Comparative evaluation of Ethambutol HCL microspheres prepared by different methods

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ABSTRACT

Ethambutol HCl microspheres were prepared by emulsion and spray drying methods using non-biodegradable but biocompatible ethyl cellulose as a polymer in core: coat ratios of 1:1, 1:2, 1:3 and 1:4. Microspheres were evaluated for drug content, in-vitro drug release and particle size analysis. Encapsulation efficiency for emulsion method and spray drying method were found to be 40-70% and 80-92% respectively. Surface morphology of microspheres was studied by SEM. Optimized formula was characterized by FTIR and DSC analysis for any possible drug polymer interaction. The in-vitro release profiles from microspheres of different polymer-drug ratios were applied on various kinetic models. The best fit with the highest correlation coefficient was observed in higuchi model, indicating diffusion-controlled principle. The n value varies between 0.23-0.54 obtained from korsemeyer-peppas model confirmed that the mechanism of drug release was diffusion controlled.

Key words: Ethambutol, microspheres, spray drying

INTRODUCTION

Microencapsulation is defined as the application of a thin coating to individual core materials that have an arbitrary particle size range from 5 to 5000 nm. It is used to modify and retard drug release. Ethylcellulose, a non-biodegradable and biocompatible polymer, is an extensively studied encapsulating material for the controlled release of pharmaceuticals. Several researchers have investigated the utilization of ethylcellulose as a polymer to microencapsulate drug by emulsion solvent evaporation technique. Ethambutol HCL is a potent first line anti tubercular drug, rapidly absorbed from GIT and. Peak plasma concentration is achieved within 2-4 hours. Ethambutol HCL has the half life of 3-4 hours, the objective of present study is to formulate and evaluate Ethambutol HCL microspheres for oral sustained drug delivery. Here comparison is made between methods of preparation of microspheres.

MATERIALS AND METHODS

Ethambutol HCL was a gift sample from M/s Micro Labs, Bangalore. Ethylcellulose (14 cps viscosity grade), chloroform (Lobachem), ethanol (lobachem), sodium CMC were also used in the study. All the reagents and solvents used were of analytical grade satisfying pharmacopeial standards.

1) Method of preparation of microspheres:

Emulsion method:

All the formulations were prepared by emulsification method with different core coat ratios like 1:1, 1:2, 1:3 and 1:4. The polymer and drug were dissolved in the chloroform, and mixed thoroughly to form homogenous solution. The resulting mixture was then added in thin stream to 0.1N HCL containing sodium CMC (0.5% w/v) in a beaker while stirring (Remi RQT 124) at 500 rpm to emulsify the added droplets. Stirring was continued for 2 to 3 hrs until chloroform gets evaporated and produces spherical microspheres. The microspheres were collected, and washed with water. The product was then dried at 40° in hot air oven for 24 hrs.

Spray drying method:

All the formulations were prepared by spray dry method with different core coat ratios like 1:1, 1:2, 1:3 and 1:4. Feed solution were prepared by dissolving the polymer in the solvent using magnetic stirrers and then adding the drug to this polymer solution and stirred to dissolve it to form clear homogenous solution. This solution was used as the feed solution for spray drying. The various optimized condition used for preparation of microspheres were inlet temperature 45°C, outlet temperature 40°C, aspiration 50 and flow rate 1.25ml/min.

2) % Encapsulation efficiency:

% Encapsulation efficiency is calculated from the below formula

Encapsulation efficiency = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100

3) Scanning electron microscopy (SEM):

The surface morphology of the microspheres was examined using scanning electron microscopy (SEM XL series, XI 30 ESEM, Phillips).

4) Fourier-transformation infrared (FTIR) spectroscopy:

The drug-polymer interactions were studied by FTIR spectrometer (Shimadzu 8400 S.)

5) Differential Scanning Calorimetry (DSC):

DSC thermograms were obtained using an automatic thermal analyzer system (Perkins Elmer DSC Instrument, Japan). DSC analysis of pure Ethambutol HCL, and drug loaded microspheres were carried out.

5) Particle size analysis:

Particle size analysis of was carried out using laser channel beam (Anskemid CIS-50). The range of the particles used for scanning is 1nm to 150 µm. The particles were suspended in liquid paraffin to give a10\(^9\) particles per/ml with a SNF value of 1.

1) In vitro drug release study:

The in vitro drug release from microspheres were
Table 1: Formulation details of microspheres of Ethambutol HCl (emulsion method)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>AB1</th>
<th>AB2</th>
<th>AB3</th>
<th>AB4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol HCl (core) mg</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Ethylcellulose (coat) mg</td>
<td>200</td>
<td>400</td>
<td>600</td>
<td>800</td>
</tr>
<tr>
<td>Sodium CMC (%w/v) in 0.1 N HCl</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Chloroform (ml)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 2: Formulation details of microspheres of Ethambutol HCl (spray drying method)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>ABC1</th>
<th>ABC2</th>
<th>ABC3</th>
<th>ABC4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol HCl (core) mg</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Ethylcellulose (coat) mg</td>
<td>200</td>
<td>400</td>
<td>600</td>
<td>800</td>
</tr>
<tr>
<td>Ethanol (ml)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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</tbody>
</table>

Table 3: % encapsulation efficiency and % drug release (at 420 mins)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>AB-1</th>
<th>AB-2</th>
<th>AB-3</th>
<th>AB-4</th>
<th>ABC-1</th>
<th>ABC-2</th>
<th>ABC-3</th>
<th>ABC-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>% drug release (DR)</td>
<td>43.56</td>
<td>50.26</td>
<td>43.67</td>
<td>31.16</td>
<td>33.39</td>
<td>38.09</td>
<td>31.05</td>
<td>27.47</td>
</tr>
<tr>
<td>Encapsulation efficiency (%)</td>
<td>38</td>
<td>44</td>
<td>48</td>
<td>53</td>
<td>29</td>
<td>33</td>
<td>3942</td>
<td></td>
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</tbody>
</table>

Table 4: Mathematical models fitting of obtained drug release data

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero Order</th>
<th>Higuchi</th>
<th>Korsmeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r²</td>
<td>K₀</td>
<td>r²</td>
</tr>
<tr>
<td>AB-1</td>
<td>0.852</td>
<td>22.01</td>
<td>0.932</td>
</tr>
<tr>
<td>AB-2</td>
<td>0.960</td>
<td>22.35</td>
<td>0.919</td>
</tr>
<tr>
<td>AB-3</td>
<td>0.913</td>
<td>22.25</td>
<td>0.849</td>
</tr>
<tr>
<td>AB-4</td>
<td>0.995</td>
<td>10.11</td>
<td>0.969</td>
</tr>
<tr>
<td>ABC-1</td>
<td>0.781</td>
<td>15.89</td>
<td>0.933</td>
</tr>
<tr>
<td>ABC-2</td>
<td>0.853</td>
<td>14.97</td>
<td>0.912</td>
</tr>
<tr>
<td>ABC-3</td>
<td>0.854</td>
<td>11.68</td>
<td>0.916</td>
</tr>
<tr>
<td>ABC-4</td>
<td>0.876</td>
<td>8.47</td>
<td>0.947</td>
</tr>
</tbody>
</table>

Figure 1: SEM images of microspheres prepared by emulsion method

Figure 2: SEM images of microspheres prepared by spray drying method

Figure 3: In-vitro drug release profile of microspheres (emulsion method)

Figure 4: In-vitro drug release profile of microspheres (spray drying method)
**Thermal Analysis Result**

**Figure: 5 DSC spectra of pure Ethambutol HCl**

**Figure: 6 DSC spectra of microspheres prepared by emulsion method**

**Figure: 7 DSC spectra of microspheres prepared by spray drying method**
RESULTS AND DISCUSSION

The entrapment efficiency of microspheres is shown in (Table 3). It can be inferred from result that the loading efficiency in the microspheres depends upon the preparation conditions, and the polymer-concentration, it increased with increase in polymer concentration. Better drug loading was achieved by emulsion method than the spray drying method. The highest % encapsulation was observed for the batch AB-2 and ABC-4. Figure 1 and 2 shows SEM photographs of microspheres prepared by emulsion and spray dried methods respectively.

From the SEM photographs it was observed that the microspheres prepared by emulsion method were found to be discrete, spherical and free flowing with smooth surface and completely covered with the polymer coat and those prepared by spray drying method were found to be spherical and very small in size and partially melted and aggregated. This indicated that the different compositions did not substantially influence the morphologic characteristics of the spray-dried microspheres.

The possible drug polymer interaction was studied by FTIR analysis. No significant drug polymer interaction was observed in any cases. This was further supported by DSC results.

The DSC curves of pure Ethambutol HCL and drug loaded microspheres prepared by both methods are shown in figure: 5, 6 and 7 respectively. It was evident from the DSC curves of pure drug that, it showed sharp endothermic peak at 202.01 °C which correspond to reported melting point (198 °C) of the drug. It was observed that drug loaded microspheres showed similar peak correspond to Ethambutol HCL at 198.39 (AB-2) and 194.64 (ABC-4) for the two formulations prepared by emulsion and spray drying method respectively. But there is a loss of its sharp appearance. It is evident that there is a significant reduction of drug crystallinity in the microspheres. The DSC profile of the blank microspheres did not exhibit endothermic peak at 202.01 °C. These studies apparently revealed that the drug was compatible with the polymer and neither drug decomposition nor drug-polymer interactions occurred in the freshly prepared microspheres.

Mean particle size of optimized microspheres prepared by emulsion method was found to be 33µm where as for spray drying method it was 79.93 µm.

The in vitro drug release(Table 3) from the microspheres exhibited initial burst effect, which was due to the presence of drug particles on the surface of the microspheres, which is desired effect to ensure initial therapeutic plasma concentration. Factors such as polymer-drug ratio and stirring speed affect the drug release. Due to presence of ethylcellulose there is less release of drug from microspheres prepared by spray drying technique, which was mainly due to migration of the drug to the surface of the particles during spray drying process. Drug release rates were slow as the polymer concentration increased. As shown in figure 3 and 4 variable release was observed for different formulations. In comparison to spray drying method, microspheres prepared by emulsion method showed higher drug release profiles.

The in-vitro release profiles were applied on various kinetic models in order to find out the mechanism of drug release (table 4). In order to confirm the drug release the data obtained were also put in Korsmeyer-Peppas model to find out n value, which describes the drug release mechanism. The release showed higher correlation with the Korsmeyer-Peppas model. The n value of microspheres of different drug to polymer ratio was between 0.32-0.54, indicating the mechanism of the drug release was diffusion controlled.

CONCLUSION

Ethambutol HCl microspheres were prepared successfully by emulsion and spray drying methods. The microspheres prepared by emulsion method were found to be best as compared to those prepared spray drying method in all aspects.

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REFERENCES


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