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In-vitro Release of Metformin Hydrochloride from Films of Chitosan-Methylcellulose Blends

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Films consisting of chitosan and methylcellulose were prepared for in-vitro study of controlled release of metformin hydrochloride. A viscous solution of chitosan-methylcellulose was prepared in 2 % acetic acid and casted into films. The films were dried at room temperature and crosslinked with glutaraldehyde. Physical characterization of films was carried out and their swelling response to different degree of crosslinking was studied. The drug release studies through the film indicated that the films can be used as a vehicle for controlled drug release.

Key Words: Chitosan, methylcellulose, controlled drug release, crosslinking, gels.

INTRODUCTION

In the recent years, a wide range of hydrophilic polymers have been explored for controlled release of drug. Chitosan (CHI), β-(1→4) linked 2–amino-2-deoxy-D-glucose, one of these hydrophilic polymers, is a deacetylated derivative of chitin (N-acetyl-d-glucosamine. Being biodegradable and biocompatible, chitosan has been used in the formulation of particulate drug delivery systems to achieve controlled drug delivery [1-2]. Drug release rates can be controlled depending on the particle size, swelling ratio and change in environment such as pH, temperature etc of the synthesized formulation [3-4]. Blending of chitosan with other polymers and crosslinking are both convenient and effective methods of improving the physical and mechanical properties of chitosan for particular applications. Chemical crosslinking agents such as glutaraldehyde (GA), ethyleneglycol diglycidyl ether and poly (ethyleneglycol) are used to enhance the controlled release of drugs from the chitosan based microparticles [2, 5]. However, the addition of these chemical substances can be limited due to their toxicity.

Methyl cellulose (MC) is an important natural polymer obtained from renewable sources. This polysaccharide is insoluble in most organic and inorganic solvents which reduces its range of applications. To overcome this problem of low solubility and therefore to extend its application, a large number of cellulosic derivatives have been investigated. Due to the initial insolubility of cellulose, the chemical modifications are generally conducted under

heterogeneous conditions, this results is heterogeneous distribution of the substituents along with polymeric chain [6].

In the present study, the films consisting of CHI and MC are synthesized and crosslinked with GA. Metformin hydrochloride (MH) 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. The swelling and drug release behaviors of films are examined.

EXPERIMENTAL

A. Materials

Chitosan (CHI) is purchased from Tokyo Kasei Kogyo Co., Ltd. Japan and is used as received. Glutaraldehyde (GA) ($C_5H_8O_2$) (MW=100.11), metformin hydrochloride (MH) (MW=165.63), acetic acid and methylcellulose (MC) ($C_7H_{14}O_5$) were procured from CDH, New Delhi.

B. Preparation of Methylcellulose-Chitosan Crosslinked Films

The measured quantity of MC was slowly added to 100 ml of distilled water at 42°C under stirring condition for about 2 hrs. Prepared mixture was kept at low temperature for overnight. 2 ml of acetic acid is added to mixture followed by addition of CHI under stirring conditions for 3 hrs at room temperature. MC-CHI blends are casted into films in the petridish and dried at room temperature. These films are dipped into GA solution for 5 min for crosslinking. To prepare drug loaded films, a known amount of MH drug (0.2 gm) is added to the MC-CHI solution before film casting. Composition of prepared films is given in Table 1.

Table 1: Composition of Chitosan-Methylcellulose Films

Sr No	CHI (gm)	MC (gm)	Acetic Acid (ml)	GA (ml)	MH (gm)
1	1.8	0.2	2	20	0.2
2	1.6	0.4	2	20	0.2
3	1.4	0.6	2	20	0.2
4	1.2	0.8	2	20	0.2
5	1.0	1.0	2	20	0.2

C. Swelling Studies

To understand the molecular transport of liquids into films, dynamic swelling studies are performed. To investigate the effect of MC/CHI ratio (10/90, 20/80, 30/70, 40/60 and 50/50) and concentration of crosslinker (1, 3 and 5%), the weighed film is put into water at room temperature under unstirred condition. After regular interval of time (i.e. 2 min), the film is taken out and blotted off carefully between tissue papers (without pressing hard) to remove the surface adhered solution. The swollen films are then weighed 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

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

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

D. Drug Release Studies

The release experiments were performed in a glass apparatus at 37°C in distilled water with constant stirring. Films containing known amount of drug are added to the release medium (100 ml). After predecided intervals, samples of 5 ml are withdrawn and assessed spectrophotometrically at 294 nm.

E. Kinetic Analysis of Drug Release

In order to have an insight into the mechanism of drug release behavior of the crosslinked films, the Power law equation and Higuchi's model are fitted into the kinetic data of drug release. Power law model can be expressed as:

$$M_t/M_\infty = kt^n \quad (2)$$

According to Higuchi's model, an inert matrix should provide a sustained drug release over a reasonable period of time and yield a reproducible straight line when the fraction of the drug released is plotted versus the square root of time.

$$M_t/M_\infty = kt^{1/2} \quad (3)$$

Where M_t and M_∞, correspond to the amount of drug release at time t and after an infinite time and k, is a constant related to the structural and geometrical properties of the drug release systemThe numerical value of diffusional exponent, n, provides information about mass transport mechanism. When $n < 0.5$, the solvent diffuses through and the drug is released through the film with a quasi-Fickian diffusion mechanism. An anomalous, non-Fickian drug diffusion occurs when the value of n lies between 0.5 and 1. When $n \geq 1$ a non-Fickian case Π or zero order kinetics can be observed.

RESULTS AND DISCUSSION

A. Physical characteristics and swelling studies of films

The synthesized films are thin and transparent. These films can be cut into the size and shape as per requirement of the experiment. After crosslinking, the films become yellowish and brittle. Crosslinking is done only for few minutes to minimize the extent of brittleness. Crosslinking results in uneven shape of the film.

Swelling response of MC/CHI blended films crosslinked with different concentrations of GA (1, 3 and 5%) is studied and shown in Figures 1-3. It is observed that the crosslinked films exhibit swelling behavior in water and there is a significant increase in percentage of swelling with time. It is shown in Figure 1 that the percentage of swelling of the crosslinked films having the same concentration of crosslinker decreases with increasing concentration of methylcellulose. MC-CHI forms immiscible blends and results in phase separation. MC is soluble in water at 42°C [7]. As swelling studies are performed

at room temperature, a part of MC present in the film remains intact. Thus, as the concentration of MC decreases the percentage of swelling increases. The effect of concentration of crosslinker on percentage of swelling is depicted in Figures 2-3. Percentage of swelling is found to be dependant on crosslinker concentration. Swelling rate decreases with increase in the degree of crosslinking. It follows the order 1% > 3% > 5% for MC/CHI films. This is due to the reason that highly crosslinked hydrogel have compact structure and thus swells less as compared to the hydrogel with lower concentration of crosslinker. Crosslinking hinders the mobility of the polymer chains and hence, higher crosslink density results in higher strength of the films thus, lower the degree of swelling.

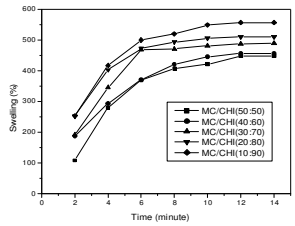

Figure 1: Swelling responses in water for MC/CHI crosslinked (with 1% GA) films

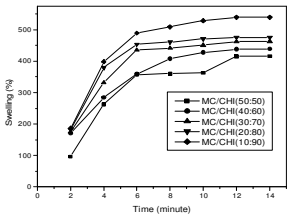

Figure 2: Swelling responses in water for MC/CHI crosslinked (with 3% GA) films

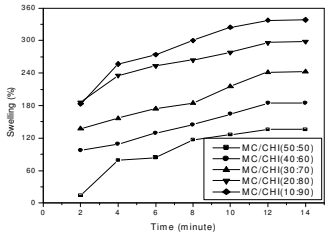

Figure 3: Swelling responses in water for MC/CHI crosslinked (with 5% GA) films

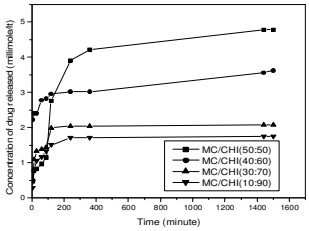

Figure 4: Drug release from different MC/CHI crosslinked films

B. Drug Release Studies

Figure 4 presents the drug release profiles from MC/CHI crosslinked films. With higher degree of crosslinking, chitosan chains are more closely associated and reduce the penetration of drug through the matrix. As the concentration of methylcellulose is increased, the concentration of drug release in the medium increases. The drug release rate was found to increase with the decrease in crosslink density. For MC/CHI (10/90) the percentage of drug released after 24 hrs is 14.58%. This may be due to the fact that the diffusion of the drug from the matrix depends on the pore size of polymer network, which will decrease with increase in crosslinking density.

C. Kinetic Analysis of Drug Release Mechanism

Drug release results are analyzed using equations (2) and (3). The values of n and k are determined by applying the linear regression method. The data for release mechanism for different formulations, along with the values of correlation coefficients, R and the standard Deviation SD are presented in Tables 2-3. The value of R is greater than 0.95 and SD is less than 0.2 indicate that the data is fitted well in Power law model and Higuchi's model. The smaller value of k indicates mild interaction between the drug and blend. The mechanism for the release of drug is quasi-Fickian as value of $n < 0.5$ (Table 4).

Table 2: Kinetic Analysis of drug release through films

Weight ratio of MC/CHI	Higuchi model			Power law model			
	k	R*	SD*	k	n*	R*	SD*
50:50	0.07	0.89	±0.06	0.05	0.27	0.97	±0.03
40:60	0.56	0.99	±0.07	0.05	0.10	0.97	±0.01
30:70	0.22	0.88	±0.11	0.17	0.35	0.94	±0.07
10:90	0.14	0.86	±0.16	0.10	0.48	0.93	±0.10

* n: diffusional exponent, R: correlation coefficient, SD: standard deviation

Conclusion

Chitosan and methylcellulose films are prepared and crosslinked with glutaraldehyde to form immiscible blends. From swelling results, it is evident that the rate of swelling of matrix is dependant on the degree of crosslinking and weight ratio of MC/CHI. Swelling results indicate that the percentage of swelling decreases with increase in concentration of methylcellulose and crosslinker. It is also found that as the concentration of MC increases, drug release increased. Moreover, drug release is sustained for long hours. The results suggest that chitosan-methylcellulose crosslinked films are suitable for controlled release of drug.

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