
Design and In vitro Evaluation of Modified release Valsartan Hydrogels.

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Abstract

An attempt was made to develop a novel cross-linked soluplus-xanthan gum-acrylamide hydrogels of valsartan by entrapping the hydrophobic drug initially in a novel polymeric solubilizer, soluplus and then hydrogels were prepared using Xanthan gum and acrylamide in as controlled release polymers in different ratios using methylene bisacrylamide as cross linking agent and Potassium persulphate as an initiator. The formulations were characterized by FTIR and DSC for compatibility, SEM for their surface morphology, swelling kinetics and in vitro drug release. FTIR and DSC showed no chemical interaction between the drug and the polymers. SEM revealed the surface morphology of the hydrogel systems before and after swelling. A significant difference of swelling behavior was observed in different media. But a dependence of the equilibrium of swelling on the pH was found to be higher in basic media when compared to the acidic. In vitro release pattern indicated that formulation 14 showed a better release of 88.27% for a period 24 hrs with 81% of swelling in phosphate buffer of pH 6.8. It was also observed that the release rate was found to be increased when the concentration of crosslinking agent was increased. The kinetic release pattern was further confirmed that it followed a zero-order non-fickian diffusion controlled release with supercase-II transport mechanism.

Keywords: Soluplus, Xanthan gum, Acrylamide, Hydrogels, diffusion, controlled release

Introduction

Hydrogels are three dimensional, hydrophilic, polymeric networks capable of imbiving large amount of water or biological fluids. They are of special interest in controlled release applications because of their soft tissue biocompatibility, the ease with which drugs are dispersed in matrix and the high degree of control achieved by selecting the physical and chemical properties of polymer network (1; 2). The hydrogels are rendered insoluble due to the crosslinking which may be physical or chemical which includes crystallites, entanglements, or weak associations like hydrogen bonds or vanderwaals forces. These crosslinks are responsible for providing the physical integrity and network structure of the hydrogels. The polymeric biomaterials like xanthan gum are used to delay the drug dissolution at a slower rate depending on the exposure of drug molecules to aqueous environment surrounding the drug delivery system (3) Natural materials like xanthan gum are promising non-toxic; freely available polymers used in drug delivery systems (4; 5; 6). Their usage is advantageous in safety, ease of manufacture, cost effectiveness, biocompatibility and biodegradability (4;7; 8;). Since its discovery in 1950, xanthan gum has been widely studied and used as tablet excipient to increase the drug rate of delivery but not much work has been reported concerning the use of this polymer for a sustained drug release [9]. Xanthan gum is a natural, high molecular weight polysaccharide produced by the process of fermentation from xanthomonas campestris [10]. It is an anionic polyelectrolyte with a β-(1→4)-D-glucopyranose glucan. The anionic character is due to the presence of glucuronic acid and pyruvic acid groups in the side chain [11]. Since its discovery xanthan gum has been widely studied and used as tablet excipient to increase the drug rate of delivery but not much work has been reported concerning the use of this polymer for a sustained drug release.

Xanthan gum has a characteristic property of rapid hydration in cold water without lump formation with reliable viscosity. Hence, it can be widely used as thickening agent, stabilizer, emulsifier and foaming agent. It was earlier reported that xanthan gum has a retardant effect on the drugs in-vitro release providing zero-order release kinetics when used in relatively small amounts [12,13]. It can be widely used as thickening agent, stabilizer, emulsifier and foaming agent. It was earlier reported that xanthan gum has a retardant effect on the drugs in-vitro release providing zero-order release kinetics when used in relatively small amounts [12,13]. It was also reported that xanthan gum tablets maintained constant plasma drug levels in-vivo [14,15] U.S. FDA/CFSAN reported that ethanol precipitate of Xanthan Gum is recognized as safe according to GRAS (GRAS Notice No. GRN000211). It was
earlier reported that polymer blends may show synergistic properties [16]. 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. Due to its bifunctional character, Soluplus acts as a matrix solubilising polymer for poorly soluble drugs. Its unique structure provides ideal interactions with drugs through hydrogen bonding and leverages stability of the system. It is also a promising polymer for its usage in the delivery systems at a broader pH range.

It is ideal for formulating novel drug substances, (Ludwigshafen, 2009). Physical entrapment of the drug into the hydrogels is one of the methods to control the release rate by swelling following either fickian or non-fickian diffusion mechanism [18,19]. Poly acrylamide is a commercially important polymer that has been widely used in various drug delivery systems due to its excellent physicochemical properties and biocompatibility. Several reports have been made on the synthesis of porous hydrogels using Poly acrylamide as a monomer [12] but the synthesis and characterization of cross linked soluplus-xanthan gum-Acrylamide polymers have not been reported yet. With slight modifications, an attempt was made to develop a novel cross linked polymer blend of soluplus-xanthan gum-Acrylamide hydrogel system using Potassium persulphate as an initiator and Methylene bis acrylamide as a cross-linking agent and potassium acryl amide as a cross linker by incorporating the insoluble drug, valsartan into the polymeric solubilizer, soluplus to explore its potential applications in the controlled drug delivery of drugs by the enhancement of solubility poorly soluble drug, Valsartan, an antihypertensive drug.

Material and Methods

Materials

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

Synthesis of cross linked xanthan gum-soluplus-acrylamide hydrogel

An accurately weighed quantity of xanthan gum was dissolved in about 15 ml of deionised water by mixing vigorously at a speed of 800-900rpm. Accurately weighed quantities of kneaded mixture of valsartan and soluplus 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. Then 0.02%w/v and 0.01%w/v of Methylene bis acryl amide as a cross-linking agent and potassium per sulfate as an initiator respectively were dissolved separately in 5 ml of deionised water and then added to the above mixture and stirring was continued for 20 mins. This above mixture was kept aside for 1 Hr. after adding 10 ml of 0.1N NaOH. It was then immersed in 100 ml of ethanol. After 48 hrs, the formed gel was filtered using membrane filter paper under vacuum and dried at50° C. Fourteen formulations were prepared as shown in the Table: 1.

Characterization of the hydrogels by FTIR Spectroscopy

FTIR spectra were recorded on a KBr 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.

Characterization of the hydrogel by Differential Scanning Calorimetry

Thermal characterization of Valsartan and soluplus and Hydrogel was 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 300°C at a heating rate of 10°C/min. Nitrogen flow rate of 20 ml/min was used for each DSC run.

Examination of Surface Morphology

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

Study of swelling behavior of the cross-linked Hydrogel

Swelling parameter is the vital factor for the characterization of hydrogels because there is a fundamental relationship between the swelling of the polymer and the nature of the swelling medium. With the differences between the polymers and the effect of pH on swelling were investigated as follows:

Circular films of thickness 0.2 -0.5mm 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 discs 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 the following equation:

\[ \text{ESR} = \frac{W_2 - W_1}{W_1} \]

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

The in vitro drug release rate of Valsartan from hydrogel was carried out in triplicate using USP type II (Basket) apparatus (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.

Evaluation of release kinetics

The mechanism of the drug release was investigated by fitting the release data using zero order, first order, Higuchi, Korsemeyer-Peppas, and Erosion models as shown in the Table: 2.

Results and discussion

Fourier Transform-Infrared Spectroscopy (FTIR)

From the FTIR spectra obtained as shown in the figure: 1, almost all the bands of polymers, without affecting its peak position and trends, which indicated the absence of well-defined interactions between drug and polymers. Also it was already confirmed that Valsartan and Xanthan gum were compatible with each other. [20]

Differential Scanning Calorimetry (DSC)

The DSC graphs were shown in the figure: 2. Thermographs showed a sharp endothermic peak at 100.5 °C related to drug melting point. The absence of a melting peak of the drug in the solid was taken as an indication that the drug was entrapred by the polymer, leading to a reduction in the overall crystalline nature of the system thus proving that there no chemical interaction between the drug and the polymers exist.

Scanning Electron Microscopy (SEM)

The surface morphology of the hydrogel before and after swelling was shown in the figures: 3a and 3b. It was clearly evident that hydrogel got swollen by imbibing the aqueous media and deswelled at faster rate.

Swelling kinetics

The swelling studies for the hydrogel were conducted in media of varying pH. The results were shown in the graphs: 1, 2, and 3. 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. Among all the nine, formulation 14 showed a better swelling which may be due to the presence of network of crosslinks between the molecules and also due to the pH of the medium. The increased swelling might be also due to the presence of amorphous nature of the soluplus which was used as the solubilizing polymer and due to its matrix network.

Mechanism and mathematical modeling of drug release from the hydrogel matrix

The results of the drug release study of the hydrogel were shown in the graph: 4. 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 condition etc. In this study the drug release from the hydrogel was affected by the concentrations of the polymers and soluplus that were incorporated within the hydrogel network. From the results obtained, 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. Also the release was influenced by the presence of soluplus due to which the solubility of the drug was enhanced. Among all, Formulation 14 showed a cumulative release of 88.27% for a period of 24 hrs as shown in the graph: 4. The release of the drug from the hydrogel matrix was may be due to very slow erosion of the polymeric matrix under the test conditions that resulted in slow diffusion of the entrapped drug. The drug release mechanisms from the swelling polymer matrices based on the relative rate of diffusion of water have been classified into three types namely Case I or simple fickian diffusion, Case II diffusion and Non-fickian or Anomalous diffusion. 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 systems. From the results obtained by the mathematical models it was confirmed that the drug release from formulation 14 followed zero-order kinetics by diffusion process with supercase-II transport mechanism.
The release profiles of the hydrogel systems were summarized as shown in the table: 3.

**Conclusion**

A controlled release oral drug delivery system of Valsartan using xanthan gum, acrylamide and soluplus was developed in the form of a hydrogel device offering solubilizing matrix for the poorly soluble drug, valsartan. Soluplus was effectively utilized for the improvement of solubility as well a good matrix polymer for controlling the drugs’ release. Further investigations are being carried out to substantiate the in vitro results.

**References**


**Acknowledgements**

My sincere thanks to Alembic Pharmaceuticals Ltd, Ahmedabad and BASF, The Chemical Company, Germany for providing gift samples.
Figure: 1 FTIR of the Hydrogel system of Valsartan
Figure: 2 DSC of the Hydrogel system of Valsartan.
Figure: 3a SEM of the Hydrogel before swelling
Figure: 3b SEM of the Hydrogel after swelling
Table: 1. Formulation of Hydrogel devices of Valsartan.

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Table: 2. Mathematical modeling for the study of release kinetics.

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<td>( Q_t = Q_0 + K_H t^{1/2} )</td>
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<td>Korsmeyer-Peppas</td>
<td>( Q_t = K_{KP} t^n )</td>
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Table 3. Results of model fitting of drug release of hydrogel in phosphate buffer pH 6.8.

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Graph 1. Swelling kinetics of Valsartan Hydrogels in double distilled water.
Graph 2: Swelling kinetics of Valsartan Hydrogels in Acidic medium (0.1 N HCl)
Graph 4. In vitro dissolution profile of Valsaratan Hydrogels