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Cross-linked pH-sensitive pectin and acrylic acid based hydrogels for controlled delivery of metformin

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Abstract: The purpose of present study is to load Metformin HCl into pH-sensitive hydrogels to have sustained release over a period of time. The hydrogel was synthesized from naturally occurring polysaccharide pectin and monomer acrylic acid (AA) using ethylene glycol dimethacrylate (EGDMA) as cross-linker under controlled conditions for polymerization at 45˚C for one hr, 50˚C for two hrs, 55˚C for three hrs, 60˚C for four hrs and finally 65˚C for 12 hrs. Hydrogels were characterized for dynamic/equilibrium swelling, sol-gel fraction analysis, diffusion coefficient and percentage porosity. Hydrogels were tested by FTIR, XRD and SEM for structure and surface morphology respectively. Experimental *in-vitro* drug release data was applied to kinetic models. Formation of strong bonding between pectin and AA was supported by FTIR. The intensity of XRD peaks was reduced in non-loaded and loaded hydrogels compared to active drug substance. The non-loaded hydrogel showed discrete porous structure whereas loaded hydrogels were fibrous and smooth. Hydrogels showed higher swelling in the solutions of pH 6.5 and 7.5 as compared to in the solutions of pH 1.2 and 5.5. The diffusion coefficient decreases with the increase of AA and pectin concentrations. It was observed upon increasing the EGDMA concentration porosity decreases. The release of drug from all compositions of hydrogels took place through non-Fickian diffusion mechanism.

Keywords: Hydrogel, pectin, acrylic acid, metformin, drug release mechanism.

INTRODUCTION

Metformin HCl (MHCl) is a bi-guanide glucose-lowering drug. It is commonly used to manage type-II diabetes (Briede *et al.,* 2007). MHCl has advantage that it does not cause weight gain, nor does it increase the episodes of hypoglycemia, or enhancing insulin secretion (Seifarth *et al*., 2013). It is believed that MHCl decreases the hepatic glucose output, reduces the intestinal glucose absorption rate and increases the glucose uptake by adiposities or muscle cells (Wilcox, 2005). The problem with this drug is that patient has to take medicine frequently due to shorter plasma half life 2 -6 hrs (Mustafa *et al*., 2015).

Its variable plasma profile due to its rapid dilution in body fluids when administered through conventional dosage forms. Therefore interest of the present study is to prepare sustained release carrier for metformin HCl delivery. Various attempts have been made to prepare various sustained release drug delivery systems including HPMC based matrix tablets (Mandal *et al.,* 2007), sodium alginate (Na-Alg) micro spheres (Balasubramaniam *et al.,* 2007) and detarium gum for developing a mucoadhesive dosage form (Adikwu *et al.,* 2004). In addition to these Na-Alg and chitosan bio adhesive tablets have also been developed and reported (El-Kamel *et al.,* 2002).

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In response to external stimuli like temperature, pH and ionic strength, hydrogels show volume changes which are desired characteristics for controlled drug release (George *et al.,* 2004). The amount of drug released from hydrogels is dependent on the rate and mechanism of diffusion of water into polymeric network (Ranjha *et al.,* 2008). Drug delivery from hydrogels is influenced by the structural parameters like charge, p*K*a of ionizable groups, degree of ionization, degree of cross linking and monomeric composition (Yu and Xiao, 2008).

Polysaccharides have attracted great attention of researchers to synthesize natural polymer-based hydrogels (Bhatia *et al.,* 2008). Pectin is a complex naturally occurring polysaccharide, derived from many plants. Pectin contains a linear chain of poly-α-(l→4)-D-galacturonic acid with variable percent of carboxylic groups esterification (Yin *et al.,* 2008). Many naturally occurring polysaccharides have been utilized to prepare the polymeric networks with AA (Jabbari and Nozari 2000). Polyacrylic acid hydrogels possess the ability to swell in water many times of their original weight. The extensive swelling of PAA hydrogel is based on the presence of carboxylic acid groups on polymer chain. Such groups are highly ionizable, strongly interact with water molecules and susceptible to the changes in ionic strength and pH. Hydrogels can be synthesized via a free-radical copolymerization where monomer units are cross-

linked with multifunctional polymer having a cross-linker and an initiator. The degree of crosslinking of polymeric network controls the phase transition, macromolecular configuration, mechanical strength and other characteristics of the hydrogels (Mudassir and Ranjha, 2008).

The objective of the present work was to synthesize pectin/AA hydrogels with the help of EGDMA as cross-linker by simple free-radical polymerization, and to investigate the extent of pH-sensitivity of pectin/AA hydrogels on varying the co-monomeric composition and degree of cross linking. Metformin HCl loaded hydrogel are expected to release drug in controlled release manner thus maintains the plasma level in safe range by reducing the chances of the drug to be diluted in body fluids.

MATERIALS AND METHODS

Metformin hydrochloride (MHCl) was gifted by Wilshire Labs, Lahore, Pakistan. The monomer acrylic acid (AA) and polymer pectin (Mw 30000-100000) with high degree of acetylation 85%) were purchased from Fluka, Buchs, Switzerland. Ethylene glycol dimethacrylate (EGDMA) and benzoyl peroxide were purchased from Merck F.R, Germany. *Synthesis of EGDMA cross-linked pectin/AA hydrogels*

Different formulations of pectin/AA hydrogels were prepared with varying compositions of pectin, AA and EGDMA as given in (table 1). Hydrogels were formulated by free radical polymerization after modification of the previous method (Peppas and Barr-Howell, 1987; Mudassir and Ranjha, 2008). Pectin was added into distilled water along with constant stirring at room temperature. EGDMA and benzyl peroxide were dissolved in AA. These solutions were thoroughly mixed with each other and distilled water was used to make up final weight 100 g. This solution was poured into glass-tubes having 16 mm internal diameter and 150mm length. Then nitrogen bubbling was performed for 15 to 20 minutes to remove air from tubes. The capped tubes were kept in water-bath along gradual raising the heat. The temperature scheme for polymerization was 45˚C for one hr, 50˚C for two hrs, 55˚C for three hrs, 60˚C for four hrs and 65˚C for 12 hrs. After cooling, cylindrical hydrogels were taken out and cut into discs of 6 mm length. The hydrogel discs were placed into freshly prepared (50% v/v) ethanol water mixture for removal of un-reacted monomer and un-reacted crosslinking agent. The hydrogel discs were subjected to washing with ethanol-water mixture until the pH of water ethanol mixture was identical as that of before washing. Washed discs were removed, dried first at room temperature and then in vacuum oven for a week at 40-45˚C. fig. 1 shows the presumptive structure of prepared EGDMA crosslinked pectin/AA hydrogel.

Fourier transform infrared spectroscopy

Drug-polymer interactions and polymer-monomer interactions were studied by FTIR spectroscopy. The spectra were recorded for MHCl, pectin, nonloaded hydrogel and loaded hydrogels using FTIR Midac2000, USA. The selected material (2mg) was ground finely in pestle and mortar before preparation. The samples were prepared as KBr discs. The scanning range was 500-4000 cm^{-1} under hydraulic pressure 150kg/cm at $2cm^{-1}$ resolution.

X-ray powder diffractometry

Crystallinity of MHCl before and after loading in hydrogel and crystallinity of pectin and nonloaded hydrogel was investigated by x-ray diffractometer (BurkerD8 Discover, Germany) having Ni-filtered CuKα radiation source. It was set up with the tube voltage of 35 kV, current of 35 mA and 5°/minute scanning rate, over 0° -70° diffraction range.

Scanning electron microscopy

Morphology of MHCl loaded hydrogel and non-loaded hydrogel was revealed by SEM (Hitachi, S 3000H, Japan). Hydrogel discs were sputter coated with gold with a vacuum evaporator to render discs electrically conductive. These discs were scanned at 25 KV to see the surface morphology of non-loaded and loaded hydrogels.

Dynamic and equilibrium swelling

The swelling behaviour of the hydrogels was measured in different United State Pharmacopeia (USP) phosphate buffer medium with constant ionic strength. Washed, dried and weighed hydrogel discs were drenched in flasks containing 50 ml buffer solution of pH 1.2, 5.5, 6.5 and 7.5 at room temperature. After regular intervals, swollen gels were taken out, blotted, weighed and placed back in the same solution. The dynamic swelling was reported at time (t). The Dynamic and equilibrium swelling ratio of each hydrogel were determined with equation 1:

$$q = W_h \ / \ W_d \qquad \text{Eq. 1}$$

Where, W_h = weight of swollen gel at time t.; and W_d = initial weight of dried disc of the hydrogel. For equilibrium ratio, swelling procedure was continued to gain a constant weight, where, W_h = weight of swollen gel at equilibrium (Crank, 1975).

Diffusion coefficient

Water diffusion coefficients of hydrogels were determined by the equation (Britton *et al.,* 1988; Yin *et al.,* 2007):

$$D = \pi\left(\frac{h.\theta}{4.Q_{eq}}\right)^2 \qquad \text{Eq. 2}$$

Where, D=diffusion coefficient; Q_{eq}=gel swelling at equilibrium; θ = the slope of linear part of the swelling curves; and *h*=initial thickness of the dry hydrogel disc.

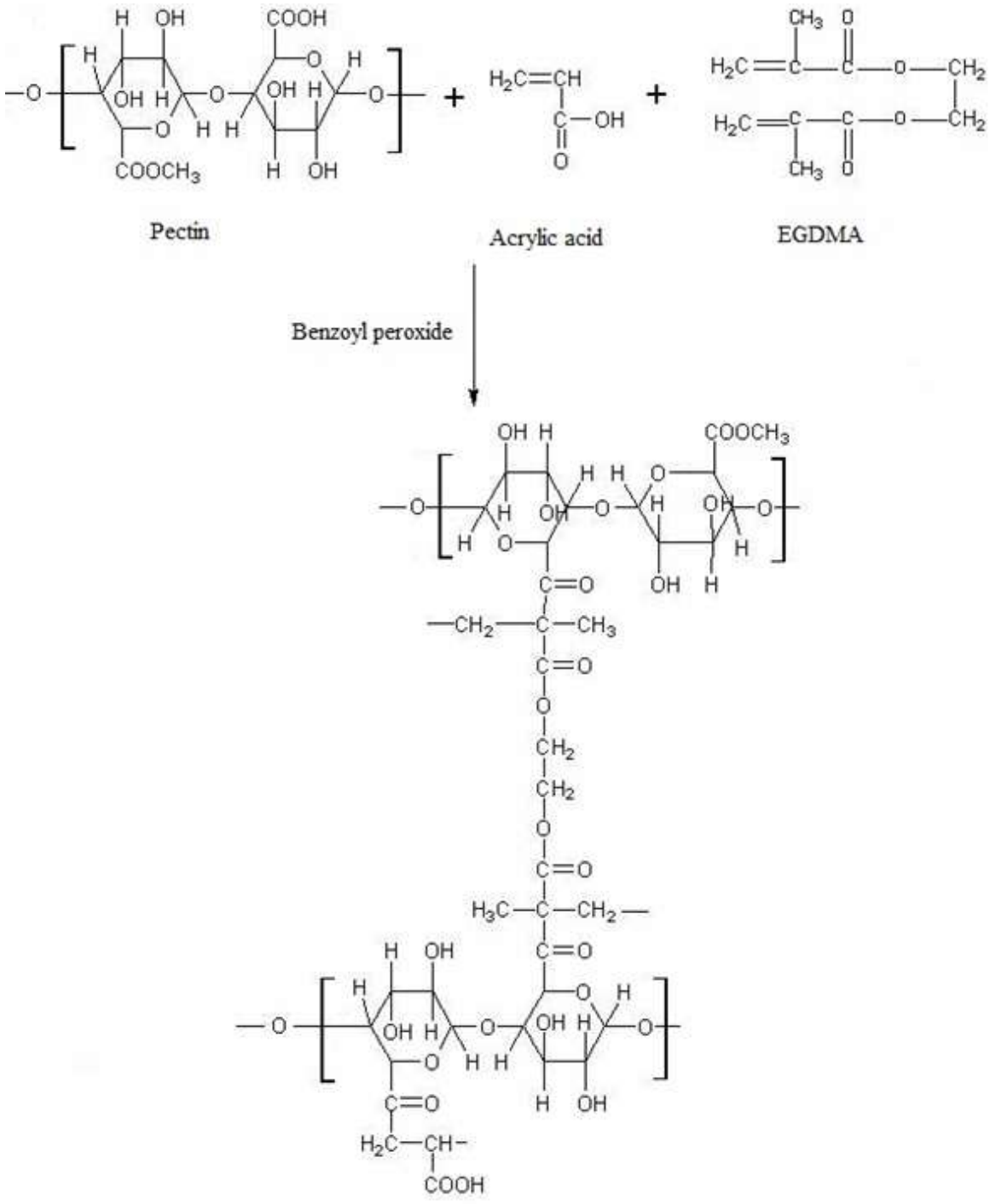

Fig. 1: Presumptive structure of pectin/AA hydrogels

Sol-gel analysis

3-4 mm length pieces of hydrogel were dried at room temperature followed by vacuum drying at 45˚C to gain uniform weight. Hydrogel was extracted in soxhelt with boiling deionized water for four hours. Un-cross-linked monomers were removed in this way and then extracted gels were oven-dried again at 45˚C to attain constant weight. The gel fraction was determined by equation:

$$\text{Solfraction}\,(\%) = \frac{W_o - W_i}{W_o} \times 100 \qquad \text{Eq. 3}$$

$$\text{Gelfraction}\,(\%) = 100 - \text{Solfraction} \qquad \text{Eq. 4}$$

W_o indicates the weight of dried hydrogel prior extraction and W_i is the weight of dried hydrogel post extraction (Siemoneit *et al.*, 2006).

Porosity measurement

Dried hydrogels were drenched in absolute ethyl alcohol overnight and weighed after removing excess solvent from the surface. The porosity (%) was determined by the equation below:

$$\text{Porosity} = \left[\frac{M_2 - M_1}{pV}\right] \times 100 \qquad \text{Eq. 5}$$

where, M_1 = weight of hydrogel before immersion; and M_2 = weight after immersion; ρ= density of absolute ethanol and *V*=volume of hydrogel (Siemoneit *et al.*, 2006).

Loading of metformin HCl into EGDMA cross-linked pectin/AA hydrogels

Three samples with different AA contents, 25.45%, 32.50%and 40% (g/100g of solution) and three samples with different EGDMA strength, 0.2%, 0.6% and 1.0% (g/100g of solution) were used for MHCl loading. Dried gel discs were placed in 1% (w/v) MHCl solution prepared in 50% (v/v) ethanol/deionized water solution. After equilibrium swelling in MHCl solution, MHCl-loaded hydrogels were removed, dried at room temperature and then in oven at 45˚C to uniform weight (Ranjha and Mudassir 2008). For MHCl loading into hydrogels was calculated by the following equation;

$$\text{Amount of drug} = W_D - W_d \qquad \text{Eq. 6}$$

$$\text{Drug loading (\%)} = \left[\frac{(W_D - W_d)}{W_d}\right] \times 100 \qquad \text{Eq. 7}$$

W_d and W_D denote weight of dried hydrogels prior and after soaking in MHCl solution. In another method, MHCl entrapped in hydrogels was calculated by several extracting the specific quantity of loaded gels by using 50% (v/v) ethanol/deionized water solution. Each time 25ml fresh 50% (v/v) deionized water/ethanol solution was continued to use until there was no drug in the solution. MHCl concentration was measured spectrophotometrically at λ_{max} 233 nm. In third method, weighed loaded gel disc was held in MHCl solution upto equilibrium swelling. After calculating the volume of drug solution absorbed, amount of MHCl uptaken was calculated (Ranjha and Mudassir 2008).

In-vitro release of metformin HCl from EGDMA cross-linked pectin/AA hydrogels

In-vitro release was conducted in dissolution apparatus (Pharmatest; PT-Dt 7, Germany) coupled with UV-VIS spectrophotometer (IRMECO, UV-VIS U2020). The weighed hydrogel discs were drenched in 500ml dissolution medium at 37˚C and apparatus operated at 100 rpm. USP phosphate buffer solutions of pH 1.2, 6.5 and 7.5 were used as dissolution medium. Each time 5ml solution was taken at following intervals: 0, 0.25, 0.5, 1.0, 1.5,2.0, 2.5,3.0, 3.5,4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 hours, diluted suitably with appropriate buffer solution and analyzed at λ_{max} 233nm and calculated by standard calibration curves constructed separately for each buffer solution. For cumulative drug release, each sample was analyzed thrice.

For the analysis of MHCl release pattern of MHCl, zero-order (Najib and Suleiman, 1985), first-order (Desai *et al.*, 1966), Higuchi (Higuchi 1963) and Peppas models (Peppas, 1985) were used (Microsoft Excel 2016).

RESULTS

Fourier transform infrared spectroscopy

The spectra of pectin and the hydrogel confirmed the presence of cross-linked grafted products (fig. 2).

XRD determination

XRD technique was employed for determination of crystallographic properties of pectin and MHCl. Pectin and MHCl showed respective characteristic intense peaks between 2θ of 0˚ and 70˚ due to their crystalline nature (fig. 3).

Scanning electron microscopy

The morphology of non-loaded and MHCl loaded Pectin/AA hydrogels was studied by SEM. The images of non-loaded and MHCl loaded hydrogel are shown in (figs. 4 a and b) respectively.

Effect of pH on swelling and on MHCl release

Hydrogels exhibited higher swelling in the solutions of pH 6.5 and 7.5 as compared to in the solutions of pH 1.2 and 5.5.

Effect of components on swelling and on MHCl release

Results showed that swelling of the hydrogel increased with an increase in feed AA concentration. From results it is observed that drug release increases on increasing the AA contents in hydrogels. Effect of polymer pectin is presented in fig. 5. The effect of increasing the concentration of pectin on swelling was not significant at low pH, however, this effect was significant at higher pH. *Effect of EGDMA* showed that swelling was decreased with increase in the feed cross-linker molecules during the hydrogel synthesis.

Diffusion coefficient of hydrogels (D)

Diffusion coefficient provides information regarding the diffusion as well as mass flow of the solvent to the polymeric network. Results (table 1) showed that diffusion coefficient decreases with the increase of AA and pectin concentrations because swelling of polymer increases as the concentration of AA and pectin increases. However, diffusion coefficient increases on increasing the degree of crosslinking because less space is available for diffusion in highly cross-linked network (Mishra *et al.*, 2008).

Table 1: Different feed compositions of pectin/AA hydrogels formulations using EGDMA as cross-linker

Sample code	pectin/100 gm solution	AA/100 gm solution	AA/pectin (Wt %)	EGDMA/100gm solution	D $=10^{-7}$ (cm^2/sec)
S1	2.72	25.45	90.34/9.65	0.178	0.50
S2	2.72	32.72	92.32/7.67	0.229	0.30
S3	2.72	40.00	93.63/6.36	0.280	0.25
S4	1.81	29.09	94.14/5.85	0.203	0.46
S5	2.72	29.09	91.44/8.55	0.203	0.41
S6	3.63	29.09	88.90/11.09	0.203	0.40
S7	2.72	32.72	92.32/7.67	0.065	0.69
S8	2.72	32.72	92.32/7.67	0.196	0.60
S9	2.72	32.72	92.32/7.67	0.327	0.42

Table 2: Amount of MHCl loaded in different formulations of Pectin/AA hydrogels calculated by three different methods.

Samples code	Amount of MHCl loaded (g/g of dry gel)		
	By swelling	By extraction	By weight
S_1	0.070	0.065	0.068
S_2	0.076	0.074	0.078
S_3	0.078	0.076	0.080
S_7	0.081	0.079	0.083
S_8	0.074	0.073	0.077
S_9	0.067	0.063	0.065

Table 3: Effect of AA amount on drug release kinetics of Pectin/AA hydrogels in different buffer solutions

Samples code	AA contents %	pH	Zero order kinetics		First order kinetics		Higuchi Model	
			K_o (h^{-1})	R^2	K_1 (h^{-1})	R^2	K_2(h^{-1})	R^2
S_1	25.45	1.2	1.5925	0.9902	0.018	0.982	0.0677	0.9935
		6.5	5.375	0.9737	0.087	0.9684	0.2319	0.9984
		7.5	6.5134	0.98	0.1246	0.9734	0.2795	0.9813
S_2	32.72	1.2	1.6908	0.9888	0.0193	0.9881	0.0725	0.9905
		6.5	5.6925	0.9799	0.0944	0.9672	0.244	0.9910
		7.5	6.7581	0.9791	0.1334	0.9716	0.287	0.9818
S_3	40	1.2	1.8175	0.9818	0.0211	0.965	0.0793	0.9836
		6.5	5.7749	0.9717	0.1027	0.9651	0.252	0.9958
		7.5	6.6533	0.9753	0.1493	0.9661	0.2924	0.9924

Table 4: Effect of EGDMA amount on drug release kinetics of Pectin/AA hydrogels in different buffer solutions

Samples code	EGDMA contents	pH	Zero order kinetics		First order kinetics		Higuchi Model	
			K_o (h^{-1})	R^2	K_1 (h^{-1})	R^2	K_2(h^{-1})	R^2
S_7	0.2%	1.2	1.994	0.9873	0.0236	0.9725	0.0868	0.9970
		5.5	5.9423	0.9849	0.1093	0.9782	0.2557	0.9883
		7.5	6.7355	0.9801	0.1546	0.9659	0.2954	0.9832
S_8	0.6%	1.2	1..8467	0.9941	0.0215	0.984	0.0797	0.9971
		5.5	5.2622	0.967	0.0898	0.9539	0.230	0.9802
		7.5	6.5352	0.9762	0.1445	0.9555	0.2882	0.9892
S_9	1 %	1.2	1.6505	0.9693	0.0189	0.9608	0.072	0.9723
		5.5	5.1893	0.9896	0.0866	0.9476	0.2277	0.9919
		7.5	6.0783	0.9597	0.1175	0.9586	0.2643	0.9769

Table 5: Effect of AA amount on drug release mechanism of Pectin/AA hydrogels in different buffer solutions

Samples No	AA contents	pH	Release exponent (n)	R^2	Order of release
S_1	25.45%	1.2	0.7281	0.9746	Non-Fickian
		5.5	0.9372	0.987	Non-Fickian
		7.5	0.9119	0.9838	Non-Fickian
S_2	32.72%	1.2	0.7462	0.9943	Non-Fickian
		5.5	0.9537	0.9815	Non-Fickian
		7.5	0.9363	0.9826	Non-Fickian
S_3	40%	1.2	0.7328	0.9895	Non-Fickian
		5.5	0.8968	0.9732	Non-Fickian
		7.5	0.8168	0.9722	Non-Fickian

Table 6: Effect of EGDMA amount on drug release mechanism of Pectin/AA hydrogels in different buffer solutions

Samples No	EGDMA contents	pH	Release exponent (n)	R^2	Order of release
S_7	0.2%	1.2	0.7117	0.9909	Non-Fickian
		5.5	0.8669	0.9811	Non-Fickian
		7.5	0.7952	0.9796	Non-Fickian
S_8	0.6%	1.2	0.697	0.9964	Non-Fickian
		5.5	0.8466	0.9977	Non-Fickian
		7.5	0.7961	0.972	Non-Fickian
S_9	1.%	1.2	0.7105	0.9809	Non-Fickian
		5.5	0.8505	0.9683	Non-Fickian
		7.5	0.7982	0.9885	Non-Fickian

Sol-gel analysis

It was found that gel-fraction of hydrogels increased along with increased concentration of pectin, AA and cross-linker.

Porosity measurement

The results show that porosity increases on increasing the concentration of pectin and AA. Loading of metformin HCl into EGDMA cross-linked pectin/AA hydrogels MHCl loading by swelling, extraction and weight is given in table 2.

In-vitro release kinetics of metformin HCl

The pH values of these buffer solutions are comparable within the range of human gastric and intestinal pH. The results showed that the amount of drug release from drug loaded gels was higher in basic pH than in pH 1.2.

Effect of AA and EGDMA amount on drug release kinetics of Pectin/AA hydrogels in different buffer solutions is shown in table 3 and 4 respectively. However results from Peppas model are presented in table 5 and 6. Standard for selecting the most appropriate model was based on the best goodness of fit presented by the data of regression coefficient nearer to 1.

DISCUSSION

The spectrum of pectin presented a peak at 3402cm^{-1} due to stretching of -OH groups. The peak at 2913cm^{-1} pointed out the presence of C-H stretching vibration. The peaks at 1756 cm^{-1} confirmed >C=O stretching vibrations due to the presence of -CO-OCH_3 group. The peaks at 1441 cm^{-1} and 1340 cm^{-1} could be of -CH_2 scissoring and -OH bending vibration. At 1023 cm^{-1} peak was of -CH-O-CH-stretching. The spectra of MHCl showed all the characteristic peaks of the pure chemical. The spectra of loaded hydrogel proved the loading of MHCl. The spectra of non-loaded hydrogel confirmed the strong interaction of pectin and monomer (Yin *et al.*, 2008).

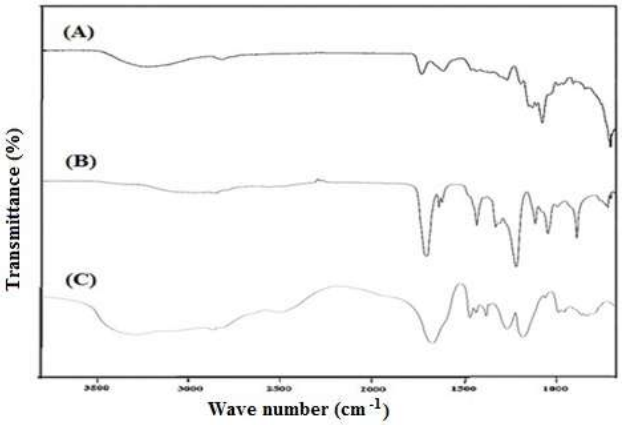

Fig. 2: FTIR spectra of (A) Pectin (B) Acrylic Acid (C) MHCl Loaded Hydrogel

The intensity of the peaks of non-loaded and loaded hydrogels was decreased, which is an indication of the reduced crystallinity. The reduced crystallinity confirmed the improved physical stability of MHCl in the loaded hydrogel indicating that the incorporated MHCl is in amorphous form (Kumar *et al.*, 2010).

It is observed from SEM micrographs that non-loaded hydrogel showed discrete porous structure. The results of the micrograph suggested that porous structure was formed which can absorb large amounts of core substances through diffusion. The SEM of loaded hydrogel shows a fibrous and smooth structure indicating that drug has been incorporated and adhered to the surface of matrix (Chen *et al.,* 2005).

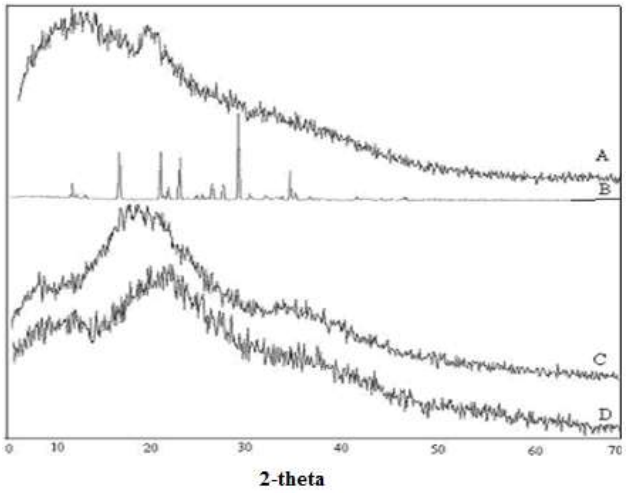

Fig. 3: X-Ray powder diffractometry of (A) Pectin (B) MHCl (C) Nonloaded hydrogel (D) MHCl loaded hydrogel

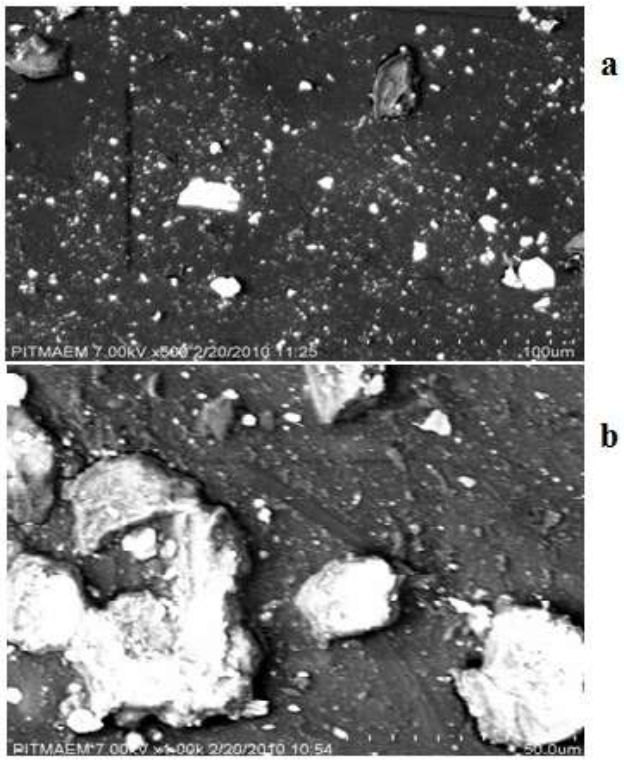

Fig. 4: SEM image of a) unloaded hydrogel b) MHCl loaded hydrogel

There was significant increase in the percentage of metformin HCl release on raising the pH of the releasing media. These findings are consistent with the results reported by Ranjha *et al* (Ranjha *et al.,* 2011). AA contains carboxyl groups having 4.26 pKa. As the pH of the surrounding medium exceeds pKa values, hydrogel swell due to ionization of -COOH groups that ultimately causes the stretching of coiled molecules.

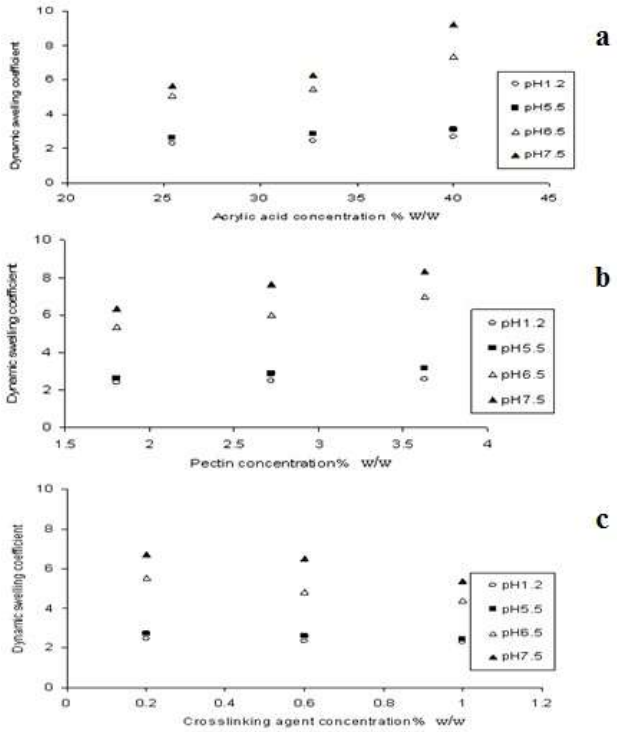

Fig. 5: Dynamic swelling coefficient of Pectin/AA hydrogels after 8 hours swelling in 0.2M phosphate buffers. The pH values are: pH 1.2 (o), pH 5.5(■), pH 6.5 (Δ), and pH 7.5 (▲). A) Effect of AA contents. B) Effect of pectin content. C) Effect of EGDMA contents.

The increase in AA contents in the reaction system led to increase in number of COOH group available for ionization which results in the increase swelling of the gels at pH higher than that of pKa of the COOH. Ranjha and Mudassir (Ranjha and Mudassir, 2008) prepared Vinyl acetate-co-acrylic acid hydrogels (VAC-co-AA) and studied the influence of AA on dynamic swelling. It was reported that swelling increases on increasing AA contents in the gels.

The presence of carboxyl and methoxyl groups of pectin, that remain protonated in acidic environment and anion/anion repulsion is eliminated. At pH >4, carboxylate groups are ionized and electrostatic repulsion of carboxyl groups resulted in swelling enhancement (Ranjha *et al.,* 2011). The carboxymethyl group (-COOCH3) of pectin remain collapsed at pH values lower than the pKa of carboxymethyl group (-COOCH3) and

results in lower swelling (Mishra *et al.,* 2008). The effect of varying pectin content on swelling was not significant and since the swelling is desired characteristics for efficient drug loading and release studies therefore these samples were not selected for further *in-vitro* MHCl loading and release studies. This is due to the fact that cross linking retarded the chain expansion and thus decreasing the swelling of the gels. Since higher swelling is responsible for greater amount of solute release from the gels therefore this increase in the content of cross-linker in the gels also results in decrease in drug release from hydrogels.

Firstly, regarding the effect of AA on gel fraction it was found that when the content of AA is less, therefore less gelation has been occurred at fixed degree of crosslinking and fixed content of pectin. Secondly, when the content of pectin was less, gel fraction was reduced. Thirdly, it was seen that when degree of cross linking was less, therefore less gelation has been formed in cross linking. Higher degree of cross linking facilitates the gel formation and decreases the sol fraction. This is because all above mentioned substances participate actively in hydrogel synthesis and increase in concentration of these reagents resulted into high degree of polymerization and gelation. These finding are consistent with the results reported by Ranjha *et al* (Ranjha *et al.,* 2011) where pectin and AA hydrogels were cross-linked using methylene bisacrylamide.

Effect on porosity was due to higher thickness of solution which prevents the bubbles flight from the mixture due to the creation of interconnected channels. It was evident that on increasing the EGDMA concentration porosity decreases. It is suggested that this is due to increase in physical entanglement between pectin and AA in the gels. The higher drug release in basic pH 6.5 and 7.5 was due to the higher swelling of the gels in basic pH. It is suggested that pH dependent swelling behavior is also contributing towards the higher drug release. Korsmeyer plots indicated that the values of n for all samples in buffers solutions lie between 0.45 and 1 indicating that the release of MHCl from all compositions of hydrogels happened through non-Fickian diffusion mechanism. It is concluded that the MHCl release is controlled by both diffusion of drug from gel during solvent penetration as well as polymer chain relaxation (Mishra *et al.,* 2008).

CONCLUSION

New formulations of pH sensitive hydrogels can be prepared by varying the amount of polymer, monomer and cross-linker. Hydrogels showed high swelling ratio, high porosity, high gel fraction with increased contents of pectin and AA. High degree of crosslinking exhibited low swelling, high gel fraction and low porosity. Hydrogels with high contents of AA and low degree of EGDMA showed high quantities of drug loading and drug release. The higher drug release in basic pH 6.5 and 7.5 was due to the higher swelling of hydrogels. MHCl from all compositions of hydrogels happened through non-Fickian diffusion mechanism. These polymeric hydrogels presented a porous structure. The intensity of the peaks of non-loaded and loaded hydrogels was decreased, which is an indication of the reduced crystallinity of drug. Findings of this study proved that pH sensitive pectin/AA hydrogels can serve as a platform for controlled release and site-specific delivery of metformin.

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