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PHARMACEUTICALS APPLICATIONS OF CHITOSAN HYDROGEL BEADS

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ABSTRACT

The paper addresses development of pH sensitive interpenetrating polymeric network (IPN) beads composed of chitosan-mono sodium glutamate cross linked with glutaraldehyde and their use for controlled drug release. The beads were characterized by SEM to understand the surface morphology and internal structure. The swelling behavior of the beads at different time intervals was monitored in solutions of pH 2.0 and pH 7.4. The release experiments were performed in solutions of pH 2.0 and pH 7.4 at 37^{o}C using salicylic acid (SA) as a model drug. The swelling behavior and release of drug were observed to be dependent on pH, degree of cross linking and their composition. The results indicate that the newly constructed cross linked IPN beads of chitosan- mono sodium glutamate might be useful as a vehicle for controlled release of drug. The kinetics of drug release from beads were best fitted by Higuchi's model in which release rate is largely were best fitted by Higuchi's model in which release rate is largely governed by rate of diffusion through the matrix.

KEYWORDS: salicylic acid, IPN, glutaraldehyde.

INTRODUCTION

Recently efforts have been made to design noval drug dosage formulations so that more and more effectiveness could be altered to the conventional dosage forms. To achieve this goal controlled release technology had originated in 1980 that developed the commercial methodology by which pre decided and reproducible release of drug up to therapeutic level into a specific environment over a prolonged time period could be maintained. Such drug delivery systems function accordingly to the changes in physiological signals with in the body and target the drug for the site of action to minimize any side effect. Nano and micro beads of polymers have been formulated using polymeric material either synthetic or natural

(1-3) origin. Therapeutic molecules complexed by polymers capable of forming gel, may also be released by diffusion. Hence drug delivery system require polymeric matrix which would be non toxic, biocompatible, biodegradable. Chitosan is such a valuable natural biocompatible polymer, nontoxic, biodegradable (4,5), mucoadhesive (6,7), easily bio absorbable (8) and also posses gel forming ability at low pH (9). Moreover, it has antacid and anti ulcer activities which prevent or weaken drug irritation in the stomach. All these interesting properties of chitosan make this natural polymer an ideal element for formulating drug delivery devices (8-13) and this material has been used to form drug carrying systems for several biomedical purposes (14-26). Chitosan is obtained by N-deacetylation of chitin which is naturally abundant muco polysaccharide and forms the exoskeleton of crustaceans, insects etc. It is well known to consist of 2-acetamido 2-deoxy-β-D-glucose through a β (1→ 4) linkage (27). Thus, chitosan is a hetero polymer having (1→ 4) 2-amino 2-deoxy β D glucose unit with (1→4) 2-acetamido-2 deoxy β-D-glucose units of original chitin in polymeric chain. Chitosan is highly basic polysaccharide. It is soluble in dilute acids such as acetic acid, formic acid etc. It posses property of forming hydrogels which are highly swollen hydrophilic polymer network, capable of absorbing large amounts of water and widely used in controlled release system (28,29). Some of the most appealing characteristics of chitosan are its bioadhesive properties and its ability to promote cell proliferation and consequently, tissue regeneration (14,15). These properties of chitosan are enhanced upon decreasing the polymer's degree of acetylation (30,31) and are of outmost importance for biomedical engineering. Its beads are solid, spherical, micron or nano sized drug carrier particles constituting a matrix type of structure. Drug may be either absorbed at the spherical beads or entrapped with in it. These polymeric beads are advantageous over pellets including relatively higher intercellular uptake. Their charge properties influence the uptake by intestinal ephithelia. The beads obtained from hydrophobic polymers has found to be higher uptake as compared to the beads prepared from more hydophillic surfaces (32). So nano/micro beads surface charges and increased hydrophobicity of polymeric matrix have been found to be effective for the gastrointestinal uptake in a positive sense. Our study is an attempt to develop cross linked beads composed of chitosan and mono sodium glutamate as spacer groups cross linked with glutaraldehyde for sustained release of salicylic acid as a model drug to investigate their swelling behavior and modeling drug release properties.

EXPERIMENTAL

Material

Chitosan was purchased by India Sea Food, Kerala, and was used as received. Its percentage of deacetylation after drying was 89 %. Salicylic acid (SA), was obtained as a gift sample from Sarthak Biotech Pvt. Ltd., HSIDC, Haryana, India. Glutaraldehyde and monosodium glutamate were procured from SD Fine Chemicals Ltd., Mumbai, India and Reidal Chemicals, India. All other chemicals used were of analytical grade. Double distilled water was used in throughout the studies.

Preparation of semi-interpenetrating polymer network (IPN) beads

Different IPN beads (C1-C6) varying in composition were prepared separately. Their composition is described in table-1. Weighed quantity of chitosan and monosodium glutamate were dissolved in 40 ml of 2% acetic acid by weight and stirred for three hours using magnetic stirrer at room temperature. The homogeneous mixture was extruded in the form of droplets using a syringe into NaOH-methanol solution (1:20 w/w) under stirring condition. The beads were washed with hot and cold water respectively. The resultant beads were allowed to react with glutaraldehyde solution as given in table-1 at 50^{o}C for about 10 minutes. Finally, the cross linked IPN beads were successively washed with hot and cold water followed by air drying.

Table 1 Composition of chitosan monosodium glutamate beads

Sr. No.	Sample Code	Chitosan (g)	Glutamic acid (g)	20 ml Glutaraldehyde (%)	2% acetic acid (ml)
1.	C1	1.0	1.0	3.13	40.0
2.	C2	1.0	1.0	6.25	40.0
3.	C3	1.0	1.0	12.5	40.0
4.	C4	1.0	1.0	25.0	40.0
5.	C5	0.8	1.0	12.5	40.0
6.	C6	1.0	0.8	12.5	40.0

Drug loaded beads of same composition were also prepared separately by adding a known amount of SA (100 mg, 200 mg) respectively to the chitosan, amino acid mixture before extruding into the NaOH- methanol solution.

Study of swelling behavior

Swelling behavior of chitosan beads (C1-C6) were studied in different pH (2.0 and 7.4) solutions. The percentage of swelling for each sample at time t was calculated using the following formula.

Percentage of swelling = $\{(W_t - W_o)/W_o\} \times 100$

Where, Wt = weight of the beads at time t after emersion in the solution.

Wo = weight of the dried beads

SEM studies

The shape and surface morphology of the beads were examined using FESEM QUANTA 200 FEG model "(FEI, The Netherlands make)" with operating voltage ranging from 200 V to 30 kV. FESEM micrographs were taken after coating the surfaces of bead samples with a thin layer of gold by using BAL-TEC-SCD-005 Sputter Coater (BAL-TEC AG, Balzers, Liechtenstein company, Germany) under argon atmosphere.

Drug release studies

The drug release experiments were performed at 37^{o}C under unstirred condition in acidic (pH 2.0) and basic (pH 7.4) solution. Beads (0.1 g) containing known amount of the drug were added to the release medium (30 ml). At pre decided intervals, samples of 2 ml aliquots were withdrawn, filtered and assessed by recording the absorbance at 193.5 nm. The cumulative SA release was measured as a function of time.

RESULTS AND DISCUSSION

SEM micrographs of C3 dried beads and its surface morphology is shown in Fig. 1 which proves that the beads were nearly spherical or some what oval in shape. The approximate size of beads is 150 µ. The beads had rough, rubbery, fibrous and folded surfaces. Half cut beads shows fine pores and tubular structures.

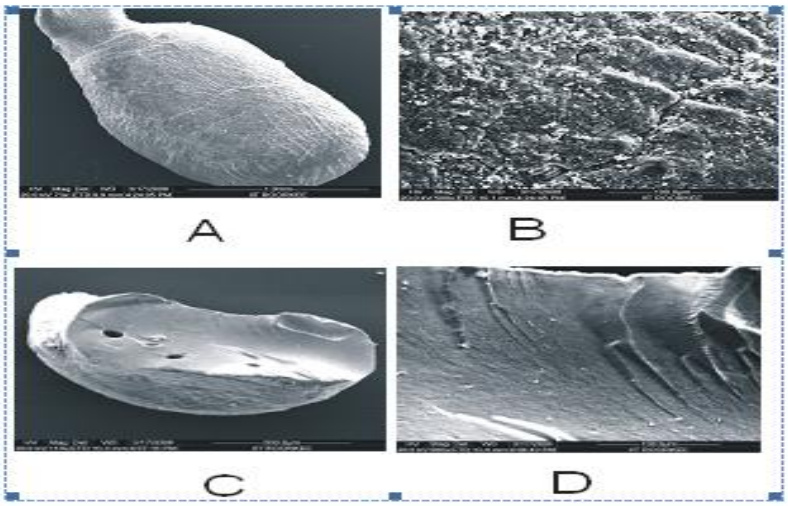

Fig. 1- SEM micrographs of C3 beads- full bead (A), magnified full bead (B), half cut bead (C), magnified cut bead (D)

Swelling studies

Swelling response of the glutaraldehyde crosslinked chitosan-glutamic acid beads in solution of pH 2.0 and 7.4 as shown in Fig. 2 and 3. It is observed (Fig. 2) that the swelling rate of the crosslinked beads having equal weight ratio of chitosan and glutamic acid with varying concentration of crosslinker follows the order C1>C2>C3>C4. When the crosslinked beads are placed in the solution, the solution penetrates into the beads and the beads subsequently try to swell. Generally, the swelling process of the beads in pH<6 involves the protonation of amino/imino groups in the beads and subsequent relaxation of the coiled polymeric chain. Initially, during the process of protonation, amino/imino groups of the bead surface are protonized which led to dissociation of the hydrogen bonding between amino/imino groups and other groups. Afterwards, protons and counter ions diffuse into the bead to protonate the amino/imino groups inside the beads and dissociating the hydrogen bond.

It is observed that the swelling rates are directly proportional to the degree of crosslinking. As the higher crosslinker density results in higher strength of the beads and lower degree of swelling, the lowest swelling rate is observed in case of C4 beads. Further, the percentage of swelling is higher in basic solution than in acidic solution. This may be due to the presence of free carboxylic ends of the chitosan glutamic acid semi IPN which are more likely to be attached by basic solutions.

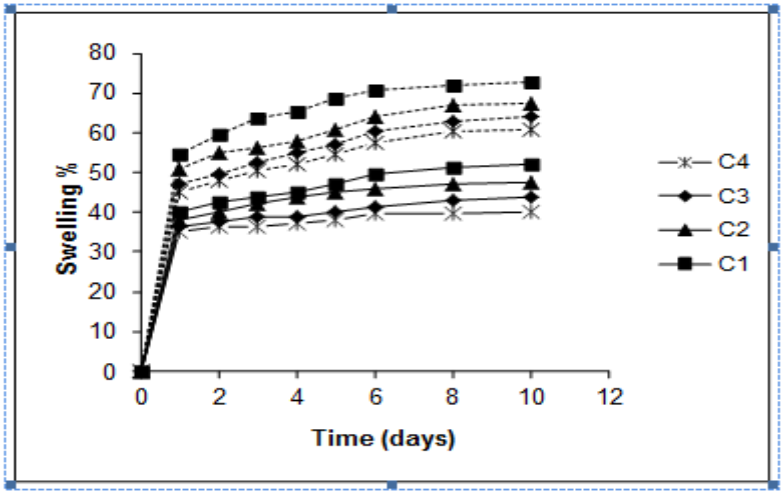

Fig. 2- Plots showing swelling percentage vs time at pH 2.0 (—) and pH 7.4 (·····) having varying concentration of glutaraldehyde.

The percentage of swelling of the crosslinked beads having the same concentration of crosslinker glutaraldehyde decreases with increasing concentration of chitosan (C5>C3>C6)

and is shown in Fig. 3. It can be explained as the percentage of glutamic acid which acts as a spacer decrease, the pore size of the beads decreases and the penetration of the pH solution into the beads became difficult resulting in lesser degree of swelling.

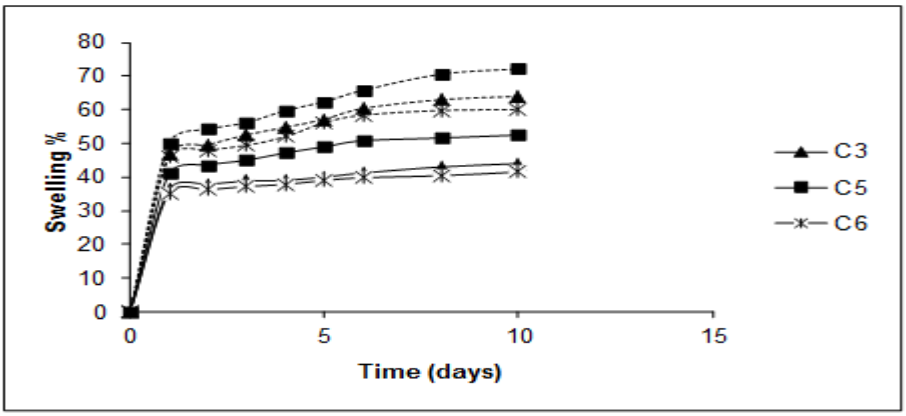

Fig. 3- Plots showing swelling percentage vs time at pH 2.0 (—) and pH 7.4 (·····) having varying concentration of chitosan.

Drug release

To understand the release of salicylic acid from the crosslinked chitosan-glutamic acid beads, the in vitro release experiments are performed with 0.2 g of sample containing 20 mg and 30 mg of drug respectively. The dissolution profile of salicylic acid from crosslinked beads at various time intervals in acidic pH 2.0 and basic pH 7.4 medium is shown in Fig. 4-7.

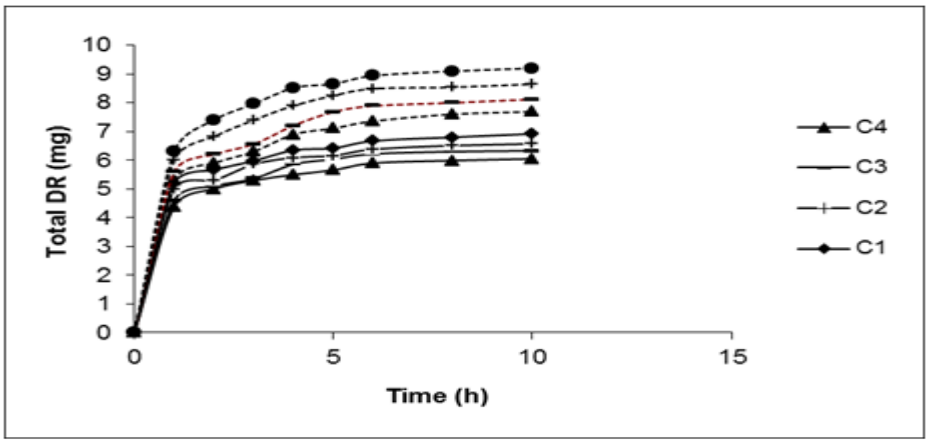

Fig. 4 - Plots showing total drug release from beads loaded with 200 mg drug at pH 2.0 (—) and pH 7.4 (·····) having varying concentration of glutaraldehyde.

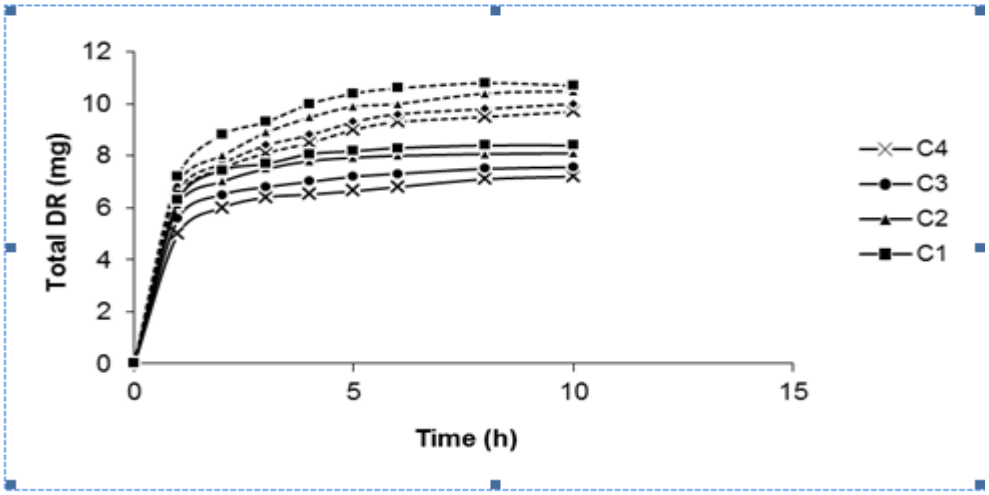

Fig. 5 - Plots showing total drug release from beads loaded with 300 mg drug at pH 2.0 (—) and pH 7.4 (·····) having varying concentration of glutaraldehyde.

A burst release is observed initially for the first hour in both media followed by a moderate release for next 5 hours and finally an almost constant release of salicylic acid from the matrix is observed for the studied period of 48 hours. The drug release rate is found to increase with the decrease in crosslink density. This may be due to the fact that the diffusion of drug from the semi IPN depends on the pore size of the polymer network, which will decrease with increase in the degree of crosslinking. The dissolution of salicylic acid from the crosslinked chitosan glutamic acid beads at various time intervals indicate that the amount of drugs released is much higher in basic solution than in acidic medium. This can be explained by the fact that the release of drug depends mainly on the percentage of swelling of beads. Initially the burst release of drug is observed due to the fast penetration of the solvent into the crosslinked beads which is governed by the Fick's law of diffusion. After few hours, a steady state is reached leading to a plateau nature of plots. A very small change in concentration of drug release is observed during 24-48 hours period. After 48 hours, no significant change in concentration of drug release was observed from the experiment data. At pH 2.0, here is less swelling, thus drug entrapped in the beads can not be released easily. However, at pH 7.4 the beads are swollen to a higher percentage, leading to faster release of drug. The higher rate of drug release in the basic medium may be due to the presence of two carboxylic ends. Since Carboxyl group is more susceptible to attack by the basic solution, the drug release in the acidic medium is less due to less interaction of acidic solution with the polar groups of Semi IPN. The release experiments are performed for the beads with varying weight ratios of chitosan and glutamic acid having the same percentage of crosslinker (12.5%). It was

observed that the beads having lower concentrations of chitosan have higher release rate, followed by the equal weight ratio of chitosan and glutamic acid. The slowest release rate is observed in case of higher concentration of chitosan. The lower concentration of glutamic acid (spacer) includes a closer association of chitosan chain leading to a decreasing rate of swelling as well as drug release.

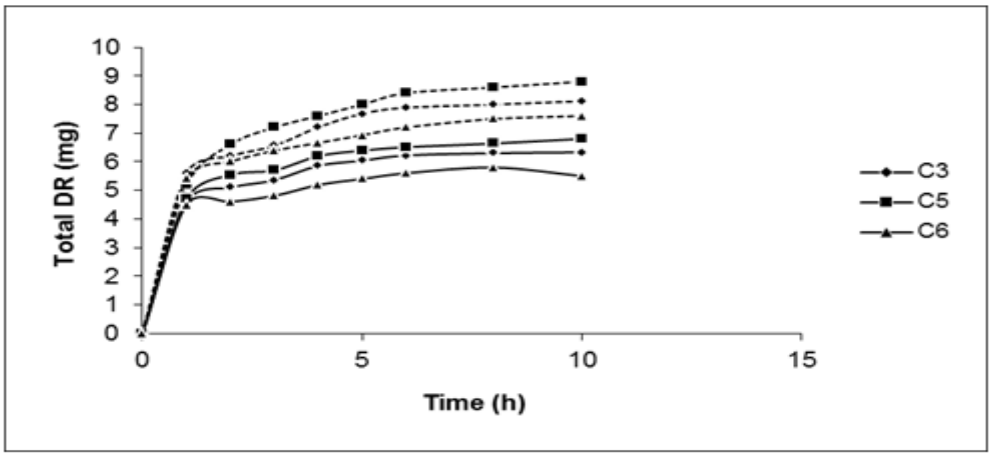

Fig. 6 - Plots showing total drug release from beads loaded with 200 mg drug at pH 2.0 (—) and pH 7.4 (·····) having varying concentration of chitosan.

The drug release also shows a dependence on the amount of drug loading. The maximum amount of drug released from 0.2 g of sample containing 20 mg of salicylic acid is 9.2 mg in basic and 6.92 mg in acidic solution and the lower limit of drug released from the same composition is 6.05 mg in acidic medium and 7.6 mg in alkaline medium. The maximum amount of drug released increases to 8.4 mg in acidic medium and 10.7 mg in basic medium in case of 30 mg salicylic acid loaded beads and the minimum amount of drug released is 7.2 mg in acidic medium and 9.3 mg in alkaline medium respectively. It is observed that the release is faster in case of 30 mg of drug loaded beads as compared to 20 mg drug loaded beads. This may be explained that due to the higher concentration gradient, there is higher rate of molecular diffusion and thus more the release of drug. Hence, the maximum amount of drug released after prolonged time approaches the maximum drug present in the sample. However, the total drug release increases with the increase in quantity of drug loaded in beads but the percentage of release of drug from beads decreases with increased concentration of drug in the beads.

In order to have an insight into the mechanism of drug release behavior Higuchi's model were best fitted into the kinetic data of drug release. Linear plots of percent cumulative

amount release verses square root of time for IPN beads have been obtained for entire data demonstrating that the release from the crosslinked polymeric microsphere matrix is diffusion controlled (33)

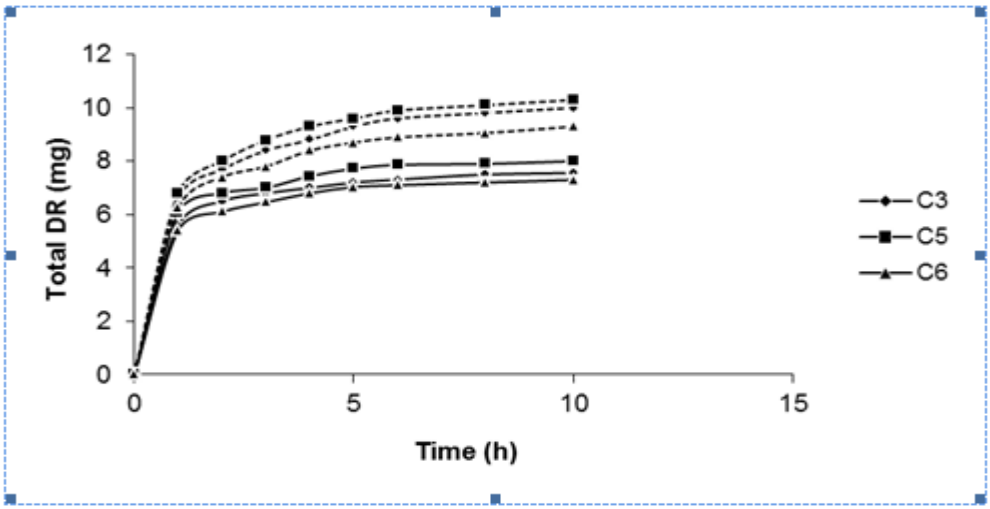

Fig. 7 - Plots showing total drug release from beads loaded with 300 mg drug at pH 2.0 (—) and pH 7.4 (·····) having varying concentration of chitosan.

CONCLUSION

The observations of the present study have shown that chitosan-mono sodium glutamate beads posses a pH dependent swelling behavior. It can be used successfully for the formulation of controlled drug delivery devices. They have optimum entrapping capacity for the studied drugs and provide a sustained release of drugs for extended periods which makes them appropriate for delivery of drug at a controlled rate.

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