DESIGN & EVALUATION OF CONTROLLED RELEASE FLOATING MICROSPHERES FOR BETTER MANAGEMENT OF HYPERTENSION

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ABSTRACT
The objective of the present work was to formulate and evaluate microspheres dosage form with Ramipril as the model drug. Ramipril is ideally suited to be formulated in an extended release drug delivery system to improve its patient compliance by bringing down its frequency of administration. Microspheres were prepared by non-aqueous emulsification-solvent evaporation technique using different combination of Ethyl cellulose and/or Eudragit L100 a polymers. The major advantage of the preparation technique includes short processing time, ambient temperature processing, and high encapsulation efficiency along with being economical. The mixing ratio of components in the organic phase affected the size distribution, drug content, percentage yield and release profile of microspheres. Best results were obtained at the ratio of drug: polymer (1:1). The microspheres formed were additionally found to be floating over gastric juice for > 8 hours. The developed Floating microspheres of Ramipril might be clinically used for prolonged drug release in GIT, for better drug utilization and improved patient compliance.

KEYWORDS: Hypertension; entrapment efficiency; floating time; microspheres; Solvent evaporation.

INTRODUCTION
Oral administration is the most convenient and preferred means of drug delivery. Extensive research work has been reported for the development of oral controlled release drug delivery systems, which can deliver the drug at constant rate for extended periods of time³¹. The present research work is focused towards formulation of oral dosage form that delivers the drug at constant rate.

Ramipril is an anti-hypertensive agent used in treatment of hypertensive disorder. It is highly lipophillic, poorly water soluble drug with absolute bioavailability of 28-35%. Ramipril converts into its active metabolite ramipril at by hepatic metabolism. The half life of Ramipril is 2 hrs respectively²². Multiparticulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In this system, the dosage of the drug substance is divided on a plurality of subunits, typically
consisting of thousands of spherical particles with diameter of 0.05 – 2.00 mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits, deliver the recommended total dose\textsuperscript{[3,4,5]}. So the objective of the present work was to formulate spherical microparticles by emulsification solvent evaporation method and to optimize the delivery of medication so as to achieve a pharmacokinetically desirable rate of delivery for better management of cardiovascular disorders.

**MATERIAL AND METHODS**

**Drug excipient compatibility study:**\textsuperscript{[6]}

Compatibility study of pure drug, polymer and physical mixture was carried out using KBr pellets at moderate scanning speed between 4000-400cm\textsuperscript{-1} in an FTIR spectrophotometer (Shimadzu 8400S, Japan). Results are shown in Figure1, Figure 2 & Figure 3.

**Preparation of Microparticles:**\textsuperscript{[7]}

Microparticles containing Ramipril as the core material was prepared by a Non-aqueous Solvent Evaporation method. Acetone, drug, and Ethyl cellulose and/or Eudragit L100 were mixed at different ratios in 10 ml of acetone. The polymer solution was slowly introduced into 40 ml of liquid paraffin containing specified amount of span80 while being stirred at 700 rpm using a mechanical stirrer equipped with a three bladed propeller at room temperature. The solution was stirred for 3 hr to allow the solvent to evaporate completely followed by collection of microspheres by filtration. Microcapsules were washed repeatedly with petroleum ether (40\textdegree-60\textdegreeC) until free from oil. Collected microspheres were dried for 1 hr at room temperature and subsequently stored in a desiccator over fused CaCl\textsubscript{2} until further study.

<table>
<thead>
<tr>
<th>Table 1: Composition of different formulations</th>
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<tbody>
<tr>
<td><strong>Ingredients</strong></td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Drug : polymer ratio</td>
</tr>
<tr>
<td>Ramipril (mg)</td>
</tr>
<tr>
<td>Ethyl cellulose (mg)</td>
</tr>
<tr>
<td>Eudragit L100 (mg)</td>
</tr>
<tr>
<td>Di butyl phthalate (%)</td>
</tr>
<tr>
<td>Acetone (ml)</td>
</tr>
<tr>
<td>Span 80 (ml)</td>
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<tr>
<td>Liquid paraffin (ml)</td>
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</table>
Yield of Microparticles

The prepared Microparticles were collected and weighted. The measured weight was divided by the total amount of all the non-volatile components used for the preparation of the Microparticles. Results are shown in Table 2.

\[
\% \text{ Yield} = \frac{\text{Actual weight of product obtained}}{\text{Total weight of excipient and drug}} \times 100
\]

Drug content and Entrapment Efficiency of the Microparticles\(^{[8,9]}\)

Crushed microparticles (100mg) were vortex –mixed for 2 hours with methanol. The extract was transferred to a 50ml volumetric flask and the volume made up using methanol. The concentration was measured by UV spectrophotometer at 209nm against appropriate blank. The amount of drug content and entrapped in the microparticles was calculated using following formula. Results are shown in Table 2.

\[
\text{Drug content} = \frac{\text{Amount of drug actually present}}{\text{Total weight of excipient and drug}} \times 100
\]

\[
\text{Drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{Total weight of excipient and drug}} \times 100
\]

In-vitro Evaluation of Floating ability\(^{[10,11,12]}\)

An in-vitro floating study was carried out using 0.1N HCl containing 0.1% SLS as a surfactant. Microparticles were spread over the surface of 250ml of dispersing medium at 37 ± 0.5°C. A paddle rotating at 100 rpm agitated the medium. Each fraction of Microparticles floating on the surface and those settled down was collected at a pre-determined time point. The collected samples were weighed after drying. Results are shown in Table 2.

Differential scanning calorimetry study (DSC)\(^{[11]}\)

Thermal analysis of Ramipril, Polymer and optimized batch was carried out using DSC (Model: DSC Q600, TA Instruments Inc., New Castle, DE). At a heating rate of 10°C /min, samples of 5.21 mg were heated from room temperature 0°C to 350°C in an open aluminum pan under a 50 ml/min stream of nitrogen purge. Universal analysis (Version 8.2) software was used for analysis. Results are shown in Figure 4, Figure 5 & Figure 6.

Surface electron microscopy (SEM)\(^{[11,13]}\)
The external and internal morphology of microparticles was analysed by SEM (JSM – 6510LV Jeol, Japan). Study was carried out at angle of incidence 90° with accelerating voltage 5KV. Results are shown in Figure 7.

**In-vitro Drug Release Study**[^10,14,15]

*In-vitro* release studies were carried out for the plain drug, marketed product and formulations in dissolution test apparatus USP type II. All formulations equivalent to 10 mg of drug were taken for study using 900ml of 0.1N Hydrochloric acid for 8 hrs at 50 rpm at 37±0.5°C. At predetermined time intervals 5ml of the aliquots were taken and analyzed for drug content in UV spectrophotometer at 209nm. Fresh dissolution medium was introduced every time to maintain sink condition. Results are shown in Figure 8.

**Results and Discussion**

Any formulation development work has to be preceded by preformulation studies including analytical investigations, choice of the analytical methods, standardization and validation of the procedures and preliminary formulation trials. There is a need for selection of a suitable polymer and other excipients, which are compatible with drugs and among themselves and also physiologically safe and biocompatible. Preliminary idea about the behavior of the dosage form formulated, using the selected ingredients and their singular and collective effect on the physicochemical and pharmaceutical properties of the dosage form also needs to be studied during this phase.

**Drug excipient compatibility study:**

**FTIR Spectrum**

![Figure 1:- FTIR spectrum of Ramipril](image-url)
The IR spectra of drug polymer physical mixture (1:1) indicated no potential incompatibility with drug and hence ethyl cellulose was chosen as polymers for further investigations. Chances of interaction between the –C=O groups of Ramipril and hydroxyl group of ethyl cellulose exist but no other potential interaction or shift in the position of peak occurs was observed.
Characterization of microspheres

Table 2: Result of all batches showing % yield, Drug content, Drug entrapment efficiency
particle size & % floating

<table>
<thead>
<tr>
<th>Batch</th>
<th>Percentage Yield (%)</th>
<th>Drug Content (%)</th>
<th>DEE (%)</th>
<th>Particle Size (µm)</th>
<th>% Floating (after 8 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>81.17 ± 0.27</td>
<td>22.70 ± 0.77</td>
<td>83.56 ± 0.59</td>
<td>441.70 ± 0.61</td>
<td>88.69 ± 0.25</td>
</tr>
<tr>
<td>F2</td>
<td>69.92 ± 0.82</td>
<td>37.10 ± 0.89</td>
<td>76.67 ± 0.28</td>
<td>572.16 ± 0.10</td>
<td>69.21 ± 0.09</td>
</tr>
<tr>
<td>F3</td>
<td>69.63 ± 1.39</td>
<td>39.62 ± 1.26</td>
<td>81.54 ± 0.88</td>
<td>531.47 ± 0.46</td>
<td>45.61 ± 0.09</td>
</tr>
<tr>
<td>F4</td>
<td>65.33 ± 0.30</td>
<td>41.80 ± 3.17</td>
<td>88.08 ± 0.84</td>
<td>523.35 ± 0.37</td>
<td>72.29 ± 0.92</td>
</tr>
<tr>
<td>F5</td>
<td>67.94 ± 0.24</td>
<td>45.48 ± 3.38</td>
<td>89.04 ± 0.31</td>
<td>516.13 ± 0.40</td>
<td>88.67 ± 0.14</td>
</tr>
<tr>
<td>F6</td>
<td>75.61 ± 0.47</td>
<td>45.13 ± 2.60</td>
<td>90.02 ± 0.47</td>
<td>507.24 ± 0.69</td>
<td>87.54 ± 0.51</td>
</tr>
<tr>
<td>F7</td>
<td>70.55 ± 1.01</td>
<td>42.55 ± 4.36</td>
<td>85.10 ± 0.01</td>
<td>612.92 ± 0.62</td>
<td>85.28 ± 0.18</td>
</tr>
<tr>
<td>F8</td>
<td>78.07 ± 1.05</td>
<td>23.07 ± 5.01</td>
<td>91.30 ± 0.34</td>
<td>496.07 ± 0.26</td>
<td>82.91 ± 0.10</td>
</tr>
<tr>
<td>F9</td>
<td>89.58 ± 1.18</td>
<td>30.16 ± 4.23</td>
<td>91.56 ± 0.08</td>
<td>485.42 ± 0.84</td>
<td>90.10 ± 0.06</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, n=3

Therefore, several preformulation trials (F1-F9) were undertaken with various proportions of drug and polymer by varying the liquid paraffin and acetone volume for qualitative and quantitative determination of microparticles characteristics.

It was also found that EC microspheres were showing better drug content (F1-22.70, F8-23.07 & F9-30.16 %), DEE (F1-83.56, F8-91.30 & F9-91.56 %), % yield (F1-81.17, F8-78.07 & F9-89.58) and floating characteristics compared to other polymer investigated.

The microparticles obtained were found to be composed of a thick polymer coat and a hollow core and on dispersion in 0.1 N HCl, the particles were found to be floating completely for prolonged period of at least 8 hours. The process also enabled good yield, high drug content, good drug entrapment efficiency and relatively uniform particle size.
Differential scanning calorimetry:

Figure 4: DSC curve of Ramipril

Figure 5: DSC curve of Ethyl cellulose

Figure 6: DSC curve of Formulation F9
The changes of DSC curves in which melting peak of drug is not showing evidence for indicating a amorphous change in formulation. This is an interesting observation, since literature search did not reveal any polymorph of ramipril. This leads us to another possibility, wherein, the molecular state of dispersion that might be achieved during solubilization of drug and polymer in acetone might open up opportunities for –C=O groups and –NH- bridge of ramipril to form hydrogen bonds / other weak interactions with –OC2H5 groups of EC backbone. This hypothesis may be supported but not proved by the absence of carbonyl stretching at 1747 cm\(^{-1}\) in the FTIR spectrogram of the formulation. Hence, there is a possibility that engagement of drug molecule by weak interaction with polymer matrix might be preventing complete recrystallization of ramipril, which could be manifested as reduced peak in DSC thermogram of the formulation.

**Surface morphology of Microparticles:**

![SEM image of optimize batch F9](image)

Shape and surface morphology of the best formulation was studied by using scanning electron microscopy. The SEM micrograph reveals that particles were spherical in shape with smooth surface.

**In vitro release profile:**

It was found that EC microcapsules were showing better control of the release profile of the drug compared to other polymers investigated. Microcapsules prepared with Combination of
Ethyl cellulose and Eudragit L100 (F5, F6, F7) were fine in size but release profile of formulations failed, hence were discarded from further investigation. Di-butyl phthalate in the range of 5 to 15% w/w ratio (F2, F3, F4) along with ethyl cellulose was attempted but release profile of these formulations also failed, hence were discarded from further investigation. Therefore, further formulations were developed with different proportions of ethyl cellulose polymer (F1, F8 & F9) to achieve standard drug release profile.

**Figure 8:- Comparison of Release Profile of F1, F8 and F9**

**Kinetic models**
The kinetic investigations of the release profile gave us useful insight into the mechanism of drug release from the microspheres. The release from optimized formulation did not show any burst effect or lag time, which is indicative of a homogeneous drug distribution, in the microspheres. The dissolution data was subjected to regression analysis and were fitted to four kinetic models, viz., Zero order, First order, Hixon-Crowell and Higuchi. From the release study of optimized batch F9 it was clear that optimized microspheres showed first order release pattern followed by Higuchi model of release kinetic.

**Table 3:- Kinetic model for optimized batch**

<table>
<thead>
<tr>
<th>Optimized batch</th>
<th>R² value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Zero-order</td>
</tr>
<tr>
<td>F9</td>
<td>0.990</td>
</tr>
</tbody>
</table>
CONCLUSION

A controlled release system for Ramipril designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating Microparticles. This type of delivery system ensures complete release of the drug before the dosage form passes into the non-absorbing zone of the intestine or colon, thereby making the delivery system more efficient and economical.

REFERENCES


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