Original Article

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STUDIES ON P^H DEPENDANT SWELLING BEHAVIOR OF ACRYLIC ACID IONIC HYDROGELS

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Abstract

The aim of the present study was an attempt to synthesise novel hydrogels using acrylic acid and xanthan gum and to study the swelling behavior and mechanism of the drug release from the hydrogels. Acrylic acid and xanthan gum were used as rate controlling polymers. Methylene bis acrylic acid was used as a crosslinking agent and potassium persulfate as reaction initiator. Swelling studies were performed in different media i.e. distilled water, 0.1N HCl and 6.8 phosphate buffer. The hydrogels showed better swelling in 6.8 phosphate buffer. Dissolution studies showed that the drug release was better observed in alkaline P^H. The release kinetics followed zero order non-fickian diffusion mechanism. Hence Hydrogel formulation of Valsartan could be effectively used as P^H dependant swellable systems and hence used as stimuli-responsive drug delivery systems.

Keywords: Hydrogels, Acrylic acid, Xanthan gum, Valsartan, Stimuli responsive hydrogels.

Introduction

A rather new development in the drug delivery systems is the emergence of Hydrogel-based technologies. Hydrogels are macromolecular three-dimensional structured materials with the ability to swell in water and retain a significant amount of water within their structures[1]. The water absorbing capacity is due to the presence of hydrophilic groups like –COOH, -OH, -CONH, $-CONH_2$, $-SO_3H$ etc. Hydrogels can be neutral or ionic in nature. In neutral hydrogels, the driving force for swelling arises from the water-polymer thermodynamic mixing contribution to the overall free energy which is coupled with an elastic polymer contribution[2, 3]. In ionic hydrogels, the swelling process is due to the previous two contributions as well as the ionic interactions between charged polymer and free ions. The ionization of the pendent ionizable groups such as carboxylic acid, sulfonic acid

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or amine groups renders the polymer more hydrophilic and thus leads to a very high water uptake[4].

The swelling properties of hydrogels are unique and dependant on the pendant functional groups. Changes in P^H, ionic strength and equilibrium, temperature, etc acts as inputs for the degree of swelling ions[5, 6, 7]. Other factors like composition of the swelling medium, valence and nature of the polymer and the counterion, etc also influence the dynamics and equilibrium swelling behavior[8]. The ability to control the dynamics of swelling by changing the P^H and ionic strength of the external swelling medium provides various opportunities for stimuli-responsive drug delivery. Xanthan gum is a natural, high molecular weight polysaccharide produced by the process of fermentation from *xanthomonas campestris* 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[9]. 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. The present work was intended to develop acrylic acid - Xanthan gum hydrogels and to study the swelling kinetics and release mechanisms of the drug from the hydrogels in different p^H media.

Materials and methods

Acrylic acid, Xanthan gum, Potassium persulfate and N, N^I-Methylene bis acrylamide were procured from Sigma-Aldrich Chemicals Ltd. Valsartan was obtained from Alembic Pharmaceuticals, Ahmedabad. All other reagents and chemicals used were of analytical grade.

Synthesis of Acrylic acid-Xanthan gum Hydrogels

Hydrogels of Valsartan were prepared by physical crosslinking method. To an accurately weighed quantity of Xanthan gum, 80 mg of valsartan was dissolved in about 15 ml of deionised water by mixing vigorously at a speed of 800-900rpm for 10 mins. To the mixture acrylic acid was added and homogenized at 1500-200 rpm for 20 mins, using ultrasonic homogenizer until they were completely mixed. Methylene bis acryl amide and potassium per sulfate were dissolved separately in 5 ml of deionised water and added to the above mixture. Stirring was continued for 20 mins. 10 ml of 0.1N NaoH and kept aside for 1 Hr. 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 at 50^o C. Five different hydrogel formulations were synthesized using various concentrations of xanthan gum.

Swelling studies

This process of swelling studies was done in different media like distilled water, 0.1 N H Cl, phosphate buffer of P^H 6.8. The swelling characteristics of the gels were investigated in triplicate at temperatures ranging from ambient temperature to 25-35^o C. Samples of the cured polymer (with drug incorporated) with a mass of 1.1 ± 0.35 g were placed in a petri dish; the petri dish was filled with media and placed in a fan oven at the required temperature. Petri dish lids and Petri Seal (Diversified Biotech Ltd.)

were placed on the petri dishes while in the oven to prevent evaporation. Periodically, excess polymer solution was removed after predetermined time intervals by pouring the solution through a Buchner funnel.

The samples were then blotted free of surface water with filter paper, and the wet weight of the gel sample was measured at room temperature. The samples were re-submerged in fresh distilled water and returned to the oven.

The percentage that the hydrogels swelled was calculated using formula (1):

$$\text{Swelling (\%)} = W_t / W_0 \times 100$$

Where,

W_t is the mass of the gel at a predetermined time and W_0 is the dry mass of the gel.

This process was continued until the sample appeared to have dissolved.

Dissolution studies

The study was carried out in triplicate using USP type I (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 P^H 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.

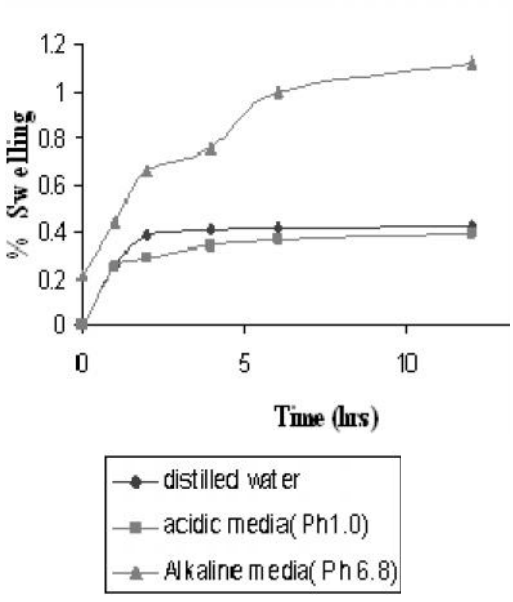
The mechanism of the drug release was investigated by fitting the release data using zero order, first order, Higuchi, Hixon-Crowell, Korsemeyer – Peppas models to predict their release profiles as shown in table 01.

Table 01: Mathematical modeling for the study of release kinetics.

Model	Equation
Zero order	$Q = Q_o + K_o t$
Higuchi	$Q_t = Q_o + K_H t^{1/2}$
Korsmeyer-Peppas	$Q_t = K_{KP} t^n$

Results and Discussion

The swelling studies for the best hydrogel were conducted in media of varying p^H. The results were shown in the graphs 1.



Graph 01: Swelling kinetics of Acrylic acid – Xanthan gum Hydrogels in different p^H

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 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 acrylic acid. Due to polymer-polymer interactions and solvent-polymer interactions a mixed phase is lowers the cross linking density. The higher 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.

Dissolution studies

Table 02: Cumulative percentage drug release of hydrogels.

Time (h)	F1	F2	F3	F4	F5
0	0.49 ± 0.31	0.44±0.018	0.40 ± 0.012	0.41± 0.00	0.38 ± 0.04
1	1.05 ± 0.04	1.06±0.000	1.48 ±0.33	1.48 ± 0.27	0.52 ± 0.14
3	3.52 ± 0.76	1.49±0.005	1.97 ± 0.02	3.66± 0.02	2.74± 0.09
4	22.9 ± 0.09	18.6±0.000	31.07.2± 0.25	47.00 ± 0.01	48.37 ± 0.04
6	31.64 ± 0.23	26.6±0.971	31.78± 0.00	49.20 ± 0.00	60.39 ± 0.18
8	39.60 ± 0.25	48.4± 0.286	38.96 ± 0.92	51.3± 0.00	64.26 ± 0.13
12	44.58 ± 0.18	55.2±0.005	44.47 ± 0.00	56.17 ± 0.15	69 ± 0.00
16	52.66 ± 0.13	57.7± 0.010	52.59 ± 0.27	69.5 ± 0.04	72.7 ± 0.09

All values are represented as mean ± S.D, n = 3.

It was shown that the cumulative percentage drug release was increased by the increase in the xanthan gum concentration. Formulation (F5) showed the best release of 72.7% at the end 16 hrs.

Mechanism and mathematical modeling of drug release from the hydrogel

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 that were incorporated within the hydrogel network. From the results obtained as shown in table 03, 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.

Table 03:
Data of kinetic models of hydrogel formulations

Formulation	Parameter (R^2)			
	zero order	First order	Higuchi Model	Korsemeyer-Peppas Model
F1	0.671	0.896	0.928	0.896
F2	0.709	0.916	0.925	0.916
F3	0.833	0.869	0.901	0.869
F4	0.834	0.84	0.829	0.84
F5	0.855	0.834	0.813	0.89

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 hydrogels followed zero-order non-fickian diffusion mechanism.

Conclusion

Cross-linked starch–xanthan gum hydrogels were successfully synthesized. The synthesis

process is straight forward and can be conducted using conventional equipments. The equilibrium swelling ratio and swelling rate of the Acrylic acid–xanthan gum hydrogels increased with increasing Xanthan gum content. The hydrogels exhibited a p^H dependant swelling. This can be selectively utilized as stimuli responsive dosage forms. The results of this work suggest that the new modified Acrylic acid- xanthan gum hydrogels are a promising material for controlled release formulations for a wide range of drugs and applications.

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References

1. Abdekhodaie, M., & Wu, X. Y. Modeling of a glucose sensitive composite membrane for closed-loop insulin delivery. Journal of Membrane Science, 335, 2009, 21–31.
2. Flory, P.JPrinciples of Polymer Chemistry, Cornell University Press, Ithaca, NY, 1953, 570- 590.
3. Kudela, V. Hydrogels. In: H.F. Mark and J.I. Kroschwitz (Eds.), Encyclopedia of Polymer Science and Technology, Vol. 7, Wiley, New York, 1985. 783-807.
4. Katchalsky, A., Lifson, S. and Eisenberg, H.Equation of swelling for polyelectrolyte gels, J. Polym. Sci. 7, 1951, 571 574.
5. Siegel, R.A. and Firestone, B.A. PH Dependent equilibrium swelling properties of hydrophobic polyelectrolyte copolymer gels, Macromolecules 21, 1988, 3254-3259.
6. Tanaka, T. Phase transitions of gels. In: R.S. Harland and R.K. Prud'homme (Eds.), Polyelectrolyte Gels, ACS Symposium Series, Vol. 480, American Chemical Society, Washington, DC, 1992, 1-21.
7. Brannon, M.L. Structural Characteristics and Swelling Behavior of pH- Sensitive Hydrogels, Ph.D. Thesis, School of Chemical Engineering, Purdue University, West Lafayette IN., 1988, 324-329.
8. Mandel, M. Polyelectrolytes. In: H. Mark and J.l. Kroschwitz (Eds.), Encyclopedia of Polymer Science and Technology, Vol. 11, Wiley, New York, 1985. 739 829.
9. Jiangyang, W. Kang, L. Meimei, H.Zhimin, Carbohydr.polym.73. 2008, 241-247.