Development and characterization of valsartan loaded hydrogel beads

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ABSTRACT

The present work was aimed for the formulation design and characterization of hydrogel beads to obtain an effective stimuli-responsive release of the antihypertensive drug, Valsartan. Hydrogel beads were prepared using xanthan gum, soluplus and acrylamide as polymers, methylene bis acrylamide as crossinker and potassium persulfate as reaction initiator. The beads were characterized by FTIR, DSC and SEM. The studies showed that there were no possible chemical interaction between the drug and the polymers and SEM revealed that the beads were of spherical in shape with good surface morphology. The beads showed a good entrapment efficiency of about 90% and the swelling rate was found to be more at higher pH. The percentage drug release was also higher as the pH increased and was observed to be reduced at higher concentrations of the crosslinking agent. The hydrogel beads followed zero order non-fickian diffusion mechanism. Thus the hydrogel bead system as an effective stimuli-responsive drug delivery system was developed which offered a solubilizing cross-linked network matrix for the poorly soluble drug, Valsartan providing the best controlled release of the drug over 24 hrs.

Keywords: Hydrogel beads, xanthangum, soluplus, acrylamide.

INTRODUCTION

An appropriately designed drug delivery system can be a major advance towards solving the two problems of spatial placement and temporal delivery of the drug. Research in the novel drug delivery in the past decades has led to increasingly sophisticated modified release systems by sustaining/controlling the drug delivery.

Hydrogels are defined as 3-dimensional, hydrophilic polymeric networks composed of homo or co-polymers which are capable of imbibing large amounts of water or biological fluids. They are composed of network crosslinks of homopolymers or co-polymers [1]. They are unique properties of having high permeability for water soluble drugs and proteins and exhibit thermodynamic aqueous compatibility which allows them to swell. Hydrogel technology can be applied for both hydrophilic and hydrophobic drugs and charged solutes. They have attracted considerable attention as excellent candidates for controlled release devices, bio-adhesive systems, targetable devices of therapeutic agents etc [2].

Valsartan is an anti-hypertensive drug and belongs to the family of angiotensin II type1 receptor (AT1) antagonists. It is rapidly absorbed orally by passive diffusion process with about 23% bioavailability. It is poorly water soluble.
and hence classified as class II drug according to BCS Classification Scheme [3]. It is mainly excreted in faeces via biliary excretion and hence associated with hepatic dysfunction and biliary cirrhosis [4].

Recently, many workers reported various techniques like formation of inclusion complexes with cyclodextrins [3], dendrimers for drug solubilization [5], self micro-emulsifying drug delivery systems [6, 12], nanoparticle technology [7], orodispersable tablets [8] etc for the improvement of the solubility and dissolution rate of poorly water soluble drugs and thus to improve their bioavailability. It is known that acrylic acid is a pH and electrically sensitive material due to its ionic repulsion between anionic charged groups forms polymer complexes with polybases [9].

Soluplus is a novel amphiphilic polymeric solubilizer specially designed for solubility enhancement. It is a polyvinyl caprolactam-polyvinyl Acetate-polyethylene glycol grafted copolymer with both hydrophilic and lipophilic properties. Natural materials like xanthan gum are promising non-toxic; freely available polymers used in drug delivery systems [10]. It was earlier reported that polymer blends may show synergistic properties [11].

Physical entrapment of the drug within the soluplus, xanthan gum and acrylamide matrix hydrogel hasn’t been tried yet.

The present work is to develop a new hydrogel beads using acrylamide and soluplus as copolymers with Methylene bis acrylamide as a cross linker and potassium persulfate as a reaction initiator that could be effectively used as a stimuli-sensitive drug delivery device in future.

MATERIALS AND METHODS

1.1. Materials
Valsartan and Soluplus were provided as gift samples by Alembic Pharmaceuticals Ltd, Ahmedabad and BASF, The Chemical Company, Germany respectively. Acrylamide, Methylene Bis Acryl amide, Potassium per sulfate were procured from SD Fine Chemicals. All other reagents used were of analytical grade.

1.2. Preparation of cross-linked Valsartan hydrogel beads:
Accurately weighed quantities of soluplus, Valsartan and acrylamide were dissolved in about 15 ml of deionised water vigorously mixing at a speed of 800-900rpm. Accurately weighed quantities of xanthan gum was then added to the above viscous mixture and homogenized at 1500-200 rpm for 20 mins, using ultrasonic homogenizer (Biologics, INC, model-3000) until they were completely mixed. To this mixture 80 mg of the drug was added and homogenization was continued for 20 more minutes. This mixture was dropped through an 22-G needle into a solution containing 0.02% w/v and 0.01% w/v of Methylene bis acrylamide and potassium per sulfate. After 48 hrs, the formed hydrogel beads were washed and filtered using membrane filter paper under vacuum and dried at 50°C.

The hydrogel beads were prepared by using different compositions of the polymers as shown in the table: 1.

<table>
<thead>
<tr>
<th>Composition</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Soluplus</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>MBA (% w/v)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.025</td>
<td>0.03</td>
</tr>
<tr>
<td>PPS (% w/v)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

1.3. Characterization :
1.31. Fourier Transform Infrared Spectroscopy:
FTIR spectra were recorded on a KBp Press Model SHIMADZU FTIR-5300 Samples were thoroughly grounded with exhaustively dried KBr and pellets were prepared by compression under vacuum and their corresponding FTIR spectra were recorded.
1.32. Differential Scanning Calorimetry:  
Thermal characterization of Valsartan and soluplus and Hydrogel beads were performed by DSC using a Universal Thermal Analyzer DSC Q200 V23.12. Samples (2-4 mg) were sealed in aluminum pans for analysis.  
The DSC thermo grams were recorded from 20°C to 120°C at a heating rate of 10°C/min. Nitrogen flow rate of 20 ml/min was used for each DSC run.

1.33. Surface Morphology:  
The SEM analysis of the samples was performed to investigate the surface morphology and homogeneity of the particles using Jeol JSM-840 (Japan) scanning electron microscope. The samples of optimized hydrogel beads were sputter-coated with gold at room temperature before examination to render the surface of particles electro-conductive.

1.34. Encapsulation efficiency:  
The drug content in the hydrogel beads was quantitatively determined by immersing the dried beads (100mg) in 100 ml of pH 6.8 phosphate buffer followed by sonication for the complete dissolving of the drug dispersed inside the beads. The sample of 5ml solution was collected and filtered.  
The drug content was determined by nm using a Shimadzu UV-1601 UV/Visible double-beam spectrophotometer (Shimadzu Corp, Kyoto, Japan) at 250nm. The encapsulation efficiency was calculated according to the following equation:  
\[
\text{Percentage encapsulation efficiency} = \frac{\text{Drug content}}{\text{Theoretical drug content}} \times 100
\]

1.35. Swelling study:  
Swelling parameter is the vital factor for the characterization of hydrogel beads because there is a fundamental relationship between the swelling of the polymer and the nature of the swelling medium. With respect to changes in the levels of cross linking agent, the concentration differences between the polymers and the effect of pH on swelling were investigated as follows:  
The hydrogel beads were placed in 10 ml of buffer solutions of different pH i.e., in 0.1N HCl, Double distilled water and pH 6.8 buffer. The Hydrogel beads were removed from their respective swelling media, blotted to remove excess water and their weights were observed on analytical balance.  
The equilibrium weight swelling ratio (ESR) of each disc was calculated using Eq. (1):  
\[
\text{ESR} = \frac{W_2 - W_1}{W_1}
\]

Where \(W_2\) represents the swollen Hydrogel bead at time ‘t’ and \(W_1\) is the weight of the hydrogel bead before swelling. This process was continued until the sample appeared to be dissolved.

1.36. In vitro-release study:  
The in vitro drug release rate of Valsartan from hydrogel beads was carried out in triplicate for each formulation using USP type I (Basket) apparatus model- Electro Lab TDT-O8L, Mumbai) , in 900 mL of 0.1 N HCl, at 37°C ± 0.5°C at 50 rpm for the first 2 hours and then replaced by phosphate buffer of pH 6.8 . A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at the appropriate time interval for 24 hours, and the samples were replaced with fresh dissolution medium after every withdrawal.  
The samples were filtered through a 0.45-μm membrane filter and diluted and absorbances of these solutions were measured at 250 nm using a Shimadzu UV-1601 UV/Visible double-beam spectrophotometer (Shimadzu Corp, Kyoto, Japan). Cumulative percentage drug release was calculated.
1.37. Evaluation of release kinetics
The mechanism of the drug release from the hydrogel beads was investigated by fitting the release data using zero order, first order, Higuchi, Korsemeyer-Peppas, and Erosion models as shown in the Table 2.

Table 2. Mathematical modeling for the study of release kinetics

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero order</td>
<td>( Q = Q_o + K_o t )</td>
</tr>
<tr>
<td>Higuchi</td>
<td>( Q = Q_o + K_H t^{1/2} )</td>
</tr>
<tr>
<td>Korsemeyer-Peppas</td>
<td>( Q = K_{rP} t^n )</td>
</tr>
</tbody>
</table>

RESULTS

3.1. Fourier Transform Infrared Spectroscopy:

Figure 1. FTIR spectroscopic picture of Valsartan (pure drug)
Figure: 2. FTIR spectroscopic picture of Valsartan hydrogel bead
3.2. Differential Scanning Calorimetry (DSC):

![DSC Graph]

Figure: 3. Differential Scanning Calorimetric Picture of Valsartan Hydrogel beads.

3.3. Scanning Electron Microscopy (SEM):

![SEM Image]

10kV X500 50μm 001180
3.4 Swelling kinetics:

![Swelling kinetics of Formulation II](image)

Figure 5. Swelling kinetics of Formulation II in various media
3.5. Encapsulation efficiency:

Table: 3. Entrapment efficiency of Valsartan hydrogel beads

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Entrapment Efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>90.36</td>
</tr>
<tr>
<td>II</td>
<td>91.25</td>
</tr>
<tr>
<td>III</td>
<td>89.59</td>
</tr>
<tr>
<td>IV</td>
<td>90.43</td>
</tr>
<tr>
<td>V</td>
<td>89.82</td>
</tr>
</tbody>
</table>

3.6. In vitro release study:

Figur 6: In vitro release of Valsartan from hydrogel beads.

Table: 4. Model fitting of drug release from Hydrogel beads

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi model</th>
<th>Korsemeyer-Peppas model</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.729</td>
<td>0.54</td>
<td>0.85</td>
<td>0.835</td>
</tr>
<tr>
<td>II</td>
<td>0.738</td>
<td>0.537</td>
<td>0.858</td>
<td>0.836</td>
</tr>
<tr>
<td>III</td>
<td>0.811</td>
<td>0.565</td>
<td>0.904</td>
<td>0.85</td>
</tr>
<tr>
<td>IV</td>
<td>0.969</td>
<td>0.692</td>
<td>0.931</td>
<td>0.931</td>
</tr>
<tr>
<td>V</td>
<td>0.936</td>
<td>0.695</td>
<td>0.919</td>
<td>0.935</td>
</tr>
</tbody>
</table>
DISCUSSION

The FTIR spectra obtained were shown in figures 1 and 2. From the graphs it was observed that valsartan showed sharp and strong bands at 3435.37 cm⁻¹ due to N-H Stretching, 3120.96 cm⁻¹ due to O-H Stretching. A band at 2963.75 cm⁻¹ showed C-H Stretching superimposed upon O-H Stretching indicating the presence of phenyl groups and a band due to C-H Stretching at 2874.06 cm⁻¹. A sharp band at 1733.12 cm⁻¹, was due to C=O Stretching. At 1602.91 cm⁻¹ sharp peak appeared due to N=N which indicates the presence of azo group and due to N-N bending a peak occurred at 1567.23 cm⁻¹.

Peaks at 1470.79 and 1458.25 cm⁻¹ appeared due to C-O-H in plane band. Due to C-O Stretching a band appeared at 1390.74 cm⁻¹ was seen. A band at 1005.92 cm⁻¹ was due to C-N Stretching. Bands at 811.10 cm⁻¹, 759.99 cm⁻¹ were due to C-H bending and C-C bending respectively.

The hydrogel formulation confirmed the compatibility between the drug and the polymers by the presence of the following characteristic bands at 1602.05 cm⁻¹, 1033.10 cm⁻¹.

The DSC picture of pure Valsartan showed an endothermic peak at 102.80°C while the hydrogel formulation, due to the presence of the drug in the entrapped state by the polymer in amorphous state showed no peak. The DSC picture of pure Valsartan showed an endothermic peak at 102.80°C while the hydrogel formulation, due to the presence of the drug in the entrapped state by the polymer in amorphous state showed no peak.

The size, shape and surface morphology of the dried beads as visualized by SEM as shown in figure: 4 for the best formulation revealed the beads are very spherical with a soft surface.

Swelling is mainly due to the presence of xanthan gum a complex extra cellular polysaccharide. The rate of swelling mainly depends upon the cross linking nature of the hydrogel. The hydrodynamic free volume is high if the gel network is less which in turn lowers the cross linking density.

The higher swelling is due to the accommodation of more of the solvent molecules. The swelling rate was found to be different basing on the concentrations of xanthan gum and acryl amide. Due to polymer-polymer interactions and solvent-polymer interactions a mixed phase is observed where a hydrogel gains its maximum of hydrophilicity and swells. From the study it was observed that the rate of swelling was low in acidic media and double distilled water while it was high in the case of phosphate buffer.

The entrapment efficiency of Valsartan in the hydrogel beads was almost similar irrespective of their concentrations and ratios.

The results of the drug release study of the hydrogel were shown in the figure: 6. The drug release from a hydrogel can be attributed by a number of factors like chemical structure of the polymers, composition of the hydrogel, network structure release condition, release conditions, concentration of the crosslinker etc. In this study the drug release from the hydrogel beads was affected by the concentrations of the polymers and the cross linking agent have been examined. From the results, it was found that the drug release was low in the acidic media due to poor swelling, but was found to be more in alkaline media due to the enhancement of swelling rate.

Formulation I showed a release rate of 79.27% and formulation II with 79.19%. The cumulative percentage drug release was observed to reduce slowly with the increase in the concentration of cross linking agent.

The data obtained from in-vitro release studies was fitted into various kinetic equations to find out the mechanism of drug release from the hydrogels. Mathematical modeling aids in understanding the physics of the drug transport, its release rate and behavior of the systems thus facilitating the advancement of desired novel drug delivery system.

The data from the table: 4 showed that formulations I, II & III showed zero order non-fickian diffusion mechanism referring that the drug release occurred by both diffusion and erosion controlled mechanism and formulations IV & V followed zero order diffusion mechanism with super case-2 transport mechanism indicating that the most of the drug release occurred by the erosion of the polymer chains.
CONCLUSION

A controlled release oral drug delivery system of Valsartan was developed in the form of hydrogel beads using various proportions of polymers (xanthan gum, acrylamide and soluplus) and different concentrations of crosslinking agent. Presence of acrylamide and xanthan gum made the hydrogel beads mechanically strong then and possibility for the bead formation and maximum swelling rate. Soluplus provided a solubilizing matrix for the poorly soluble drug. Increasing the concentration of crosslinking agent can be used further to control the drug release.

Thus the hydrogel bead system as an effective stimuli-responsive drug delivery system was developed which offered a solubilizing cross-linked network matrix for the poorly soluble drug, Valsartan providing the best controlled release of the drug over 24 hrs.

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REFERENCES