ABSTRACT

Objective: Carvedilol is a non-selective beta blocker that was formulated as microspheres by using ethyl cellulose as a carrier.

Methods: These ethyl cellulose microspheres were prepared by the solvent evaporation method. The prepared microspheres were subjected to various evaluation parameters and in vitro release studies. Highest percentage of entrapment was obtained by increasing the amount of polymer with respect to uniformity of drug. The particle sizes of the prepared microspheres were determined by optical microscopy method and morphology by SEM analysis.

Results: The prepared microspheres have gained good spherical geometry with smooth surface as evident by SEM studies. The entrapment efficiency for F1 was found to be 97.5±0.1527% with maximum drug loading of 45.26 around. The best-fit release kinetics was achieved with Korsmeyer-Peppas plot followed by zero order and first order kinetics. The release of drug was influenced by the drug to polymer ratio and particle size and was found to be both diffusion and dissolution controlled.

Conclusion: The study showed that Carvedilol microspheres of 1:2 (F1 batch) ratio got better sustained effect over a period of 12 hours. Finding of all this investigation conclusively demonstrate prolongation of drug release at a constant and controlled rate.

Keywords: Carvedilol, Ethyl cellulose, Entrapment efficiency, SEM, in vitro-profile.

INTRODUCTION

The primary objective of zero-order release is to uphold constant drug concentration in blood for a prolonged period of time. Microspheres have played a vital role in the development of controlled/sustained release drug delivery systems [1-2].

It blocks beta-1 and beta-2 adrenergic receptors as well as the alpha-1 adrenergic receptors. Carvedilol is a non-selective beta blocker indicated in the treatment of mild to moderate congestive heart failure (CHF).

Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and controlled drug release. Different kinds of controlled drug delivery systems have been developed for various routes of administration, since they require less frequent drug administration, provide more efficient therapeutic effects, and reduce the incidence of side effects. To develop a drug delivery system for oral administration, the preferred route of administration, it is necessary to optimize the release rate of an active ingredient from the system. One of the most extensively studied methods is microsphere [3].

The overall aim and objective of project was the formulation of carvedilol microspheres and their evaluation of microspheres with their release kinetics.

MATERIALS AND METHODS

Drugs and Chemicals

Carvedilol was a gift sample obtained from Chandra labs, Hyderabad, Ethyl cellulose, Dichloro methane, Poly vinyl alcohol was supplied from Research Fine Chem Industries, Mumbai.

Drug and excipients compatibility studies

To investigate any possible interactions between the drug and excipients used, the FTIR spectra of Carvedilol and its physical mixture with ethyl cellulose, ethanol, dichromethane and polyvinyl alcohol were carried out using Bomem FTIR MB-II spectrophotometer. The samples were prepared as KBr (potassium bromide) discs compressed under a pressure of 10 Ton/nm². The wave number selected ranged between 400 and 4800 cm⁻¹. The results were summarized in and discussion made in table 1. The Fourier Transform Infra red analysis was conducted for the structure characterization. FTIR spectra of the formulated microspheres and drug were recorded. Microspheres were taken in a KBr pellet using Bomem FTIR MB-II instrument. Approximately 5mg samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500-3500cm⁻¹, with a resolution of 4cm⁻¹.

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer has occurred. The wave numbers of final formulation and individual ingredients were compared, hence it was conclude that there was no chemical interactions were found among excipients and the drug.

Solvent Evaporation Method [4-7]

Carvedilol microspheres were prepared by solvent evaporation technique. For this carvedilol was dissolved in dichloromethane and then polymer was dissolved in ethanolic solution. Both drug and polymer solutions were mixed well to form a uniform solution. The obtained drug and polymer solution was added drop wise to the PVA solution under constant stirring at 1500 rpm by using homogenizer. The beaker and its content were heated to 80⁰ c with constant stirring for 1hr until the aqueous phase was completely removed by evaporation. The microspheres formed were collected by whatmann filter paper and washed 3 times with distilled water and dried at a room temperature for one day.

Surface morphology

The surface morphology and structure were visualized by scanning electron microscopy (SEM). The samples were prepared by lightly
sprinkling the microspheres powder on a double side adhesive tape which already shucked on aluminum stubs. The stubs were then placed into fine coat ion sputter for gold coating. After gold coating, samples were randomly scanned for particle size and surface morphology.

**Drug entrapment efficiency**

Microspheres equivalent to 5 mg of Carvedilol were crushed using a glass mortar and pestle and the powdered microspheres were suspended in 25 ml of phosphate buffer pH 6.8. After 24 hrs, the solution was filtered, 1 ml of the filtrate was pipette out and diluted to 10 ml and analyzed for the drug content by using Ellico SL-159 UV Visible Spectrophotometer at 242 nm.

The drug entrapment efficiency was calculated using the following formula.

\[
\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{theoretical drug content}} \times 100.
\]

### Table 1: FT-IR Spectra data of Carvedilol and polymer

<table>
<thead>
<tr>
<th>S. No</th>
<th>Functional group</th>
<th>Characteristic peak cm(^{-1})</th>
<th>Observed peak for drug cm(^{-1})</th>
<th>Peaks for Microspheres formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-H</td>
<td>3500-3300</td>
<td>3342.89</td>
<td>3342.89</td>
</tr>
<tr>
<td>2</td>
<td>C-H</td>
<td>2950-2800</td>
<td>2922.72</td>
<td>2973.57</td>
</tr>
<tr>
<td>3</td>
<td>C-O</td>
<td>1260-1000</td>
<td>1098.28</td>
<td>1052.91</td>
</tr>
<tr>
<td>4</td>
<td>O-H</td>
<td>1250-970</td>
<td>980.10</td>
<td>980.10</td>
</tr>
</tbody>
</table>

### Table 2: Formulation of Carvedilol microspheres

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Batches of Carvedilol microspheres prepared</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carvedilol</td>
<td>F(_1) 250mg</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl Cellulose</td>
<td>F(_1) 250mg</td>
</tr>
<tr>
<td>3</td>
<td>Dichloro Methane</td>
<td>F(_1) 250mg</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>F(_1) 250mg</td>
</tr>
<tr>
<td>5</td>
<td>Poly vinyl Alcohol</td>
<td>F(_1) 250mg</td>
</tr>
<tr>
<td>6</td>
<td>Distilled water</td>
<td>F(_1) 250mg</td>
</tr>
</tbody>
</table>

### Table 3: Percentage yield, entrapment efficiency, drug loading of microspheres [8]

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Percentage yield (%)</th>
<th>Entrapment efficiency(%)±SD</th>
<th>Drug loading±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F(_1)</td>
<td>61.6</td>
<td>62.6±0.378</td>
<td>81.14±0.0208</td>
</tr>
<tr>
<td>F(_2)</td>
<td>71.5</td>
<td>88.6±0.208</td>
<td>51.75±0.0152</td>
</tr>
<tr>
<td>F(_3)</td>
<td>73.6</td>
<td>97.5±0.1527</td>
<td>45.26±0.114</td>
</tr>
</tbody>
</table>

Values are represented as mean± standard deviation (n=3)

### RESULTS AND DISCUSSIONS

#### Evaluation of Microspheres

The experiments were carried out and the results of percentage yield of microspheres were 61.6% to maximum of 73.6%. The maximum yield was obtained with formulation F\(_3\). The entrapment efficiency was found to be between 62.6% - 97.2%. As the polymer concentration increases the drug encapsulation was found to be increasing in microspheres. The results of percentage yield and drug entrapment were shown in table 3.

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Fig. 1: FTIR Spectra of Ethyl cellulose, Ethanol, Poly vinyl alcohol and mixture.
Mean Particle Size [9]

Mean particle size was determined by optical microscopy method [10-11] and the average particle size was calculated. The results were shown in table - 4.

Table 4: Mean particle size of Carvedilol microspheres.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Batches</th>
<th>Mean Particle Size(µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₁</td>
<td>36.42</td>
</tr>
<tr>
<td>2</td>
<td>F₂</td>
<td>42.96</td>
</tr>
<tr>
<td>3</td>
<td>F₃</td>
<td>50.41</td>
</tr>
</tbody>
</table>

Scanning Electron Microscopy [12]

The microspheres prepared by solvent evaporation method and results have proved a good sphericity with smooth surface in its morphology with SEM studies based, and the particles were distributed uniformly without forming any clumps.

The results profiles of in-vitro studies profile were displayed in given following figure No.6.

In-vitro release studies

The in-vitro release profile of carvedilol microspheres were conducted in a pH 6.8 buffers for 12 hrs. with 60 RPM by using Dissolution apparatus USP 1 Racket type at temperature of 37.0 ±0.5°C. The sampling was withdrawn for every one hour up to 12 hrs. At different time intervals various aliquots were withdrawn and replaced by an equal volume of dissolution medium in order to maintain constant volume. After suitable dilution, samples were analyzed spectro photometrically at 242 nm. All the experimental units were analyzed in triplicate (n=3). Cumulative percentage drug release was calculated using an equation obtained from a standard curve.
CONCLUSION

The ethyl-cellulose microspheres of Carvedilol were successfully prepared by solvent evaporation technique and confirmed that it is a best method for preparing carvedilol loaded microspheres from its higher percentage yield. The formulation F2 has highest milligram of drug content followed by other formulations. The drug entrapment efficiency of three formulations were found to be F1 62.6%, F2 88.6%, F3 97.5 percentages and the percentage yield of three formulations were found to be F1: 61.6%, F2: 71.55 and F3: 73.6.

The particle size of a microsphere was determined by optical microscopy technique and all the batches of microspheres have given uniform size distribution. The Mean particle size was found to be F1: 36.42, F2: 42.96, and F3: 50.41. The prepared microspheres had good spherical geometry with smooth as evidenced by the scanning electron microscopy. The in vitro dissolution studies showed that Carvedilol microspheres formulation F2 showed better sustained effect over a period of 12 hours. Dissolution results of different formulations were found to be F1: 83%, F2: 84.5% and F3: 86.43% and in which F1 formulation shows maximum drug release at 10th hour, F2 at 11th hour and F3 at 12th hour. Hence the drug release of F3 formulation gets sustained than other formulations for a period of 12 hrs.

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, Higuchi, Korsmeyer Peppas and finding the R² values of the release profile corresponding to each model. It was concluded that as the polymer concentration increases, density of polymer increases that results in increased diffusion path length, in which the drug molecules have to traverse so, the drug release of F3 formulation takes long time than other formulations.

For all the formulations dissolution profile graph and percentage of drug releases versus time was plotted. From basis of all the parameters which mentioned above and taken into consideration of parameters including surface characteristics of the formulation, drug-polymer ratio and time, F3 shows the good reliable results.

ACKNOWLEDGMENTS

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REFERENCES