Asian Journal of Chemistry Vol. 22, No. 10 (2010), 7661-7674

Effect of Cross-Linkers on Isabgol Husk-Sodium Alginate Matrix Type Drug Delivery Devices

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The inherent characteristics of the incorporated polymers *e.g.*, high molecular weight, chain flexibility, nontoxicity, low cost, hydrophilic groups along with high surface tension *etc.* are required for dosage forms fabrication. Also, the versatility of the other agents as crosslinking agents has their own impact on the release of the incorporated drug and other parameters associated with formulations. In the present study, isabgol husk and sodium alginate were applied as polymeric skeleton for metformin hydrochloride encapsulation in beads form along with calcium chloride/barium chloride as crosslinking agent. The formulations were prepared by orifice-ionic gelation method. The effect of polymer ratio and ionic strength of crosslinking agents was analyzed on drug entrapment efficiency, particle size, swelling index, drug entrapment efficiency, curing time, drug release pattern. The drug-polymer compatibility was analyzed by FTIR and DSC. The beads prepared in barium chloride were more spherical and regular in surface than in calcium chloride. The size of the beads was also smaller in barium chloride. Swelling index in phosphate buffer (pH 7.4) of barium crosslinked formulations was significantly different than in 0.1 N HCl for both barium and calcium crosslinked formulations ($p < 0.001$). More prolonged release was observed in barium crosslinked beads which remained intact after dissolution in simulated intestinal fluid but on the other hand calcium crosslinked formulations were disintegrated completely. FTIR and DSC study revealed the identity of metformin after fabrication in polymeric network.

Key Words: Microparticulate system, Ionic gelation, Isabgol husk, Crosslinking agents.

INTRODUCTION

The controlled release technology has been developed by utilizing a broad range of approaches to achieve the theoretical goal of delivering a drug to a specific site and a specific pattern. To a certain extent, the inherent characteristics depend upon the polymeric backbone and the factors governing the fabrication of the drug delivery device. Among various delivery systems, oral dosage forms are dominant in the

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market despite of the advancements made in other routes of drug administration. However, such single unit solid dosage forms could be disastrous if they fail to release the drug at the desired rate and in the desired amount or if they release the entire amount of drug so as to cause dose dumping[1]. Microencapsulation has been employed to sustain the drug release and to reduce or eliminate gastrointestinal irritation[2]. In addition, microparticulate delivery systems can be distributed widely throughout the gastrointestinal tract providing a possibility of achieving a longer lasting and more reliable release of drugs[3].

Natural polymers, such as polysaccharides, are widely used in pharmaceutical applications due to their good biocompatibility and biodegradability. Isabgol husk (*Psyllium*), an indigenous natural fiber consisting of the epidermal and collapsed adjacent layers removed from the seeds of *Plantago ovata* Forsk. (*P. ispaghula* roxb.) is particularly rich in alimentary fibers and mucilage[3]. It is widely used for its different therapeutic effects *e.g.*, ulcerative colitis, hemorrhoids, constipation, hypercholesterolemia, diabetes mellitus, colorectal cancer *etc*[4,5]. Two polysaccharides fractions have been separated from the husk mucilage; one (eq. wt. 700; uronic acid 20 %) is soluble in cold water while another (eq.wt. 4000; uronic acid 3 %) is soluble in hot water[6]. Applicability of thermally modified husk for the development of modified release formulations has been reported[7]. Also, natural isabgol husk has been used for the development hydrophilic matrix and microparticulate system for different drugs[8,9]. Alginates are also naturally occurring polysaccharides obtained from marine brown-algae consisting of two monomeric units; β-D-mannuronic acid (M) and α-L-guluronic acid (G). These residues are arranged in homopolymeric blocks (GG and MM) and in heteropolymeric blocks (MG). Alginates show gelling properties in the presence of multivalent cations such as Ca^{2+}, Ba^{2+}, Al^{3+} *etc*.

Metformin hydrochloride is a biguanide glucose lowering agent used in type II diabetes (NIDDM). It has a short half-life (1.5-4.5 h), so repeated administration (250 mg twice or thrice daily) is required to maintain effective plasma concentration. Administration of a sustained release, once-a-day metformin hydrochloride dosage form could reduce the dosing frequency and improve patient compliance.

This study was undertaken to develop the controlled release formulations of metformin hydrochloride of isabgol husk and sodium alginate by using calcium chloride and barium chloride solutions in different concentrations as crosslinker. The effect of crosslinking was evaluated on various characteristics of the formulations *viz*. particle size, swelling behaviour, water uptake content, entrapment efficiency, drug release pattern.

EXPERIMENTAL

Isabgol husk was purchased from the local market (Sidhpur, Gujarat). Metformin hydrochloride was procured as a gift sample from Alkem laboratories Ltd, Mumbai. Calcium chloride and barium chloride was obtained from Rankem, New Delhi. All

other chemicals and reagents used were of analytical grade from commercial source and used without further modification.

Methods

Fabrication of micro-particles composed of isabgol husk-sodium alginate: The beads of isabgol-sodium alginate containing metformin hydrochloride were prepared by ionic gelation method[10]. The dispersions of sodium alginate and isabgol husk were prepared in distilled water separately and the drug (250 mg) was added in isabgol husk dispersion which was homogenized at 1000 r/min. Both the dispersions were mixed and homogenized again at 1500 r/min for 15 min at room temperature. The dispersion was added *via* a 23-gauge needle into a gently agitated cross linker solution. For each dispersion, the droplets instantaneously gelled into discrete, free flowing, brown coloured beads upon contact with the cross linking agent solution. Each batch of beads was left for 10 min for curing until specified in the contact of cross linker solution. The solution was decanted and each batch was washed three times with 500 mL distilled water.

The batches were separated from solution and dried at 40 ºC for 50 h and stored in vacuum desciccator. Different variables such as calcium chloride and barium chloride concentration, sodium alginate concentration, curing time (0-24 h) were analyzed to determine the effect of these factors on drug entrapment efficiency, drug loading, particle size, swelling behaviour in different media, *in vitro* release behaviour.

Particle size determination: The particle size was measured microscopically by taking the beads on a glass slide under the optical microscope (Olympus) at 5X.

Swelling behaviour: Swelling of beads was measured gravimetrically by measuring initial and swelling weight after removing the adsorbed surface water. The study was performed in distilled water, 0.1 N HCl and phosphate buffer (pH 7.4). The swelling index was calculated by the formula:

$$\text{Swelling index} = \frac{\text{Wet weight} - \text{Dry weight}}{\text{Dry weight of beads}} \times 100$$

Drug entrapment efficiency: About 25 mg beads were taken into 50 mL phosphate buffer (pH 7.4) for 48 h with shaking and than filtered through whatman filter paper (No. 41). The filtrate following suitable dilution assayed spectrophotometrically at 233 nm. The drug entrapment efficiency was determined from the following relation[10].

$$\text{Drug entrapment efficiency}\,(\%) = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

***In vitro* release study:** *In vitro* release study of formulations was performed in the six stage tablet dissolution test apparatus (USP, IP, BP, Campbell Electronics, Mumbai) by using basket type model at 50 r/min with 900 mL dissolution media (0.1 N HCl and phosphate buffer pH 7.4) at 37.5 ± 0.5 ºC. At each specific time

interval, 5 mL sample was withdrawn for the drug content analysis by UV-visible spectrophotometer at 233 nm which was replenished with fresh pre-warmed media into dissolution medium after each sampling to maintain it constant.

Fourier transform infrared spectroscopy: The spectra were recorded for metformin hydrochloride, isabgol husk, sodium alginate, blank beads, drug loaded beads (Perkin Elmer 808). The scanning range was 4000-450 cm^{-1} and resolution was 2 cm^{-1}.

Differential scanning colorimetry: The DSC analysis of polymers, drug and formulations was carried out using Mettler Toledo (Model SW 810) within temperature range 25-250 ºC to evaluate any possible drug polymer interaction[11].

RESULTS AND DISCUSSION

In ionic gelation method, when sodium alginate with isabgol husk and drug comes in contact with crosslinking agent, the Na^+ in the droplets is substituted by multivalent ion, thus yielding the alginate gel. At this point a circular boundary is formed within the microsphere, constituting the boarder of the ion exchange between Na^+ and multivalent ion. These circular boundaries gradually shrink with progression of curing and finally disappeared[12]. Alginate is usually gelled by the addition of Ca^{2+} to form a Ca-alginate, since insoluble calcium alginate is formed by cation exchange between Na^+ and Ca^{2+}. The gelation and cross-linking are due to the stacking of guluronic acid (G) blocks of alginate chains with the formation of the egg-box junctions.

In isabgol husk, polysaccharides chains are present with terminal acidic arabinoxylan[13]. The acidic groups of uronic acid may take part in crosslinking with calcium chloride. These polysaccharide chains may entangle among mannuronic acid and guluronic acid content of sodium alginate to affect the crosslinking.

Particle size analysis

Effect of cross-linker concentration: The effect of different concentration of calcium chloride/barium chloride on isabgol-sodium alginate beads has been summarized in the Table-1. The size was comparatively smaller in higher ratio of sodium alginate. Also, on increasing the concentration of calcium chloride/barium chloride, the particle size was decreased in both the cases. But the effect of barium chloride was higher than calcium chloride. It may be due to tight crosslinking in presence of barium chloride. It seems that in higher concentration of the sodium alginate, more homopolymeric blocks (MM, GG) and heteropolymeric blocks of alginate are present to be cross-linked. The more crosslinked chains come in intimate contact occupying small space resulting in smaller size. In case of higher calcium concentration, the more content of Ca^{2+} can enter in the "egg-box" structure present in alginate while at low concentration these are crosslinked superficially and represent low effect on size[14]. These eggs-boxes like structures may carry the adjacent polysaccharide chains in close intimate resulting in smaller size.

TABLE-1
FORMULATIONS OF METFORMIN HYDROCHLORIDE IN ISABGOL HUSK, SODIUM ALGINATE BEADS CROSSLINKED BY CALCIUM CHLORIDE AND BARIUM CHLORIDE

Formulation code	Isabgol husk:sodium alginate	Conc. (% w/v) crosslinking agent		Entrapment efficiency (mean[a] % ± SD[b])	Particle size (μm ± SD[b])
		$CaCl_2$	$BaCl_2$		
FC1	2:3	2	–	39.94 ± 2.25	1258.03 ± 0.2933
FC2	2:3	5	–	49.18 ± 1.81	1238.62 ± 0.7412
FC3	2:3	8	–	58.22 ± 2.95	1181.33 ± 0.5533
FC4	2:3	13	–	60.33 ± 3.26	903.66 ± 0.4294
FC5	1:2	2	–	44.75 ± 1.40	1295.47 ± 1.1490
FC6	1:2	5	–	58.13 ± 1.36	1208.78 ± 0.7485
FC7	1:2	8	–	64.62 ± 2.07	1154.41 ± 0.7485
FC8	1:2	13	–	70.97 ± 1.95	898.86 ± 0.7484
FB1	2:3	–	2	36.51 ± 3.00	1082.62 ± 0.4360
FB2	2:3	–	5	47.72 ± 1.57	944.64 ± 0.4394
FB3	2:3	–	8	52.96 ± 1.20	932.05 ± 0.5938
FB4	2:3	–	13	65.15 ± 1.52	885.82 ± 0.8892
FB5	1:2	–	2	49.30 ± 3.60	921.57 ± 0.4872
FB6	1:2	–	5	62.34 ± 1.26	888.63 ± 1.4278
FB7	1:2	–	8	66.26 ± 3.50	882.87 ± 0.6300
FB8	1:2	–	13	72.49 ± 2.10	875.41 ± 0.9233

[a]Average of three successive values; [b]SD-Standard deviation (n = 3).

Effect of curing time: The beads size prepared in different curing time condition has been summarized in Fig. 1. On increasing the contact time of crosslinking agent, the particle size was decreased. The effect of curing on size was higher in formulations prepared in barium chloride than calcium chloride formulations. It may be due the rearrangement of crosslinked chains of alginate and isbagol husk. But after 12 h, the effect was negligible which indicated that the polysaccharides chains arranged sequentially.

Effect of stirring speed: The effect of different stirring speed on microsphere size of FC1 and FB1 has been shown in Fig. 2. It may be assumed from the figure that on increasing the speed, the beads size was decreased. The size of the spherical matrix can be controlled by varying the stirring speed of the system and the concentration of alginate added to the system. The tendency of the droplets to coalesce and aggregate at lower speed appeared correspondingly high, resulting in larger mean of beads. At higher speed, a vigorous, uniform, increased mechanical shear resulted. This suggested that the size of the droplets formed during microencapsulation could, therefore be related to the size of the final beads, which increased by decreasing the stirring speed.

Kawashima *et al.*[11] proved an inverse relationship between the stirring speed and mean size. The beads at high speed in barium chloride were smaller than calcium chloride. Here, the stirring rate provided the required energy to the polymer dispersion to be dispersed as fine droplets in the suspension medium and, therefore, higher stirring rate created beads smaller in size.

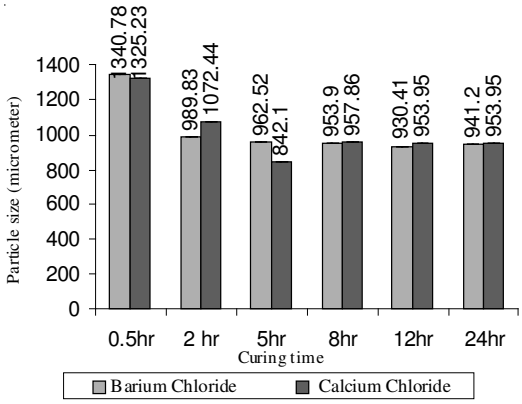

Fig. 1. Effect of curing time on beads size

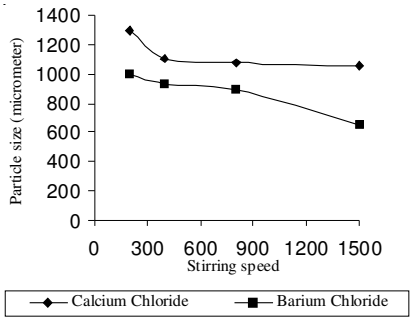

Fig. 2. Effect of stirring speed on beads size

In the swelling process, the macromolecules of isabgol husk and sodium alginate involved in the formulation fabrication became stretched and the elastic forces increased as swelling proceeded. At the equilibrium of swelling process, the restoring forces of macromolecules were balanced by swelling process. In crosslinked beads, these restoring forces were generated by crosslinked chains.

Effect of cross-linker on swelling in 0.1 N HCl: The swelling of different formulations prepared in different calcium chloride concentrations has been shown in Fig. 3. It was observed that the beads swelled slowly in initial stage and after 2-3 h, they were swelled as much as possible afterwards showed negligible swelling as shown in figure by a probably straight line after 2-3 h in swelling index.

It was also analyzed that the swelling was decreased on increasing the concentration of calcium chloride/barium chloride. The rate of swelling of barium crosslinked formulation was different than formulations of 3:2 ratio of sodium alginate to isabgol prepared in similar concentration of calcium chloride. Also, the swelling in the initial stage was slow. It was considered due to carboxylic groups present in isabgol and sodium alginate. As being acidic in nature, some of these-COOH groups could be unionized in 0.1 N HCl due to ionization depression resulting in the polymeric network as such. The swelling index of formulations prepared in different $CaCl_2$ concentration was different and lower on higher concentration. The increased crosslinking on increasing $CaCl_2$ concentration was also supported by beads size determination which was also decreased on increasing $CaCl_2$ concentration.

Calcium alginate maintained apparently enough elasticity to allow the beads to be swelled. It was also observed that on higher sodium alginate ratio to isabgol (2:1), the initial swelling was lower than 3:2. Similarly, on increasing the $CaCl_2$/$BaCl_2$ concentration, the swelling was decreased. But the rate was significantly different than 2:1 formulations prepared in similar concentrations of calcium chloride ($p < 0.001$). It was considered due to the increased number of -COOH groups to be crosslinked by Ca^{2+} on increasing sodium alginate ratio. In isabgol husk, aldobiouronic acid content is present which may increase the total no of -COOH group

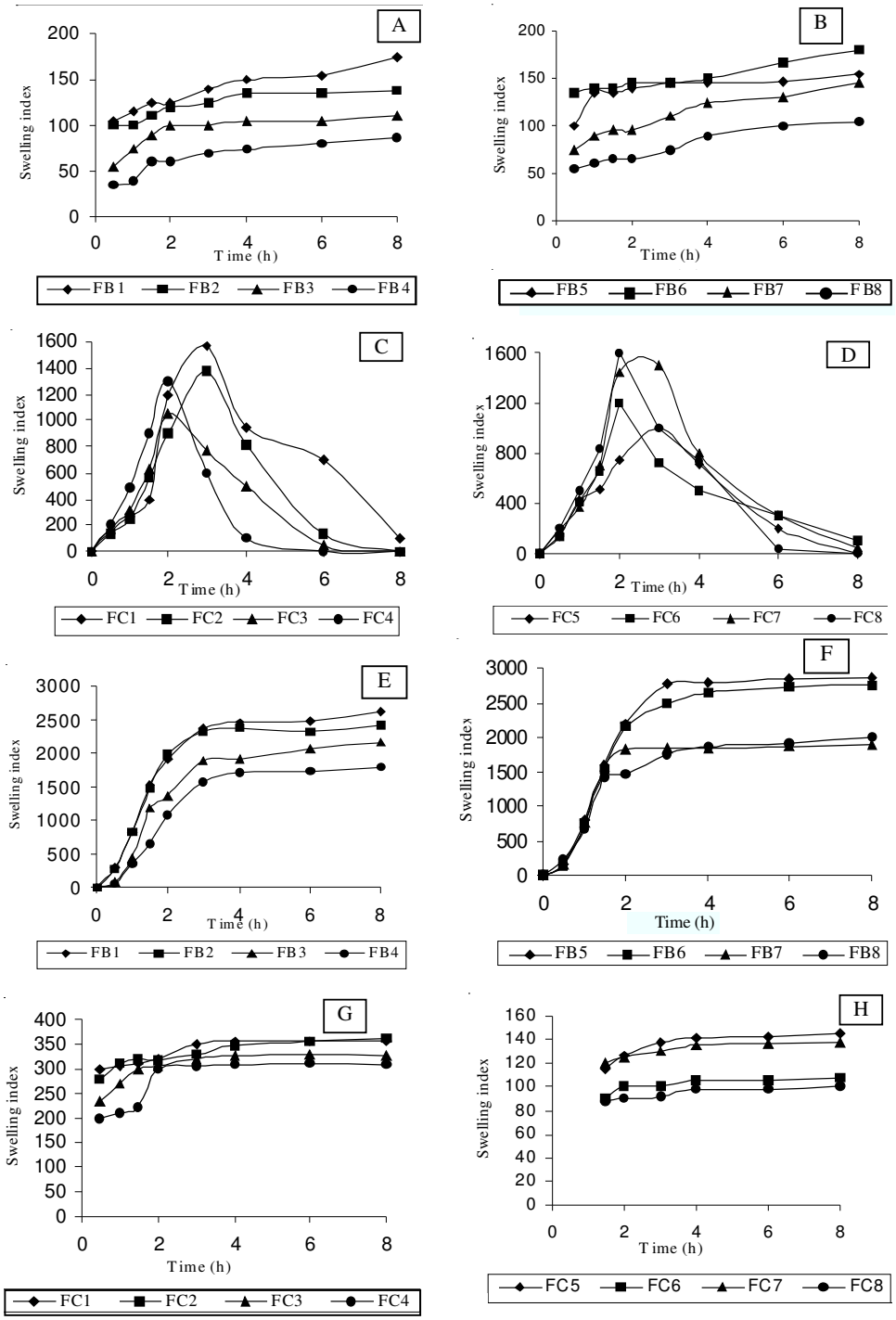

Fig. 3. Swelling behaviour of different formulations in 0.1 N HCl (A, B, G and H) and phosphate buffer pH 7.4 (C, D, E and F)

in the polymeric backbone of beads undergoing for crosslinking. The higher crosslinking may produce the diffusion barrier for entering 0.1 N HCl, the medium used for swelling. It was also supported by particle size analysis that beads size was comparatively smaller in 2:1 formulations than 3:2 formulations.

Effect of cross-linker on swelling in phosphate buffer (pH 7.4): The swelling behaviour of beads prepared in different $CaCl_2$ concentration has been presented in Fig. 3. The swelling index of 3:2 and 2:1 formulations were different from swelling index of the same in 0.1 N HCl. It was observed that in phosphate buffer (pH 7.4), the beads swelled very fast and attained maximum swelling within 3-4 h which were prone then to erosion. Afterwards, the swelling and the disintegration in alkaline medium was considered due to sodium/calcium exchange by the affinity of calcium to phosphate. Consequently, the intermolecular forces were weakened resulting in erosion.

The swelling index of formulations prepared by 3:2 ratios of sodium alginate and isabgol husk in 2, 5, 8 and 13 % w/v concentration of barium chloride was different than 2:1 ratio formulations prepared in similar concentration of barium chloride. It was observed that the rate of swelling was comparatively large than the rate in 0.1 N HCl. It may be due to the affinity of barium to phosphate ions of buffer to form barium phosphate. The beads remained swelled without erosion after the swelling study. It seems that the polymeric network of husk may also enter in the crosslinked chain of sodium alginate. Therefore only superficial uncross linked chains may be free to absorb the swelling medium which result in low swelling in 0.1 N HCl. But in alkaline conditions, the nature of husk polysaccharide chains may be changed resulting in more swelling. It is also the inherent nature of husk to swell in intestinal alkaline pH to show the bulk laxative effect. The decreased swelling rate on increasing barium chloride concentration may be due to higher crosslinking. Lowest rate of swelling was observed in 2:1 formulation prepared in 13 % w/v barium chloride.

The entrapment efficiency of different formulations has been summarized in Table-1. In formulation FC1, lower dug entrapment efficiency may be due to low crosslinking of the -COOH groups present in alginate. At lower concentration of the divalent ions, the beads may have larger pores due to insufficient crosslinking resulting in lower entrapment but in formulations in same calcium chloride concentration but having high alginate content, it was higher[15]. It may be due to the higher alginate content available for crosslinking. On higher crosslinking concentration, the entrapment efficiency was gradually increased. It may be due to higher calcium chloride concentration used in formulations which cross linked more alginate -COOH content. Also, the drug entrapment efficiency may be higher due to the ionic attractive forces between cationic drug (metformin HCl) and carboxylate units present in alginate and isabgol husk present in the formulations.

The entrapment efficiency was improved in barium chloride than calcium chloride. It may be due to the tight crosslinking between alginate and Ba^{2+}. Also, the improved

entrapment efficiency of water soluble metformin hydrochloride may be due to participation of isabgol husk in cross linking with Ba^{2+} and Ca^{2+}. Calcium is coordinated between classes of certain uronic acids containing polysaccharides. Such complexes can explain the tight bonding of calcium and other multivalent ions in polysaccharide structures. These bivalent ions complexes can induce the gel formation in the acidic polysaccharides. Ross-Murphy *et al.*[16] analyzed that association of ordered polysaccharide chains into a weak but continuous network is prolonged by salt with divalent cations (Ca^{2+}) proving particularly effective. The husk has a linear backbone of xylan backbone with terminal α-D-galactouronic acid[17]. It seems that this uronic acid content may participate in the crosslinking consequently enhancing the entrapment efficiency.

Effect of curing time on entrapment efficiency: The entrapment efficiency of different formulations at different curing is represented in Fig. 4. The short curing time in $CaCl_2$/$BaCl_2$ solution resulted in the high drug entrapment. The decrease in entrapment may be due to the diffusion of the drug in crosslinking solution. It appears that in barium chloride, tight junctions are formed which is a time taking process. Some of the drug may enter in crosslinked uronic acid content in isabgol husk present in twisted three fold ribbon like structure which would take time to come out. In formulations crosslinked by calcium chloride, the decrement of entrapment was higher than barium crosslinked formulations. It may be due the flexibility of calcium crosslinked chains through which the drug gradually may come out. The contact time 12 and 24 h did not improve significantly the loading efficiency in the formulations prepared in $BaCl_2$ as shown in Fig. 4.

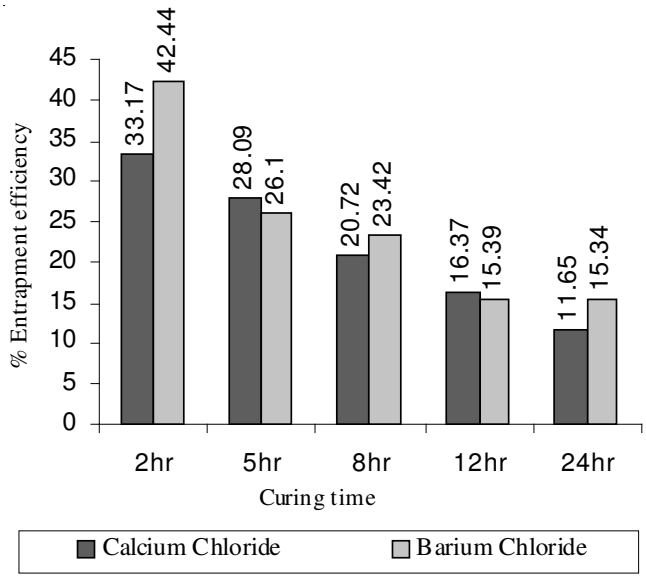

Fig. 4. Effect of curing time on entrapment efficiency

In vitro release profile

Release of metformin hydrochloride in 0.1 N HCl: The release curves from the different formulations in 0.1 N HCl has been shown in Fig. 5. It was observed that in initial stage (0-2 h) of release, the formulations released the drug very fast but later on the drug was released slowly. It was considered as burst effect as the drug being a weak base was dissolved rapidly in acidic condition giving the burst effect[10]. The drug release was slower down on increasing the concentration of $CaCl_2$/$BaCl_2$. It was observed that in FC1, FC2, FC3, FC4, FB1, FB2, FB3 and FB4 the release was varied from 29-67 % within 12 h. The rate of release in FB1, FB2, FB3 and FB4 was lower than FC1, FC2, FC3 and FC4. The release of the drug from FB5, FB6, FB7 and FB8 was statistically significant than FB1, FB2, FB3 and FB4 ($p < 0.001$). It was considered as increasing the concentration of Ca^{2+}/Ba^{2+}, the permeability of the matrix was decreased resulting limited drug diffusion. Also, on higher concentration of cross-linker, these ions can enter the egg box system resulting in dense crosslinking[14]. The ionic content present in isabgol backbone beads can be exchange with media due to basic nature. This exchange phenomenon may be responsible for loose gel structure of beads for drug release. But in isabgol, acidic content (aldobiouronic acid) undergone for crosslinking with calcium/barium ion may contain these complexed ions in three fold polymeric network which will take more time to be exchanged. This phenomenon may be responsible for prolonged release of metformin. The permeation of drug across the hydrophilic polymeric system is through the microscopic water saturated pore channels within the polymer structure. The crosslinking agents can decrease the porosity and increase the tortoisity of the polymeric structure. Furthermore the polymeric structure of isabgol may also affect the release of drug. In husk, β-(1→4) xylans backbone is present which do not have hydroxymethyl group at C-6. The xylan chains has considerably greater conformational freedom than cellulose and packs in the solid state as twisted three fold ribbon, not in the extended two fold structure, characteristics of cellulose material[17]. The packaging arrangement incorporating columns of bound water can be displaced to accommodate monosaccharide side chains at C-2 and or C-3 of the xylan backbone without affecting the lattice structure[13]. This three dimensional structures with replaced columnar water may further hinder the release of drug.

In formulations FC5, FC6, FC7 and FC8, the release was also lowered on increasing the calcium chloride concentration. In these formulations, the Ca^{2+} concentration showed its influence on release in 12 h release study. It was considered as the combine effect of aldobiuronic acid, higher ratio of sodium alginate and calcium chloride on crosslinking. There was significant difference in the release study for 12 h between these formulations and FC1, FC2, FC3, FC4 ($p < 0.05$).

Release of metformin hydrochloride in phosphate buffer (pH 7.4): The release curve of metformin from the formulations has been shown in the Fig. 5. It was observed that initially the release was slow but after 4-5 h, 80-90 per cent of the

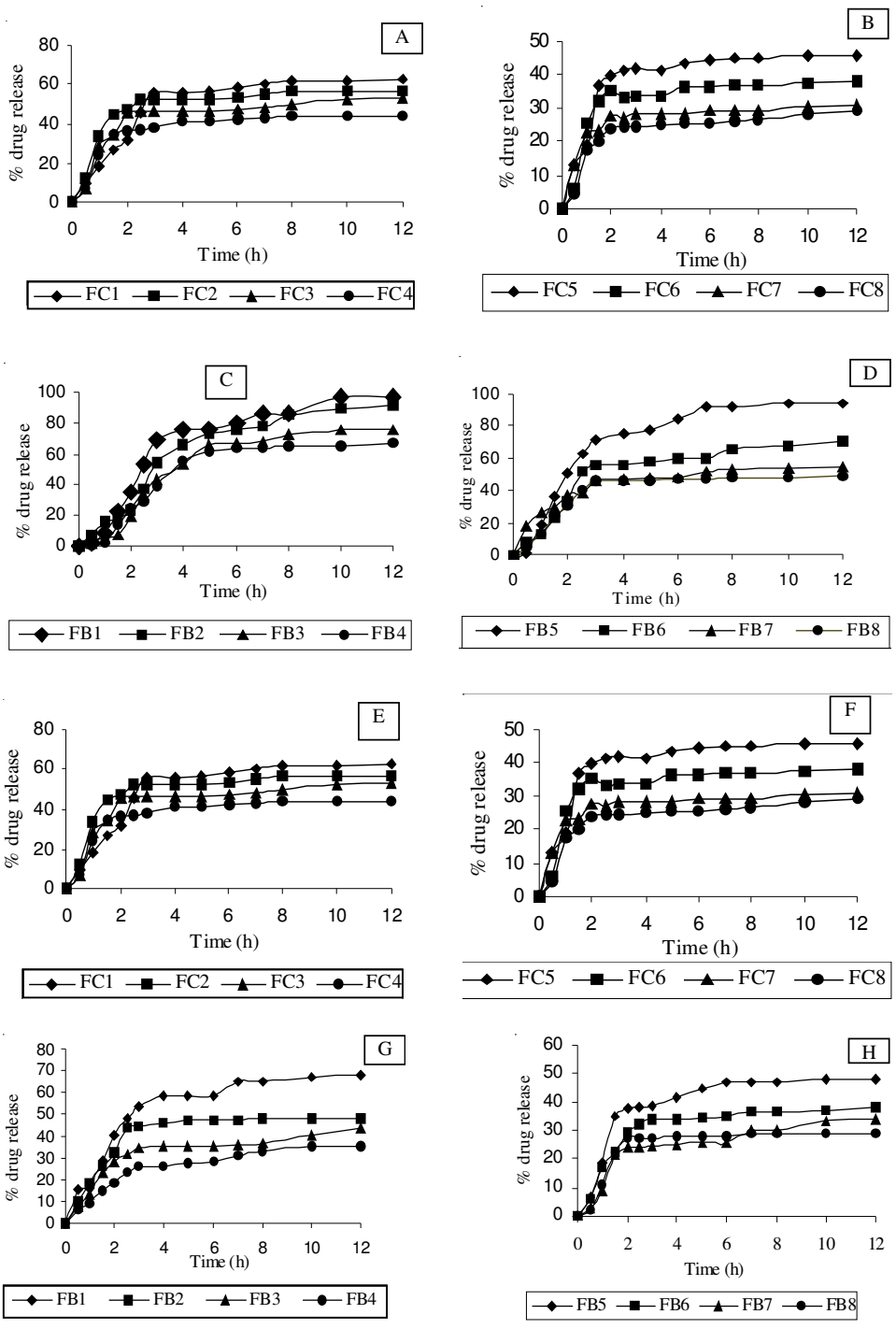

Fig. 5. Release pattern of different formulations in 0.1 N HCl (A, B, G and H) and phosphate buffer pH 7.4 (C, D, E and F)

drug was released. The release of FB1, FB2, FB3 and FB4 was different from the release of similar formulations in 0.1 N HCl ($p < 0.05$). The higher release from alginate beads crosslinked by calcium chloride may be due to the presence of phosphate ions in dissolution medium which at neutral pH chelate the Ca^{2+} [18]. The Ca-alginate beads disintegrated fast at pH 7.4 as observed in swelling study. It was due to the high affinity of Ca^{2+} with the phosphate ions. It was also analyzed that on increasing the calcium chloride concentration, the amount of drug release was decreased in formulations FC1, FC2, FC3 and FC4 as well as in the formulations FC5, FC6, FC7 and FC8. It was considered due to the association of ordered polysaccharides of isabgol into an ordered continuous network which was promoted by Ca^{2+}, proving particular effect.

Additionally, isabgol gel may form the gel layer of polysaccharides around the drug[19]. Release of drug as well as amount was higher in all formulations of 3:1 and 2:1 ratio of sodium alginate and isabgol husk than the similar formulations in 0.1 N HCl. It was considered as the rapid erosion reducing the path length of diffusion and consequently resulting in faster drug release[20].

But in case of barium chloride, barium formed inflexible crosslinked chains. Also, the ionic radius of Ba^{2+} ion is higher (0.135 Å) than Ca^{2+} which may fill the large pore during the crosslinking and may result relatively less porous gel network. On increasing the barium concentration, the porosity goes towards decreasing resulting in slow release of the drug. Also, the Ba^{2+} ions can not be chelated by phosphate ions[21] resulting in slow erosion. This property can maintain the long diffusion path of the drug causing slow release.

The FTIR transmissions have been summarized in the Fig. 6. In drug infrared spectroscopy, the peaks were obtained at 3375, 3306, 3317, 1632 and 1476 cm^{-1}. These were in the rage of 3370-3300 and 1660-1590 cm^{-1}. These transmissions were due to the groups -NH- and -C=NH present in the drug. In the study of drug loaded beads with calcium chloride/barium chloride, the peaks obtained for stretching of -NH- and -C=NH were 3401, 3399, 1038 and 1035 cm^{-1}, respectively. It also showed that drug maintained its identity after microencapsulation with isabgol husk and sodium alginate. It cleared that there is no interaction of metformin hydrochloride with polymeric network.

The drug could be either dispersed in crystalline/amorphous form or dissolved in the polymeric matrix during the process of microencapsulation[22]. Also, any abrupt or drastic change in the thermal behaviour of either the drug or polymer may indicate a possible drug-polymer interaction. The thermal curves of beads components are presented in Fig. 7. A sharp and symmetric endotherm (T_g 223.4 ºC) was observed for metformin hydrochloride corresponding to its melting point. The peak of drug did not appear in the thermogram of prepared beads containing the drug. It indicated that most of the drug was uniformly dispersed at the molecular level in the beads.

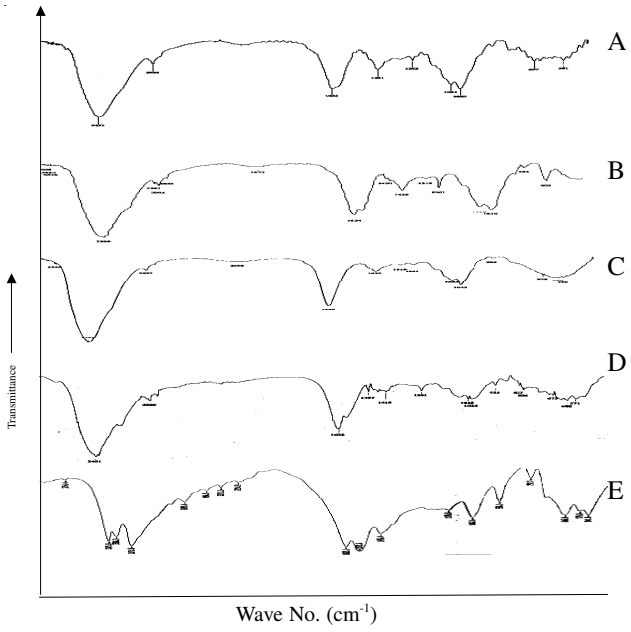

Fig. 6. FTIR spectrogram of blank beads-barium crosslinked (A), drug loaded beads-barium crosslinked (B), blank beads-calcium crosslinked (C), drug loaded beads-calcium crosslinked (D), metformin hydrochloride (E)

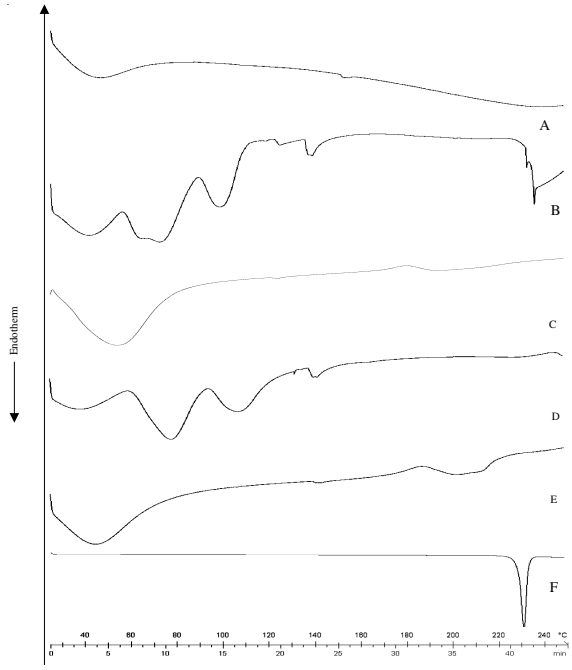

Fig. 7. DSC thermogram of isabgol husk (A), blank beads (B), drug loaded beads (C), blank beads (D), drug loaded beads (E), metformin hydrochloride (F)

Conclusion

The formulations prepared with high concentration of Ca^{2+}, Ba^{2+} and sodium alginate provided the smaller size, lower swelling index, higher drug entrapment and slower erosion. Due to aldobiouronic content, isabgol may participate in complex formation with bivalent ions used in the study. Barium provided stable beads even in phosphate buffer due to non-chelation with phosphate ion. Also, it provided the sustained and prolonged release in basic and acidic media due to more space filling capacity of polymeric network. Instrumental characterization of beads by FTIR confirmed no interaction of the drug with polymeric network. Single endotherm (DSC) in the drug and its absence in drug loaded formulations again supported the molecular level dispersion in preparations. The study disclosed that in ionic gelation method, barium chloride may play a pivot role as crosslinker for fabrication of stable and prolonged released formulations.

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(*Received*: 12 January 2010; *Accepted*: 22 July 2010) AJC-8887