made to lend patient derive maximum benefits of drug. The drug should be delivered to specific target sites at a rate and concentration that permit optimal therapeutic efficacy while reducing side effects to minimum. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres can be described as small particles (in 1-1000micrometer size range) for use as carriers of drugs and other therapeutic agents consisting of proteins or synthetic polymers which are of biodegradable in nature (Remington, 2006; Vyaas and Khur, 2006).

Ibuprofen is a non-steroidal anti-inflammatory drug, which possess analgesic and mild antipyretic action, because of its short half-life (1-3 hours) it was selected as model drug in this study (Saravanan et al., 2004). Its activity is more than indomethacin, naproxen and other NSAIDS. Ibuprofen reduce the inflammation by acting on cyclooxygenase and it inhibit the lipoxygenase pathway, which in turn decreases the production of leukotrienes by the leukocytes and the synovial cells. It also masks T cell suppressing the production of rheumatoïd factors. Most frequent adverse effects associated with ibuprofen are gastro intestinal disturbance; peptic ulceration and gastrointestinal bleeding. Site specific drug delivery of ibuprofen will reduce these toxicities considerably by maintaining a low and constant level of drug in the blood (Surendiran and Yuvaraj, 2010; Goodman and Gilmans, 2001). These sustained release microspheres may be produced by several methods utilizing emulsion system (oil-in-water, oil-in-oil, water-in-oil-in-water), as well as by spray drying. The common method used to produce microspheres is emulsion solvent evaporation method. This relatively simple method enables the entrapment of a wide range of hydrophobic drugs (Thompson, 2007; Abbaspour et al., 2008). Ethyl cellulose is non-biodegradable, bio-compatible, non-toxic synthetic polymer and widely used in oral and topical formulation (Ainley and Paul, 1994). The main objective of this work was to investigate the possibility of obtaining a sustained release formulation of ibuprofen microspheres by using ethyl cellulose in various drug and polymer ratios.

**MATERIALS AND METHODS**
Ibuprofen was obtained as a gift sample from Dr. reddy Labs. Ltd, Hyderabad. Ethyl cellulose was supplied from S.D Fine chemicals Ltd, Mumbai.

Method: preparation of ibuprofen microspheres:
Ethyl cellulose was taken and dissolved in chloroform to form a homogenous solution. Ibuprofen was added to the homogenous solution and mixed thoroughly. This dispersion was then added as a thin stream to 100ml of aqueous mucilage of 0.5% sodium cmc contained in a 250 ml beaker while being stirred at 700 rpm to emulsify the added dispersion as fine droplets. The solvent was removed by continuous stirring at room temperature for three hours to produce spherical microspheres. The microspheres formed were collected by filtration and washed repeatedly with distilled water. The product was then air dried.

Formulations

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug : polymer</th>
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<tbody>
<tr>
<td>F1</td>
<td>9:5</td>
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<tr>
<td>F2</td>
<td>9:6</td>
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<tr>
<td>F3</td>
<td>9:7</td>
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</tbody>
</table>

Characterization of Microspheres

1) Percentage Yield
The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula (Ziyaur et al., 2006).

\[
\text{Percentage yield} = \left(\frac{\text{the weight of microspheres}}{\text{the weight of polymer + drug}}\right) \times 100
\]

2) Drug Content
The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of phosphate buffer PH 7.2 in two necked round bottomed Flask. With the help of mechanical stirrer the dispersion was stirred for 3 hours and filtered. The UV absorbance of the filtrate was measured using a UV spectrometer at 221nm (Saravanan et al., 2004).

3) Entrapment Efficiency
The prepared formulations were examined for entrapment efficiency. 40mg of the prepared formulation was taken in equivalent quantity of 7.2 phosphate buffer. The suspension is ultra-centrifuged at 17240rpm for 40 minutes. The free concentration of the drug in the supernatant was measured spectrophotometrically. Entrapment efficiency is calculated by the following equation (Rakesh et al., 2012; Vyas and Khur, 2002).

\[
\% \text{ Entrapment efficiency} = \left(\frac{W-w}{W}\right) \times 100
\]

4) Invitro Drug release Study of Microsphere Formulations in Phosphate Buffer pH 7.2
The dissolution rate testing apparatus was employed to study the release of ibuprofen using phosphate buffer pH 7.2 as a dissolution medium. 50mg equivalent of ibuprofen containing ethyl cellulose microspheres was taken and dissolution test was being carried out at 50rpm maintained at 37\(^\circ\)c ± 0.5\(^\circ\)c. 5ml of sample were withdrawn at specific time interval for 24 hours. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometrically at 221nm. the same procedure was repeated for other formulations also.

5) Particle Size Analysis and Zeta Potential Measurement
The average particle size and size distribution of Ibuoprofen loaded microspheres was determined by dynamic light scattering (DLS), using Malvern Zeta Sizer. The Zeta potential (Surface Charge) which indicates the stability of the microspheres can be defined as electro kinetic potential that is determined by electrophoretic mobility. Sample was prepared by diluting with doubled distilled water and corresponding zeta potential measured using Malvern Zeta Sizer.

6) Determining the Size and Surface Morphology of the Microspheres
Suspension was made to obtain Photomicrographs of the ibuprofen loaded microspheres using the SEM Scanning Electron Microscopy is used to determine the shape, size and surface morphology of the microspheres.
RESULTS AND DISCUSSION

Percentage Yield

The percentage yield of the formulations F1, F2 and F3 was found to be 74.5%, 78.3% and 83.5% respectively. On comparison F3 formulation with 9:7 drug to polymer ratio was showing highest yield.

![Percentage yield of microspheres](image1.png)

**Figure 1** Percentage yield of Ibuprofen loaded microspheres

Drug Content

Drug content of F1, F2, F3 formulations was compared. On comparison F3 formulation was showing maximum drug content.

![Drug content of microspheres](image2.png)

**Figure 2**: Drug content of Ibuprofen loaded microspheres

Entrapment Efficiency

Entrapment efficiency of F1, F2, F3 formulations was found to be 27%, 40%,50% respectively. Among all F3 formulation was showing highest entrapment efficiency (50%).

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Zeta Potential
Zeta potential of the prepared ibuprofen loaded microspheres was measured using zeta meter. F3 formulation was showing highest stability bearing a zeta potential value of –23.5 mV when compared with that of other two formulations.

SEM: The prepared microspheres were found to be spherical in shape Figure 5.
Research Article

Invitro Drug release Studies
Invitro drug release data was depicted in figure no. 6. From the figure the %of drug release for F1, F2, and F3 was found to be 97%, 99% and 94.8% respectively in a time period of 12 hours.

The drug release data was fitted into various kinetic models to know the order of drug release, mode and pattern of drug release.
Figure 7: Zero order plot of F1, F2 and F3 formulations

Figure 8: First order plot of F1, F2 and F3 formulations
Discussion

Ibuprofen loaded ethyl cellulose microspheres were prepared by solvent evaporation technique. Three formulations were prepared by varying the concentration of polymer. The drug to polymer ratio was maintained as 9:5, 9:6, 9:7 for formulation 1, 2 and 3 respectively. The effect of polymer concentration upon percentage yield, drug content, and entrapment efficiency was studied. Dissolution studies were compared to determine the best sustained release formulation.

The size of the prepared microspheres was determined by means of SEM. The particles were found spherical in shape. On comparing the mean particle diameters of F1, F2, and F3 formulations F1 was showing the minimum particle diameter of 1.9um. This was mainly because of the less polymer concentration in formulation1. When the polymer concentration was increased from F1to F3, the entrapment efficiency was also increased, particle diameter was also increased with increase enhancement.
in entrapment efficiency, product yield, drug content, entrapment efficiency were found to be higher in F3 formulation. This may be because of enhanced polymer concentration in F3. When invitro dissolution data was compared, among the three formulations maximum drug release was observed in formulation 1. As the particle size of the formulation 1 was less, drug release was found to be high. Small particles will exhibit higher surface area hence drug release will be more. Burst release can be seen in formulation 2. Where as formulation 3 shows sustained release up to 12 hours. Only 94% of the drug has been released from F3 in a time period of 12 hours. Where as F1, F2 shows 97% and 99% drug release with initial burst release in the same time period of 12 hours respectively. This data reveals that by increasing the polymer concentration sustained release can be obtained with less initial burst.

The invitro release data of ibuprofen was processed to understand the linear relationship which follows first order of kinetics because it shows highest regression value of 0.958 and then followed by higuchi and zero order. According to Korsmeyer-Peppas equation, the value of n is 0.701 which is more than 0.5 which indicates it follows non-fickian diffusion

**Conclusion**

F3 formulation with increase in polymer concentration was showing promising results with mean particle diameter 1.4μm and entrapment efficiency of 50%. F3 formulation was able to sustain the drug release for more than 12 hours. Based on these results it can be concluded that F3 formulation with 9:7 drug to polymer ratio was considered as best formulation for the preparation of ibuprofen loaded ethyl cellulose microspheres.

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