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Controlled Release of Metformin hydrochloride through crosslinked blends of chitosan-starch

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ABSTRACT

Chitosan has wide range of applications as a biomaterial, but barriers still exist to its broader use due to its physical and chemical limitations. In this work, blends of chitosan (CHI) and starch (ST) are prepared and crosslinked with glutaraldehyde and sodium hexameta phosphate. Beads of CHI and ST are prepared in different weight ratios of CHI/ST (90/10, 80/20, 70/30, 60/40 and 50/50). The blends are characterized using differential scanning calorimeter (DSC) and Fourier transform infrared spectroscopy (FTIR). Swelling studies show that the rate of swelling of matrix is dependent on the degree of crosslinking and composition of beads. To prepare drug loaded beads, a known amount of metformin hydrochloride is added to the CHI-ST solution before extruding into sodium hydroxide-methanol solution. Drug release studies in acidic and basic environment are carried out using UV- VIS spectrophotometer indicates that the release is sustained over a long time. The results suggest that CHI-ST crosslinked beads are suitable for controlled release of drug.

Keywords: Controlled drug release, chitosan, DSC, FTIR, crosslinking.

INTRODUCTION

Biodegradable polymers are extensively used for the development of drug delivery systems during the past two decades. Various biologically active agents, such as antibiotics, contraceptives, enzymes, anticancer drugs, have been introduced to controlled release matrices. Chitosan is one of such biopolymer, reported to be non-toxic and bioabsorbable [1] and has been explored for the release of many drugs [2-4]. Chitosan is a fiber-like substance derived from chitin, a homopolymer of ß-(1→4)-linked *N*-acetyl-D-glucosamine. Chitin is the second most abundant organic compound in nature after cellulose [5]. Chitin is widely distributed in marine invertebrates, insects, fungi, and yeast [6]. Chitosan possesses positive ionic charges, which give it the ability to chemically bind with negatively charged fats, lipids, cholesterol, metal ions, proteins, and macromolecules [7].

Starch is a natural polymer, regenerated from carbon dioxide and water by photosynthesis in plants [8]. Owing to its complete biodegradability [9], low cost and renewability [10], starch is considered as a promising candidate for developing sustainable materials. In view of this, starch has been receiving growing attention since 1970s. Starch itself is poor in processability, also poor in the dimensional stability and mechanical properties for its end products [11]. Therefore, native starch is not used directly. Chemical crosslinking agents such as glutaraldehyde, ethyleneglycol diglycidyl ether and poly (ethyleneglycol), can be used to enhance the controlled release of drugs from chitosan derivatives [12-13]. However, the addition of these chemical substances can be limited due to their toxicity.

In the present work, blended beads of chitosan and starch are prepared. These beads are utilized as a carrier for metformin hydrochloride (MH) as a model drug. Glutaraldehyde and sodium hexameta phosphate are used as crosslinkers for chitosan and starch, respectively. Metformin hydrochloride is used as a model drug. It is the first line of drug of choice for the treatment of Type 2 Diabetes, particularly in overweight and obese people. Metformin Hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) a white crystalline powder, is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

MATERIALS AND METHODS

Materials

Chitosan (MW 5000 Daltons) was purchased from Tokyo Kasei Kogyo Co. Ltd., Japan and used as received. Starch $(C_6H_{10}O_5)_n$ soluble GR was purchased from Merck Chemicals India. Glutaraldehyde ($C_5H_8O_2$) (MW 100.12 gm and density 1.13 kg/lit) was purchased from Central Drug House, New Delhi, India. Sodium hexameta phosphate, a physical crosslinker of starch, was purchased from Pioneer Chemical Co. New Delhi. Other chemicals were of analytical grade.

Preparation of Chitosan/Starch Crosslinked Beads

20 ml of 2% acetic acid solution (in water) was taken in a beaker and a known quantity of chitosan was added slowly under stirring condition followed by stirring for about 2hrs. A starch solution was prepared separately by dissolving a known quantity of starch in 10ml of water. The prepared starch solution was added into chitosan solution under stirring conditions and mixed together for 3hrs at room temperature. The prepared mixture was kept at room temperature (20^oC) over night.

Sodium hydroxide-methanol (1:20 w/w) solution was prepared. Chitosan and starch solution was extruded through a syringe into a homogenous solution of sodium hydroxide-methanol at room temperature. Freshly prepared beads were washed thrice with distilled water and resultant beads were allowed to react with 20 ml of sodium hexameta phosphate (SHMP) 25% solution for 10 minutes at room temperature. Physically cross linked beads were washed and dipped into 20 ml of glutaraldehyde (GA) (25%) solution for 10 minutes at 60°C. Finally, the cross linked beads were washed with distilled water and dried in oven at 40°C for 12 hours.

To prepare drug loaded beads, a known amount of metformin hydrochloride (0.2 gm) was added to the chitosan-starch solution before extruding into sodium hydroxide-methanol solution. Composition of prepared beads is given in Table 1.

Table 1: Compositions of Chitosan-Starch Beads

Sr. No	Chitosan (g)	Starch (g)	2% Acetic Acid (ml)	GA 25% solution (ml)	SHMP 25% solution (ml)	Metformin hydrochloride (gm)
1	0.5	0.5	20	20	20	0.2
2	0.6	0.4	20	20	20	0.2
3	0.7	0.3	20	20	20	0.2
4	0.8	0.2	20	20	20	0.2
5	0.9	0.1	20	20	20	0.2

Miscibility Studies

Miscibility of different composition of CHI -ST blends was studied with the help of differential scanning calorimeter (DSC). Samples were weighed (5-10 mg) on the Mettler microbalance and scanned in the DSC machine at 10°C/min in the temperature range of 0-230 °C under static air. Graphs obtained were studied to know the miscibility of the blends.

FTIR spectral analysis

Infrared transmission spectra of blended beads were studied by Perkin Elmer Spectrum RX1 Fourier transforms infrared (FTIR) spectrometer. The samples were thoroughly grounded with dry KBr and tablets were prepared by compression under vacuum.

Swelling Studies

To understand the molecular transport of liquids into beads, dynamic swelling studies were performed. The beads were weighed before dipping them into acidic (2pH) and basic (7.2pH) solutions, separately for swelling. After regular interval of time (1 hour) these beads were taken out and blotted off carefully in between tissue paper (without pressing hard) to remove the surface adhered solution. The swollen beads were then weighed (W_t) on the electronic balance (Schimadzu, A100X) to an accuracy of ± 0.01 mg. The percentage of swelling for each sample at time t, is calculated using the relationship

$$\text{Percentage of swelling} = \{(W_t - W_o)/W_o\} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where W_o and W_t are the weights of the beads before and after swelling, respectively.

Drug Release Studies

The release experiment was performed in a glass apparatus at 30°C into acidic (2pH) and basic (7.2pH) environment. Beads (0.2 gm) containing known amount of drug (metformin hydrochloride) were added to the release medium (100 ml). After predecided intervals, samples of 5 ml were withdrawn from the beaker and collected in a test tube. These samples were assessed spectrophotometrically for the amount of drug released at 294 nm. This is done on UV-VIS Spectrophotometer.

RESULTS AND DISCUSSION

Miscibility studies

The thermal behavior of the pure chitosan, starch and blended beads is studied with the help of differential scanning calorimeter. Figure 1 illustrates the thermogram of pure chitosan (powdered form), starch and blended beads from 0 to 250 ^oC. A small transition in the temperature range of 111.44 ^oC to118.5 ^oC is observed in Figure 1(a). The glass transition of pure chitosan begins at a peak corresponding to the temperature T_g = 113.8 ^oC. A similar thermogram is observed for

starch which has slightly low glass transition temperature i.e. T_g= 112.9 ^oC. No significant change in the thermogram of blended beads is observed indicate that the blends are missible.

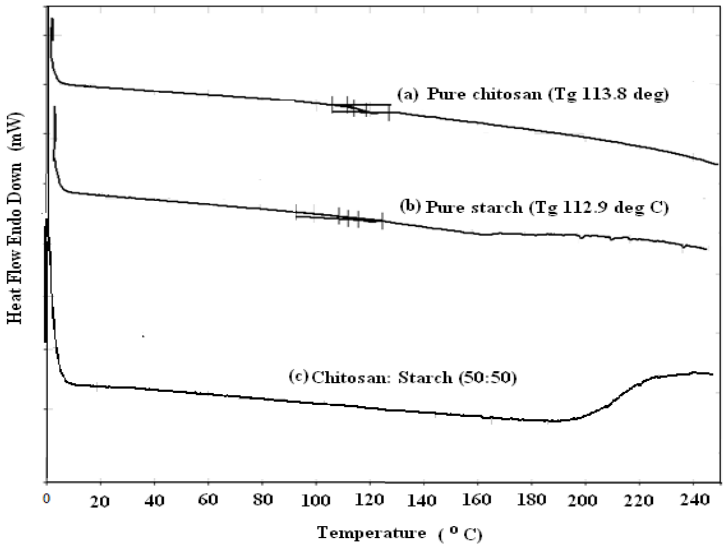

Figure 1: DSC thermograms for (a) chitosan, (b) starch and (c) chitosan: starch (50:50) blend

Fourier Transform Infrared Spectrometry

FTIR spectroscopy is used to study the interaction between the starch, chitosan and crosslinkers. The infrared spectra of chitosan powder, starch powder and blends are presented in Figure 2. Figure 2(a) reveals the IR spectra of chitosan at 3435.7 cm^{-1} is the OH stretching, which overlaps the NH stretching in the same region. The peak at 2923.3 cm^{-1} is typical C-H stretch. A small peak at 1633 cm^{-1} was due to the C=O

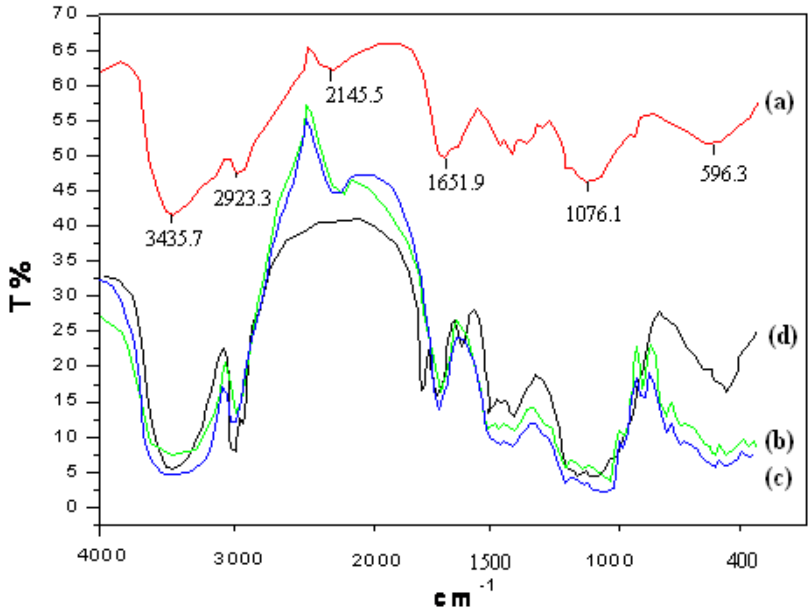

Figure 2: FT-IR spectra of (a) chitosan, (b) starch, (c) chitosan: starch (50:50) blend (d) and chitosan: starch (50:50) blend with Glutaraldehyde and sodium hexameta phosphate (25%)

stretching (amide I), and the peak at 1580 cm^{-1} has been reported as amide II peak. The band at 1076.1 cm^{-1} is due to the C-O stretching vibration in chitosan. In the spectrum (b) for starch, the broad band at 3436.4 cm^{-1} is due to the hydrogen-bonded OH groups that contribute to the complex vibrational stretches associated with free inter- and intramolecular bound OH group, which make up the gross structure of starch. The sharp band at 2928.1 cm^{-1} is characteristic of C-H stretches associated with the ring methane hydrogen atoms. The bands at 1656.2 and 1456.1

cm^{-1} are assigned to the δ (O-H) bendings of water and CH_2, respectively [14]. The bands from 764.2 to 1161.5 cm^{-1} attributed to the C-O bond stretching. When two components are mixed, the physical blends versus chemical interactions are affected by changes in the characteristic spectra peaks [15]. The FTIR spectrum (c) of blended beads shows a broad band around 3600-3200 cm^{-1}, indicating enhanced hydrogen bonding compared to that of chitosan or starch alone. In the spectrum of starch and chitosan blend, the amino group peak of chitosan shifted from 1651 to 1671 cm^{-1}. This phenomenon pointed out that interactions were present between the hydroxyl group of starch and the amino group of chitosan [16-17]. Figure 2(d) represents FTIR spectra of CHI/ST (50:50) blends with Glutaraldehyde (25%) and sodium hexameta phosphate (25%).

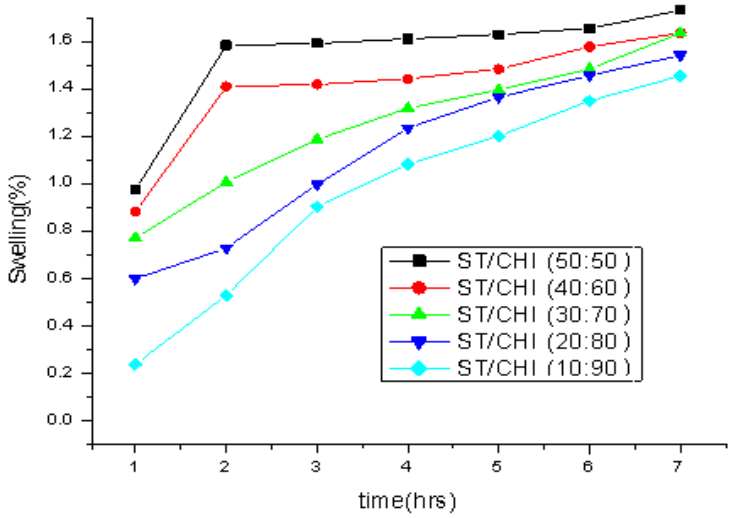

Figure 3: Swelling responses in acidic medium for ST/CHI crosslinked Beads.

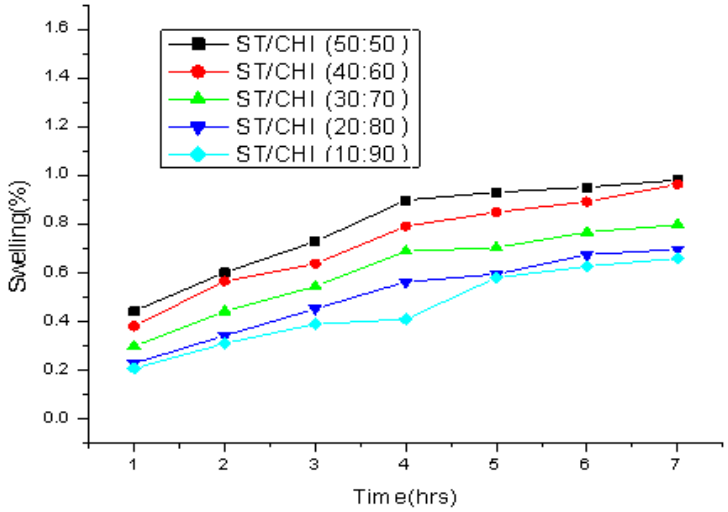

Figure 4: Swelling responses in basic medium for ST/CHI crosslinked Beads

Swelling studies

Swelling studies of blended beads are performed in acidic and basic mediums. Swelling response in acidic basic and medium (2pH and 7.2pH) of five different concentrations of ST/CHI (50:50, 40:60, 30:70, 20:80, and 10:90) blended beads with a particular concentration of glutaraldehyde and sodium hexameta phosphate are shown in Figures 3-4. A significant increase in swelling % with time is observed. While comparing swelling of beads of different compositions it is observed that percentage of swelling of the crosslinked beads decreases with increasing the

concentration of starch. As starch is soluble at 70°C in water and different studies are performed at room temperature, so ST part remains intact. During the swelling of beads at different pH values, it was observed that acidic media has a pronounced effect on swelling of beads as compared to the alkaline media due to the formation of ammonium salt (NH_3^+) [18]. The protonation of $–NH_2$ group thus ensures chain penetration, leading to faster intra-hydrogen-bond dissociation (breakage of self association of chitosan and starch) and efficient solvent diffusion. In alkaline media, the swelling is mainly driven by solvent diffusion, but the chain penetration due to protonation of amino groups is absent.

Drug Release Studies

To understand the release of metformin hydrochloride from the crosslinked beads, the in vitro release experiments are performed with 0.2 gm of sample containing known amount of drug. The results are shown in Figures 5-6. A fast release is observed, initially for the first four hours followed by moderate release in next two hours and finally an almost constant release of drug is observed for the studied period of 10 hrs. It is observed that as the concentration of starch decreases the concentration of drug release in the medium increases. This is due to the fact that ST/CHI is a miscible blend. More crosslinked chitosan means less penetration of drug through the matrix as chitosan chains are closely associated.

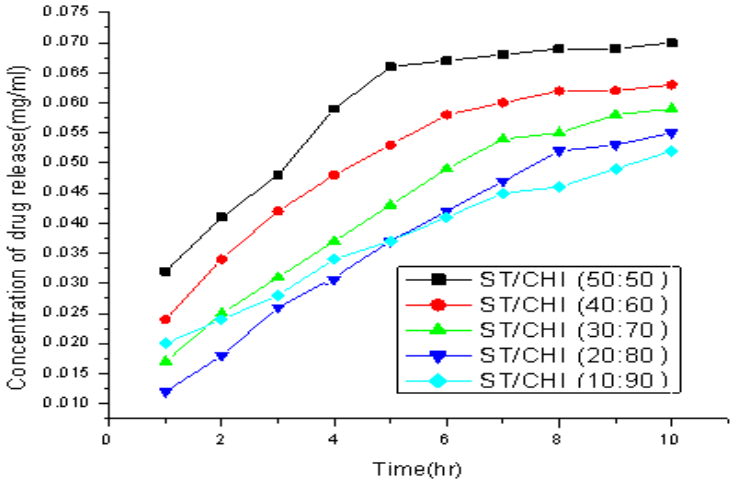

Figure 5: Drug release from different ST/CHI crosslinked beads in acidic medium.

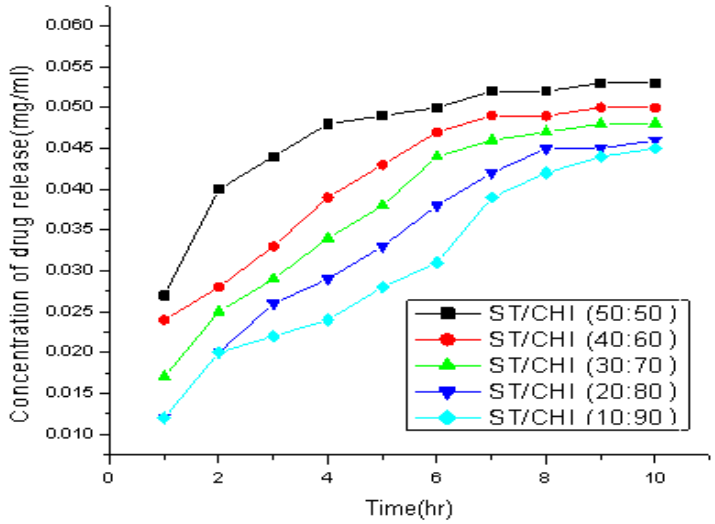

Figure 6: Drug release from different STCHI crosslinked beads in basic medium.

The drug release rate is also affected by the nature of release medium. It is observed that the rate of drug release is much higher in an acidic environment than in a basic one. The appreciable increase in the rate and the extent of swelling at a lower pH can be attributed to the higher porosity of the blend, which seems to govern the diffusion of solvent in the network

CONCLUSION

Chitosan and starch blended beads are prepared and crosslinked with glutaraldehyde and sodium hexameta phosphate to form miscible blends. In case of blend, the miscibility is studied in DSC and FTIR characterization. FTIR analysis of starch-chitosan blend beads indicate that introduction of chitosan increased the crystalline peak structure of starch film. The amino group band of chitosan molecule in the FTIR spectrum shifted from1651 cm^{-1} in the chitosan film to 1671 cm^{-1}. These results pointed out that there was a molecular miscibility between starch and chitosan.

From swelling results, it is evident that the rate of swelling of matrix is dependent on the concentration of chitosan and starch. The drug delivery through hydrogels is estimated by UV-VIS Spectrophotometer. The drug release is found to be fast for initial 4-6 hours, gets slow for next two hours and finally the release becomes constant for long hours. The release of the drug from beads is found to be dependent on the concentration of chitosan and starch. As the concentration of starch increases, drug release increased. The results suggest that chitosan-starch crosslinked beads are suitable for controlled release of drug.

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