FORMULATION AND EVALUATION OF ALGINATE MICROBEADS OF PROPRANOLOL HYDROCHLORIDE BY USING NATURAL POLYMERS

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ABSTRACT

The aim of the present research was to formulate and evaluate alginate microbeads of propranolol hydrochloride by using ionotropic gelation technique. The prepared microbeads were evaluated for various parameters like percentage yield, particle size, flow property, entrapment efficiency, surface study, in-vitro drug release, X-Ray diffraction analysis, etc. It was found that all formulations showed improved flow behavior as compared to pure drug, it was observed that on increasing the polymer concentration of formulations the entrapment efficiency and particle size were increased. The surface morphology study by SEM indicated that microbeads were spherical with rough outer surface. There was no interaction between the drug and the polymers, as studied by FTIR study. In-vitro drug release study showed that on microsphere formulation its release was sustained and its release was affected by polymer concentration and it followed Higuchi model. Therefore, it can be concluded that Propranolol Hydrochloride loaded algino-chitosan microbeads can be formulated for sustained drug delivery of Propranolol Hydrochloride.

KEYWORDS: Microbeads, propranolol hydrochloride, Ionotropic gelation technique, Algino-chitosan microbeads.
INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily\(^\text{1,2}\).

Microbeads\(^\text{3,4}\) are controlled release novel drug delivery dosage forms, Microbeads encapsulate drug and release it at controlled rates for relatively long periods of time. Microbeads can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time. Several commercial products are based on polymers. These usage ease of medication, controlled\(^\text{5}\) release of drug most importantly the patient compliance.

Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy\(^\text{6}\) of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window. Sustained release system have benefits like patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system\(^\text{7,8}\).

PropranololHCl\(^\text{9}\), an orally active beta blocking agent used in the treatment of anginapectoris, hypertension and arrhythmia. It is highly water soluble drug and is rapidly and almost completely absorbed from the GIT following oral administration but undergo extensive metabolism. The biological half-life of the drug is 4.5hr. Since PropranololHCl has low bioavailability and shorter half-life, developing a controlled release system can maintain the plasma drug concentration in therapeutic window and increase the therapeutic efficacy of drug.

MATERIALS AND METHODS

Propranolol HCl was procured from Spectrum Laboratories, Hyderabad. Sodium Alginate, Xanthan Gum, Chitosan were purchased from BMR Pharmaceuticals, Hyderabad. All the other chemicals used were in analytical grade.
Preparation of Alginate beads\textsuperscript{10}

The microbeads were prepared by ionotropic gelation technique. Sodium alginate was dissolved in distilled with gentle heating. Then the drug was dispersed in the above 50ml solution with continuous stirring. Then Xanthan gum and Chitosan was added with continuous stirring. Then the pregelation liquid is dropped in to the 100 ml of 2\% CaCl\textsubscript{2} solution through a 5ml syringe with a flat tip hypodermic needle of size 20 guage at a constant height to the CaCl\textsubscript{2} solution in the beaker with constant stirring using magnetic stirrer. The droplets instantaneously gelled in to Propranolol Hcl loaded microbeads. The microbeads were kept a side 1hr without disturbing it. The formed microbeads were washed with water to remove excess amount of calcium impurity on the surface of the microsphers. The microbeads were dried at room temperature over night.

EVALUATION OF PROPRONOLOL Hcl MICROBEADS\textsuperscript{10}

Particle Size Analysis

The particle size has significant effect on the release profile of microbeads. Particle Size and Size distribution was determined by sieve analysis. The drug loaded micro beads were separated in to different size fractions by sieving for 5 min using standard sieves. Particles were passed through one sieve but were retained on the other were collected and weighed and the distribution was analysed based on the weight of fraction on each sieve. The particie size and distribution and mean particie size of microbeads were caluculated using the following formula and is shown in the

\[
\text{Mean Particle Size} = \frac{\sum (\text{mean particle size of the fraction} \times \text{weight fraction})}{\sum (\text{weight fraction})}
\]

Determination of drug entrapments efficiency

The drug entrapment of prepared microbeads were tested by taking 100 mg of the formulation in 50 ml of phosphate buffer of pH 6.8 in a volumetric flask. The resulting was kept 1hr, aside after shaking it occasionally. The solution was filterd, after suitable dilution propranolol hcl content in the filterate was analysed at 290 nm using UV-visible Spectrophotometer. The Obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Caluculating this concentration with dilution factor we get the percentage of actual drug encapsulated in microbeads. The drug entrapment efficiency was determined using following relation.
Encapsulation efficiency (%) = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100

**Estimation of drug content & Percent Yield**

The percentage yields of all prepared microbeads were determined on weight basis with respect to the initial weight of material.

\[
\text{Yield (\%)} = \frac{\text{weight of microbeads}}{\text{Total Expected weight of drug and polymer}} \times 100
\]

**Scanning Electron Microscopy**

The surface morphology especially with respect to surface topography and photomicrography was done with Scanning Electron Microscopy (SEM)\textsuperscript{[13]}, by using the instrument JSM 5610LV SEM, JEOL, Japan. The figures of microbeads after SEM analysis are depicted in Figure-1.

**FTIR**

The FTIR study was carried out using Perkin-Elmer FT-IR. The sample of pure drug, pure polymers (sodiumalginate and guargum, egg albumin, PVA) and formulation containing both the drug and polymers were scanned to study the possible interaction between drug and polymers.

**IN-VITRO DRUG RELEASE STUDIES**

100 mg of drug is placed in the USP Dissolution test apparatus USP type-1. 900 ml of 0.1N HCl is used for first 2 hrs and followed by phosphate buffer solution (\text{P}^\text{H} 6.8) remaining hrs the dissolution medium was maintained at 37°C. The basket was rotated at a speed of 50 rpm. 5ml of medium was withdrawn at various time intervals of 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 9hr, 10hr, 11hr and 12hr., with the help of 5ml pipette and replaced by 5ml of phosphate buffer solution (\text{P}^\text{H} 6.8). The drug content was estimated by UV Spectrophotometer at 290 nm and thereby the cumulative percentage drug release was calculated.

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RESULTS AND DISCUSSION

Particle size analysis
The mean particle size of 8 formulations ranged between 496.37 μm to 502.8 μm. It was found that mean particle size of the formulations was increased with polymer concentration for the formulations F1, F2, F3, F4, F5, F6, F7, F8. This may be due to the increase in relative viscosity at higher concentrations of polymer.

Percentage of the Yield
The yield obtained from all the batches was good. The range for % yield was 75.21 to 98.0 for the prepared microbeads, the result showed a moderate increase in yield. Table.No.2 depicts the detail data of percentage yield.

Drug Entrapment Efficiency
The drug entrapment efficiency for various formulations was found to vary between 77.18 to 94.60%. It was observed from the obtained data that with increase in polymer concentration larger microbeads were formed, with greater amount of drug entrapped. This may be due to the greater availability of active calcium binding sites in the polymeric chains.

IN VITRO DISSOLUTION STUDIES
In formulation F1 the Propranolol Hcl microbeads were prepared with the ratio of 1:10 Xantham Gum and Sodium Alginate, they shown drug release of 94.629% in P.B.S at ends of 12 hrs. This is due to the less concentration of Xantham Gum so it increase the the drug release. In formulation F4 the Propranolol Hcl microbeads were prepared with the ratio of 1:5 xanthanm gum and Sodium Alginate, they shown drug release of 89.311% in P.B.S at ends of 12 hrs. This is due to the more concentration of Xantham Gum, when compared to the F1 formulation decrease the drug release. In formulation F3 the Propranolol Hcl microbeads were prepared with the ratio of 1:2 Xantham Gum and Sodium Alginate, they shown drug release of 85.189% in P.B.S at ends of 12 hrs. This is due to the more concentration of Xantham Gum, when compared to the F2 Formulation decrease the drug release. In
formulation F4 the Propranolol Hcl microbeads were prepared with the ratio of 1:1 PVA and Sodium Alginate, they shown drug release of 79.186% in P.B.S at ends of 12 hrs. This is due to the more concentration of Xantham Gum, when compared to the F3 Formulation decrease the drug release. In formulation F5 the Propranolol Hcl microbeads were prepared with the ratio of 1:10 Chitosan and Sodium Alginate, they shown drug release of 95.959% in P.B.S at ends of 12 hrs. This is due to the less concentration of Chitosan, due to the less concentration of Chitosan increase the drug release. In formulation F6 the Propranolol Hcl microbeads were prepared with the ratio of 1:5 Chitosan and Sodium Alginate, they shown drug release of 91.88% in P.B.S at ends of 12 hrs. Due to the increase the concentration of Chitosan decrease the drug release. In formulation F7 the Propranolol Hcl microbeads were prepared with the ratio of 1:2 Chitosan and Sodium Alginate, they shown drug release of 89.010% in P.B.S at ends of 12 hrs. Due to the increase the concentration of Chitosan decrease the drug release. In formulation F8 the Propranolol Hcl microbeads were prepared with the ratio of 1:1 Egg Albumin and Sodium Alginate, they shown drug release of 72.993% in P.B.S at ends of 12 hrs. Due to the increase the concentration of Chitosan decrease the drug release. The best formulation(F8) When compared with pure drug and shows the controlled release.

**IN-Vitro Release Kinetics**

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix Peppasmodel for formulation F1 to F8 depicted in fig. 1 to 9 respectively. The regression coefficients values for formulation F1, F2, F3 and F4 of zero order plots were found to be 0.939, 0.950,0.873 and 0.991 respectively. The regression coefficients values for formulation F3, F4, F5 and F6 of First order plots were found to be 0.990, 0.992, 0.986 and 0.988 respectively. This Higuchi plot with regression coefficient values of 0.935, 0.937, 0.964 and 0.908 for formulations F1, F2, F3 and F4 respectively and shows that the drug release following higuchi mechanism. The regression coefficients values for formulation F5, F6, F7 and F8 of zero order plots were found to be 0.819, 0.791, 0.900 and 0.717 respectively. The regression coefficients values for formulation F5, F6, F7 and F8 of First order plots were found to be 0.991, 0.987, 0.972 and 0.969 respectively. This Higuchi plot with regression coefficient values of 0.976, 0.975, 0.964 and 0.979 for formulations F5, F6, F7 and F8 respectively and shows that the drug release following higuchi mechanism. The ‘n’ value for F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 were found to be 1.242, 1.165, 1.148, 1.144, 1.250, 1.174, 1.429, 1.411, 1.239 and 1.418 respectively The ‘n’ values of formulation F1,F2, F3, F4, F5, F6, F7 and F8 indicates that the release was Super Case – II Transport mechanism.
because microbeads are polymeric dosage forms. From the in-vitro dissolution data it was found that formulation F1 to F8 showed the controlled drug release for 12 hours. From the above formulations F8 formulation showed the better controlled drug release. The remaining formulations shows good controlled release for 12 hrs.

**IR SPECTRA**

The IR spectra of all the tested samples showed the prominent characterizing peaks of pure drug Propranolol Hcl, individual polymers, Sodium Alginate, Xantham gum, Chitosan, and the admixture of drug and polymers and was confirmed that no chemical modification of the drug has been taken place and thus they were proved to be compatible with each other and hence suitable for preparation of all controlled release microbeads.

**SCANNING ELECTRON MICROSCOPY**

The scanning electron micrographs (SEM) of the microbeads are shown in Figure 1(A), Figure 1(B). The SEM results revealed that Propranolol Hydrochloride loaded microbeads were discreate and spherical in shape with rough outer surface. The surface of the microbeads was rough due to the density of the polymer matrix which in turn justifies controlled release.

**Table.No.1: Composition of Drug and Polymers in mg**

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
</tr>
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<tr>
<td>Propranolol Hcl</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Xantham Gum</td>
<td>-</td>
<td>-</td>
<td>200</td>
<td>500</td>
<td>1000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chitosan</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodium alginate(4%)</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>100</td>
<td>200</td>
<td>500</td>
<td>100</td>
</tr>
<tr>
<td>Calcium Chloride Solution(2%)(ml)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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**Table.No.2: percentage yield, particle size and entrapment efficiency of Propranolol Hydrochloride loaded microbeads**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Average Particle Size (µm)</th>
<th>Yield (%)</th>
<th>Encapsulation Efficiency (%)</th>
</tr>
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<tbody>
<tr>
<td>F1</td>
<td>502.8</td>
<td>84.73</td>
<td>87</td>
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<tr>
<td>F2</td>
<td>497.64</td>
<td>82.67</td>
<td>86.60</td>
</tr>
<tr>
<td>F3</td>
<td>480.68</td>
<td>75.21</td>
<td>77.18</td>
</tr>
<tr>
<td>F4</td>
<td>501.98</td>
<td>92.24</td>
<td>90.46</td>
</tr>
<tr>
<td>F5</td>
<td>500</td>
<td>90.25</td>
<td>84.86</td>
</tr>
<tr>
<td>F6</td>
<td>496.37</td>
<td>81.26</td>
<td>73.61</td>
</tr>
<tr>
<td>F7</td>
<td>500.26</td>
<td>82.78</td>
<td>94.50</td>
</tr>
<tr>
<td>F8</td>
<td>498.37</td>
<td>98.0</td>
<td>79.32</td>
</tr>
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</table>
### Table NO.3: Comparative In-Vitro Dissolution profile of all formulations

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>2</td>
<td>24.634</td>
<td>25.080</td>
<td>31.837</td>
<td>44.925</td>
<td>38.153</td>
<td>41.644</td>
<td>28.901</td>
<td>16.457</td>
</tr>
<tr>
<td>3</td>
<td>42.968</td>
<td>39.973</td>
<td>45.969</td>
<td>46.774</td>
<td>50.197</td>
<td>49.813</td>
<td>35.952</td>
<td>21.323</td>
</tr>
<tr>
<td>4</td>
<td>53.784</td>
<td>41.935</td>
<td>53.377</td>
<td>51.391</td>
<td>62.659</td>
<td>58.634</td>
<td>47.674</td>
<td>29.405</td>
</tr>
<tr>
<td>5</td>
<td>68.277</td>
<td>60.562</td>
<td>55.242</td>
<td>53.709</td>
<td>70.921</td>
<td>69.944</td>
<td>58.223</td>
<td>32.405</td>
</tr>
<tr>
<td>6</td>
<td>71.696</td>
<td>65.319</td>
<td>60.513</td>
<td>58.536</td>
<td>75.966</td>
<td>77.193</td>
<td>66.932</td>
<td>43.108</td>
</tr>
<tr>
<td>7</td>
<td>75.600</td>
<td>73.023</td>
<td>69.400</td>
<td>60.253</td>
<td>80.863</td>
<td>79.565</td>
<td>70.163</td>
<td>49.190</td>
</tr>
<tr>
<td>8</td>
<td>82.187</td>
<td>81.703</td>
<td>70.478</td>
<td>64.838</td>
<td>85.767</td>
<td>80.886</td>
<td>71.462</td>
<td>52.183</td>
</tr>
<tr>
<td>9</td>
<td>88.773</td>
<td>82.543</td>
<td>72.672</td>
<td>67.548</td>
<td>88.427</td>
<td>81.677</td>
<td>72.694</td>
<td>56.670</td>
</tr>
<tr>
<td>10</td>
<td>89.945</td>
<td>85.344</td>
<td>76.245</td>
<td>73.426</td>
<td>88.850</td>
<td>85.498</td>
<td>74.201</td>
<td>64.917</td>
</tr>
<tr>
<td>11</td>
<td>93.604</td>
<td>87.728</td>
<td>79.074</td>
<td>78.285</td>
<td>93.606</td>
<td>89.905</td>
<td>85.509</td>
<td>67.183</td>
</tr>
<tr>
<td>12</td>
<td>94.629</td>
<td>89.311</td>
<td>85.189</td>
<td>79.186</td>
<td>95.959</td>
<td>91.88</td>
<td>89.010</td>
<td>72.993</td>
</tr>
</tbody>
</table>

**Fig. No.1:** Comparative In-Vitro dissolution profile of formulations F1-F4

**Fig. No.2:** Comparative In-Vitro dissolution profile of formulations F5-F8
Fig. No. 3: Comparative first order release profile of formulations F1-F4

Fig. No. 4: Comparative first order release profile of formulations F5-F8

Fig. No. 5: Higuchi Release profile of formulations F1-F4
Fig.No.6: Higuchi Release Profile of Formulations F5-F8

Fig.No.7: Koresmeyer&Peppas Release Kinetics of Formulations F1-F4

Fig.No.8: Koresmeyer&Peppas Release Kinetics of Formulations F5-F8
CONCLUSION

From the above discussion, it was concluded that the release of drug from prepared microbeads follows First Order, Super Case – II transport mechanism. Among the eight prepared microbeads formulations by using ionic gelation method, the formulation F₆ had shown more retarding release. As this F₆ Formulation (PVA: S.A, 1:1 ratio) releases 72.993% of drug in 12 hrs. But the drug release profile of any proposed formulation is not exactly matched with that of the pure drug release profile. Hence, the work is to be further extended to formulate controlled release microbeads of Propranolol Hcl.

ACKNOWLEDGEMENT

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