PREPARATION, CHARACTERIZATION AND RELEASE OF VERAPMIL HYDROCHLORIDE FROM POLYCAPROLACTONE/ ACRYLIC ACID (PCL/AA) HYDROGELS

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ABSTRACT

In this study pH sensitive, biocompatible and controlled released hydrgels were prepared and their localized drug delivery effect was analyzed. Polycaprolactone and acrylic acid (PCL/AA) were reacted by free radical polymerization and developed inter penetrating polymeric network (IPN) hydrogels. Benzylperoxide was used as initiator and N, N methylenebisacrylamide [NNMBisAm] was employed as a cross-linking agent. Different concentrations of monomer, polymer and cross-linking agent were used and the reaction parameters were optimized. The obtained PCL/AA hydrogels were fully characterized by Fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), and thermogravimetric analysis (TGA) that determined the polymer structure, its morphology and strength respectively. Verapamil, a calcium channel blocker was loaded by incubation of polymerization method. Controlled release Verapamil hydrogel was developed due to its low solubility; low permeability and having very short half life of 1.2-2 h. The dynamic swelling, equilibrium swelling and drug release were carried out in a buffer solution of pH 1.2, 4.5 and 6.8. Concentration of Acrylic acid showed direct, while Polycaprolactone inverse relation to swelling and drug release due to their hydrophilic and hydrophobic nature respectively. Cross-linking agent also had the contrary effect on swelling. Diffusion coefficient (D) of hydrogels was determined by using Flory-Rehner theory. Drug release and swelling data were analyzed by different kinetic models, like Zero order, First order, Higuchi, Korsmeyer's and Peppas. The release and diffusion was best described by the first order kinetics where n value was <0.5 for all the formulations indicating Fickian drug release mechanism.

Keywords: Polycaprolactone, Acrylic acid, Scanning Electron Microscopy, Thermogravimetric analysis.

INTRODUCTION

Hydrogels are three dimensional cross-linked polymeric structures which are able to swell in the aqueous environment and can retain a significant amount of water (Cristi *et al*., 1996; Ying *et al*., 2006). The network structure of hydrogels can be formed by chemical initiation (Karadeg *et al*., 1996; Krasnov *et al*., 2004) or ionizing radiation method, inter polymeric complexes and semi-interpenetrating polymerization (Chen and Hoffman, 1991; Komatsu *et al*., 1999; Sheppard, 1991). Hydrogels are used extensively in medicine and pharmacy as drug delivery systems, contact lenses, catheters, wound dressings and biosensors (Marriott and Hughes, 1990; Sheppard, 1991). One of the most important applications of hydrogels is in controlled release systems and for targeting drug to specific areas of the body. When intimate contact is established to the target site, the rate and duration of drug release depends on the swelling behavior of the hydrogel (Edith *et al*., 1999; Blanco-Fuente *et al*., 1996; Donini *et al*., 2002).

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Acrylic acid is a pH sensitive, synthetic polymer extensively used in the area of the site-specific drug delivery of the gastrointestinal tract (Chaaya *et al*., 1999). Because of the presence of carboxylic acid groups, the swelling behavior of the acrylic acid hydrogel is highly dependent on the pH of the surrounding medium (Chu *et al*., 1995; Hariharan and Peppas, 1993). Since pKa of acrylic acid is between 4.5 and 5.0, acrylic acid hydrogels showed significant swelling in small intestine. However, they do not swell significantly below pH 4 in stomach (John *et al*., 1995). Therefore, one of the major applications of acrylic acid gels is sustained gastro-intestinal drug delivery systems (Marriott and Hughes, 1990).

Polycaprolactone also plays a very important role in the preparation of hydrogels. It is a well-known, FDA-approved biodegradable and biocompatible material with hydrophobic characteristics, which has been widely used in biomedical fields (Henry *et al*., 2007; John *et al*., 1995). Mechanical properties of hydrogels can be stabilized by coating the hydrophilic material to hydrophobic layer but the coating of hydrogels provides

an additional manufacturing step and the bonding of hydrogel to hydrophobic biomaterial often raise problems with respect to the persistence of the coating. One method that may be used to enhance the mechanical properties of hydrogels is the formation of interpenetrating polymeric network (IPN) (Allans and Hoffman, 2002).

Verapamil hydrochloride is a calcium channel blocker; BCS class II drug having low solubility and high permeability. With an elimination half life ranging from 1-2 hour it is a potential agent for the controlled release formulations.

In the present work a novel pH sensitive, interpenetrating polymeric (IPN) hydrogels of PCL/AA were developed, which has one hydrophilic i.e., acrylic acid (AA) and one hydrophobic i.e., polycaprolactone (PCL) component. A series of samples with varying monomeric, polymeric composition and degree of crosslinking were synthesized and then Verapamil hydrochloride was loaded successfully. The influence of AA, PCL, N-N methylene bisacrylamide (NNMBisAm) and pH on swelling and drug release were investigated. Hydrogels characteristics were studied by FTIR, SEM and TGA to investigate their structure, surface morphology and thermal stability respectively while Flory Rehner theory was used to determine Diffusion coefficient (D). Verapamil HCl drug released data were analyzed using different model for penetrant diffusion (Peppas and Klier, 1985).

MATERIALS AND METHODS

Materials

Acrylic acid (AA) used as a monomer and polymer was polycaprolactone (PCL), ($Mw=1x10^4$) purchased from Fluka Chemical Company (Buchs, Switzerland). N, N methylene bisacrylamide (NNMBisAm) obtained from Merck Chemical Company (F.R, Germany) used as a crosslinking agnet. Verapamil Hydrochloride was gifted by Novartis (Pakistan). Dichloromethane (DCM), ethanol and Benzyl peroxide all were analytical grade and purchased from Sigma-Aldrich (USA).

Synthesis of semi interpenetrating polymeric [IPN] hydrogels

Series of different cross linked hydrogels of PCL/AA having varying monomeric, polymer and degree of crosslinking agent were synthesized (Xiuyu *et al*., 2006). The synthesis procedure comprised of slow feeding of PCL in 5ml dichloromethane (DCM) solution, and 20ml of ethanol was added under constant stirring for 2 hours to hydrate it in 50ml round bottom flask. N, N-methylenebisacrylamide (NNMBisAm) as a cross-linker was dissolved in acrylic acid. Benzyl peroxide was used as an initiator, at a concentration of 0.5 wt % of AA. Final weight of the solution was kept 100 gm by adding ethanol. Solution poured into polyethylene tubes with 5 x 150 mm internal diameter and length respectively. Nitrogen degassing was done for 15-20 minutes. The capped tubes were placed in the water bath and the temperature was gradually increased to 45°C for 1 h, 50°C for 2 h, 55°C for 3 h, 60°C for 4 h, 65°C for 24 h. After cooling to room temperature, cylinders were removed from the tubes and were cut into 8 mm lengths with a razor blade. The cylinders of PCL/AA were washed with 50% v/v ethanol for 1-2 weeks, for complete removal of the un-reacted monomers. During this period the solvent was changed daily until the pH of the washing liquid became same as that of ethanol water mixture before washing. The prepared disks were dried, first at room temperature and then in an oven at 40-45°C for 1 week. Table 1 shows the prepared samples, their compositions and degree of crosslinking used for hydrogels. Fig. 1 shows the presumptive structure of crosslinking hydrogels.

Loading and release of Verapamil Hydrochloride

There are two methods of drug loading first by polymerization, second by incubation after polymerization; the later method provides some advantages over the former method. Incubation after polymerization removed all non reacted monomers and decomposed products of the catalyst. Verapamil hydrochloride was loaded by hydrolysis in incubation

Table 1: Composition of monomer polymer and crosslinking agents of different formulation of hydrogels.

	Name	PCL/100gm	AA/100 (gm)	NNMBisAm:AA	Methylenebisacrylamide (NNMBisAm) (gm)
1	F1	6	66.7	1:100	0.667
2	F2	6	50	1:100	0.50
3	F3	6	37.5	1:100	0.375
4	F4	3.75	37.5	1.5:100	0.562
5	F5	3.75	37.5	2:100	0.750
6	F6	3.75	37.5	2.5:100	0.937
7	F7	5	37.5	2.5:100	0.9375
8	F8	2.5	37.5	2.5:100	0.9375
9	F9	1.25	37.5	2.5:100	0.9375

after polymerization system. Selected hydrogels having almost same size (8 x 11 mm), contains 3.75/37.5, 5/37.5, 6/50, 6/66.7 PCL/AA and 0.750, 0.937, 0.50, 0.667, % w/w NNBisAm swelled in 50% ethanol solution containing 1%Verapamil for one week. For drug loading 50% ethanol was selected due to maximum swelling ratio of hydrogels at that concentration. The drug loaded monolithic were first dried at room temperature and then in oven at 40-50°C. Drug loaded hydrogels remain same in physical appearances.

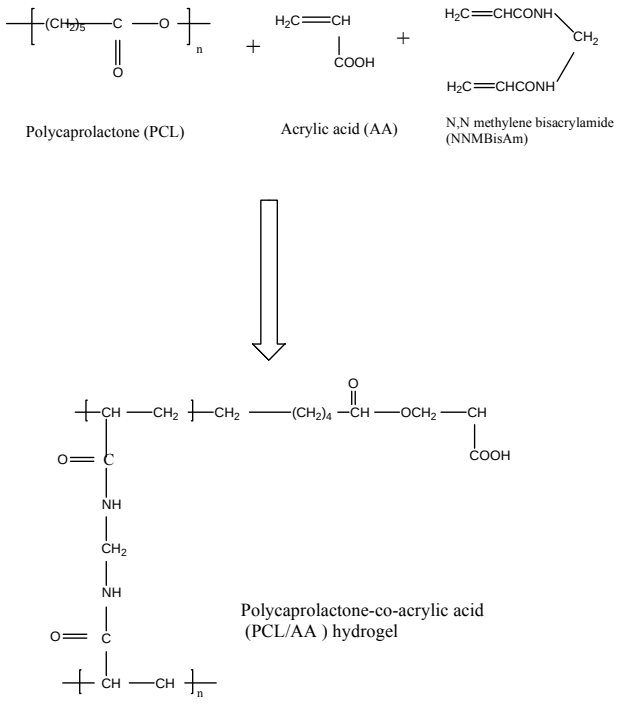

Fig. 1: Presumptive structure of Polycaprolactone/Acrylic acid (PCL/AA) hydrogels.

Release profile was determined in freshly prepared USP phosphate buffer solution pH 6.8 using the USP paddle apparatus at 37°C and 100rpm. 3ml aliquot was withdrawn from 500ml dissolution medium up to 24 h and replaced by same quantity of fresh medium. Verapamil HCl concentration was analyzed using double beam UV–VIS spectrophotometer, (IRMECO U2020). Standard verapamil hydrochloride from 1-100 µg/ml was analyzed by dissolving it in 0.01 N HCl at 278 nm after filtration and concentration was calculated in mg (Yihong *et al*., 2007).

Swelling parameters

Dynamic swelling analysis

The dynamic swelling experiments were carried out in 100 ml solution of 0.1M HCl (pH 1.7) and USP phosphate buffers pH 4.5 and 6.8 solution at 37°C. Dry discs were weighed and immersed in solutions. Samples were withdrawn at regular intervals till 10 hours, weighed after removing the excess surface water by dabbing with the help of filter paper.

Equilibrium swelling analysis

The swelling of the various samples were continued until they attained constant weight. The equilibrium swelling ratio Q was calculated using following equation (Burugapalli *et al*., 2001).

$$Q = \frac{W_t}{W_0} \quad (1)$$

Where W_t is the weight of swollen gel at time t and W_0 is the initial weight of dry gel. Equilibrium swelling ratio showed in Fig. 3 and was calculated by the following equation (Burugapalli *et al*., 2001; Xiuyu *et al*., 2006).

$$Q_{eq}(\%) = \left[\frac{W_t - W_0}{W_0}\right] \times 100 \quad (2)$$

Where W_t is the weight of swollen gel at equilibrium, and W_0 is the initial dry weight.

Sol-gel analysis of Hydrogel

For sol-gel analysis non washed samples were used. Samples of 8 mm length were cut into pieces, dried in a vacuum oven at 45°C to constant weight, and were subject to Soxhlet extraction with de ionized water as solvent. Uncross linked polymer was removed with this extraction from the gel structure. Extracted gels were dried again in a vacuum oven at 45°C to constant weight. The sol fraction was calculated by using following equation (21).

$$SolFraction(\%) = \left[\frac{W_d - W_1}{W_d}\right] \times 100 \quad (3)$$

W_d and W_1 are the initial and extracted dried weights of gels respectively.

Swelling Kinetics and diffusion coefficient of PCL/AA Hydrogels

Swelling behavior of diffusion controlled hydrogels was calculated by following equation (Yihong *et al*., 2007).

$$\frac{W_t}{W_\infty} = Kt^n \quad (4)$$

W_t/W_∞ denote the amount of 50% ethanol solvent diffused into the gel at time t and infinite time (at equilibrium) respectively, k is a constant related to the structure of the network, and the exponent n is a numerical value to determine the type of diffusion.

Diffusion coefficient (D) depends on the polymer segmental mobility and was calculated by the following equation (Edith, 1999).

$$\frac{W_t}{W_\infty} = 4\left(\frac{Dt}{\pi\delta}\right)^{1/2} \quad (5)$$

Where δ is the thickness of hydrogel before swelling, t is time and W_t and W_∞ are the initial and equilibrium weights of hydrogels.

Analytical Techniques

Scanning electron microscopy (SEM)

The morphology of the drug loaded or unloaded hydrogel samples were investigated by using scanning electron microscope SEM (S3400-N, Hitachi High technology, Europe) at different magnifications range of 10-50 µm.

FT-IR spectroscopic analysis

Crosslinked hydrogel samples were crushed with pestle in an agate mortar, was mixed with potassium bromide (Sigma-Aldrich Chemical Company (IR grade)) in 1:100 proportions at 40°C. The mixture was compressed to a 12 mm semitransparent disk by applying a pressure of 65 kN (Pressure gauge, Shimadzu) for 2 min and spectrum was measured over the wavelength range 4000-400 cm^{-1} FT-IR (8400 S, Shimadzu Corp, Japan).

Thermo gravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was carried out Micro/Macro Thermogravimetric Analyzer (Shimadzu Corp-50, Japan) at a heating rate of 10°C min^{-1} and nitrogen at flow rate of 20 ml min^{-1} over a temperature range from 25°C up to 600°C.

Verapamil release Studies

Release Pattern Analysis

Based on the relative rate of diffusion and swelling of the polymers drug release profiles from the PCL/AA hydrogels have been studied by Zero order, First order, Higuchi and Korsmeyer-Peppas models (Alfrey *et al*., 1996; Peppas and Korsmeyer, 1986). These models are generally used to analyze those release mechanisms when more than one type of release phenomenon is involved. The drug release patterns of various samples of PCL/AA hydrogels with different monomeric, polymeric composition and degree of cross linking agent were determined in dissolution medium of pH 6.8 phosphate buffer. Following equations (6-9) were used in the determination of release kinetics for zero order, first order, Higuchi release model and Korsmeyer-peppas model.

$$F_t = K_0 t \quad (6)$$

Where F_t represents the fraction of drug release in time t and K_0 is the apparent rate of zero order release constant (Peppas and Klier, 1985).

$$\ln(1-F) = -K_1 t \quad (7)$$

Where F represents the fraction of drug released in time t and K_1 is the first order release constant.

$$F = K_2 t^{1/2} \quad (8)$$

Where F represents the fraction of a drug released in time t and k_2 is higuchi constant.

$$\frac{M_t}{M_\infty} = k_3 t^n \quad (9)$$

Where K_3 is a constant incorporating the structural and geometric characteristics of the gels, n is the release exponent. M_t/M_∞ is the fraction of drug release at time t.

RESULTS

Swelling behavior of hydrogels depend upon its composition, pH and temperature. Hydrogels with different concentrations of acrylic acid 37.5, 50, 66.7% w/w and 1% w/w NNMBisAm was swelled in 0.1M HCl, and buffer solutions of pH 6.8 with fixed PCL concentration i.e., 6%. Result explained that both dynamic and equilibrium swelling ratio increased with increasing of AA because AA is an ionizable component that can be ionized at higher pH above its pKa value i.e., 4.5.

Table 2: Effect of polymer (PCL), Monomer (AA) and crosslinking agent (NNMBisAm) on dynamic swelling (%) of PCL/AA hydrogels at pH 6.8.

Formula-tions	AA	PCL	NNMBisAm
F1	98.345±0.5	-	-
F2	88.564±0.5	-	-
F3	75.234±0.5	-	-
F4	-	-	67.342±0.5
F5	-	-	45.786±0.5
F6	-	-	42.564±0.5
F7	-	32.564±0.5	-
F8	-	38.342±0.5	-
F9	-	45.980±0.5	-

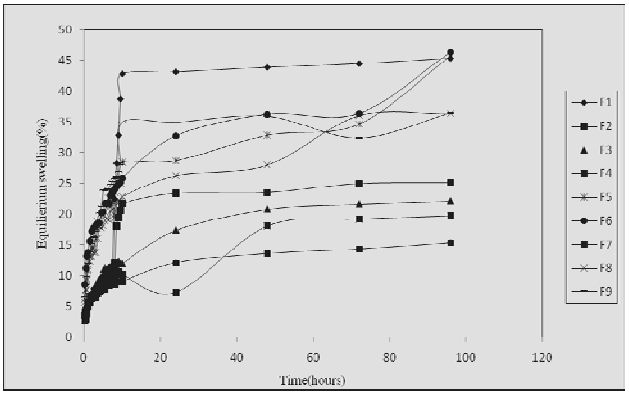

Fig. 2: Equilibrium swelling of PCL/AA hydrogels at (pH 1.2) without loaded drug.

Polycaprolactone is a hydrophobic polymer. Equilibrium and dynamic swelling was observed by using PCL 1.25, 2.50, 5 %w/w with AA and NNMBisAm was kept fixed i.e., 37.5 and 2.5 % w/w respectively at phosphate buffer pH 6.8.

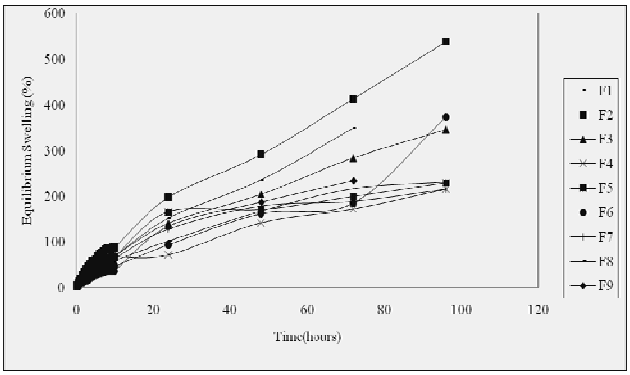

Fig. 3: Equilibrium swelling PCL/AA Hydrogels with trend lines at (pH 6.8).

It was observed that the swelling ratio increased with increasing pH from 1.2, 4.5 to 6.8. It was due to the AA dissociation which had the pKa value from 4.5-5.0. Swelling behavior of PCL/AA hydrogels were studied with different amount of NNMBisAm 1.5, 2 and 2.5 %w/w (F4-F6) at fixed AA and PCL i.e., 37.5% and 3.75% respectively. Swelling ratio showed inverse relation with NNMBisAm as in table 2, F4 (1.5 %) showed the maximum swelling ratio 67.342% and F6 (2.5%) showed minimum 42.564 %. Hydrogel samples had greater proportion of PCL and NNMBisAm showed greator gel fraction when sol fraction was observed high in AA alone or maximum concentration as shown in table 4. Similar behavior was also reported by Pourjavadi *et al*. they also prepared crosslinked polyacrylic acid-co-acrylamide 2 methylpropa- nnesulphonic acid chains onto K-carrageenan through free redical polymerization (Silva and Oliveira, 2007).The diffusion coefficient in buffer solution of pH 6.8 listed in table 4. SEM micrographs of PCL/AA hydrogels at different magnifications showed the PCL/AA hydrogels with (fig. 4a) and without Verapamil hydrochloride (fig. 4b). FT-IR spectra of PCL/AA hydrogel are shown in the fig. 5 which had the five characteristics signals. Four existing carbonyl groups (C=O) of structural unit of PCL, AA and NNMBisAm of the sample were observed at 1650-1734cm^{-1}. Other characteristics peaks were detected at 3340cm^{-1} for –NH, at 2922-2950cm^{-1} for –CH-, at 1161cm^{-1} for -C-O-C- and at 3340cm^{-1} for –OH bonding. Different vibrations represent the presence of the interpolymeric network of polycaprolactone and acrylic acid.

Table 4: Diffusion co-efficient and sol-gel fraction of PCL/AA hydrogels at pH 6.8.

PCL/AA (gm)	Sol Fraction (%)	Gel Fraction (%)	D (Cm^2min^{-1})
F1	60	40	0.2780
F2	65	35	0.1150
F3	69	31	0.0958
F4	35	65	0.1342
F5	30	70	0.0575
F6	25	75	0.0479
F7	20	80	0.2013
F8	23	77	0.2205
F9	28	72	0.3931

Thermostability of pure PCL, AA and PCL/AA hydrogels were analyzed and results explained that PCL pure samples were more stable as compare to AA and PCL/AA hydrogels. All PCL/AA hydrogels undergo multiple stage thermal decomposition. However, the major weight loss occurs within the temperature range 200-350^{o}C as shown in fig 6. *In vitro* release mechanism was studied using various dissolution models such as zero order, first order, Higuchi and Korsmeyer-Peppas for 5 different formulations hydrogels.

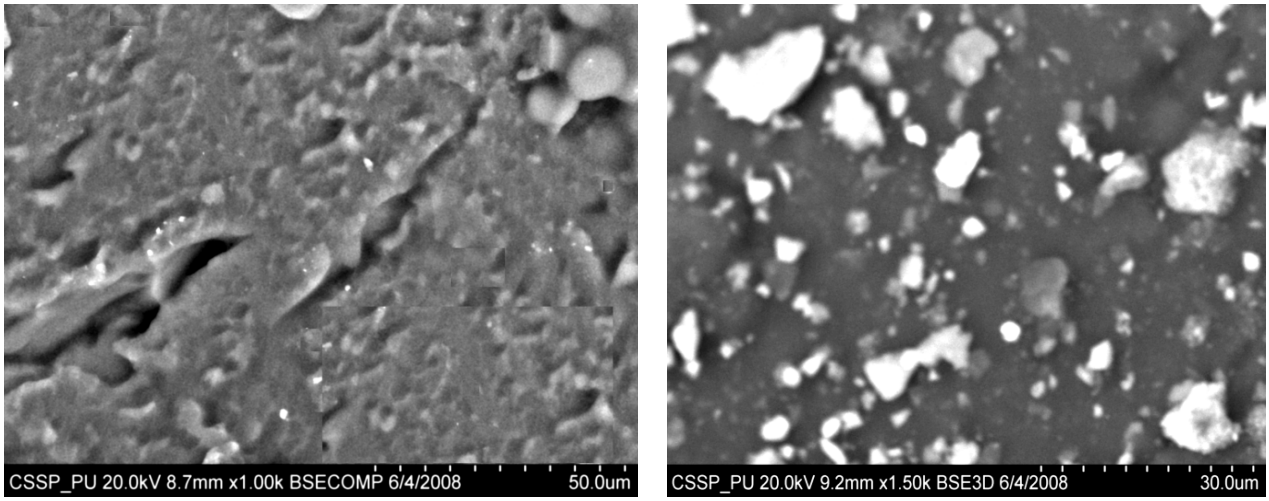

Fig. 4: SEM Analysis of PCL/AA hydrogels (50 µm (a) without drug and 30 µm (b) with Verapamil hydrochloride)

Table 6: Relaese Kinetics of Verapamil Hydrochloride from PCL/AA hydrogels.

PCL/AA	Zero order release		First order release		Higuchi Model		Korsemeyer & Peppas Model		
	r^2	$K_0(h^{-1})$	r^2	$K_1(h^{-1})$	r^2	$K_H(h^{-1/2})$	r^2	n	$K_{kp}(h^{-n})$
F1	0.636	1.555	0.863	-0.126	0.764	10.29	0.944	0.120	1.85
F2	0.753	1.723	0.801	-0.06	0.887	11.28	0.948	0.232	1.791
F5	0.703	1.509	0.918	-0.071	0.850	10.54	0.930	0.123	1.682
F6	0.895	2.03	0.966	-0.05	0.968	12.75	0.969	0.302	1.491
F7	0.830	2.267	0.887	-0.04	0.976	13.42	0.962	0.354	1.40

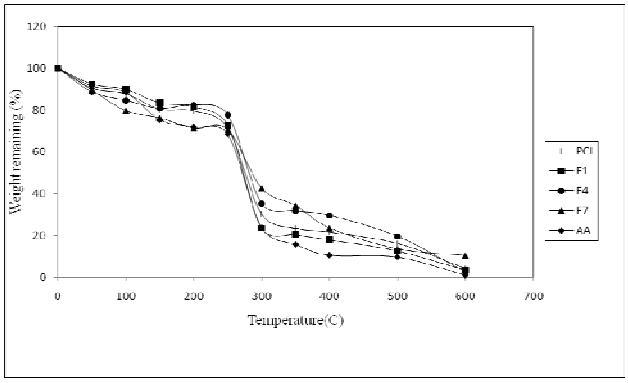

Fig. 6: Thermogram of pure PCL, AA and PCL/AA The effect was observed to be increasing with the increasing number of carbon atoms.

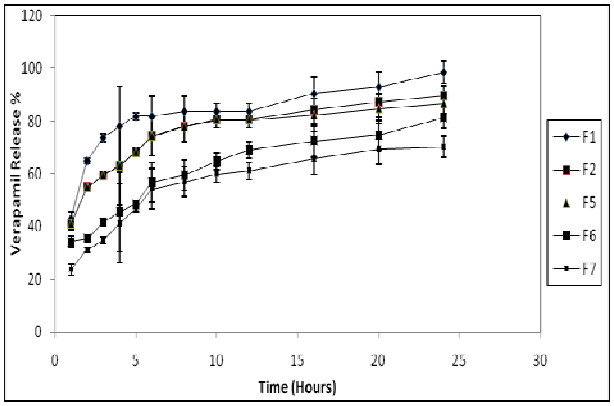

Fig. 7: Verapamil Hydrochloride release (%) in selected Hydrogel formulations.

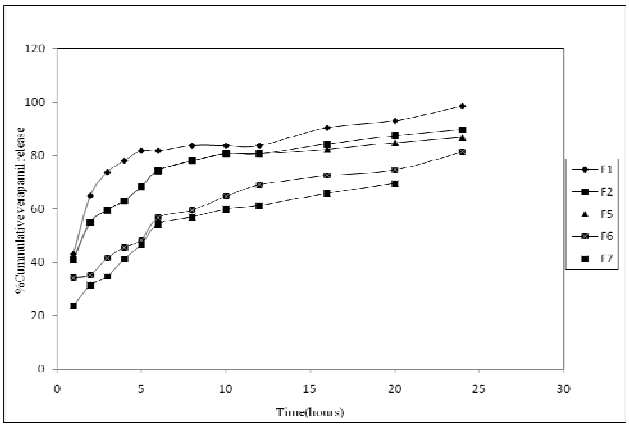

Fig. 8: Zero order kinetic release of Verapamil hydrochloride loaded hydrogel.

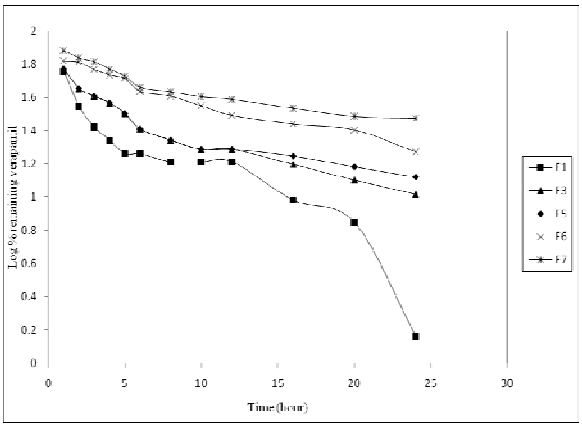

Fig. 9: First order kinetics of Verapamil hydrochloride loaded PCL/AA hydrogels.

DISCUSION

Effect of AA on PCL/AA hydrogels

Table 2 showed the dynamic while figs. 2 and 3 showed the equilibrium swelling ratio of 66.7% AA (F1) higher than 37.5% (F3) and 50% (F2) due higher concentration of anionic AA in first 20 hours but greater number of repulsive forces had broken the hydrogels in 80 hours. So F2 (50%) AA had shown the greatest equilibrium swelling at pH 6.8 as shown in fig. 2. In anionic polymer after the ionization of the carboxyl group, an electrostatic repulsion along the chain takes place causing an expansion of the originally coiled molecule (William, 1982) Shin and colleagues reported that there was a similar expansion of the polymeric chain when there was an increase of ionic groups in the formulation. Similar finding were also reported by Xiuyu *et al*, 2006, who prepared gaurgum/poly(acrylic acid) semi-inter-penetrating polymer network hydrogels in the presence of NNMBisAm as a crosslinking agent (Ranjha and Doelker, 1999).

Effect of PCL on PCL/AA hydrogels

The dynamic and equilibrium swelling ratio of hydrogels at PCL 5%w/w (F7) was low as compared to 1.25 (F9) and 2.5(F8) %w/w as shown in table 2 and fig 3 respectively. Two main reasons were expected; first the hydrophobic unit acted as a physical cross links and was effectively offered resistance against the diffusion of water molecules into the hydrogels.

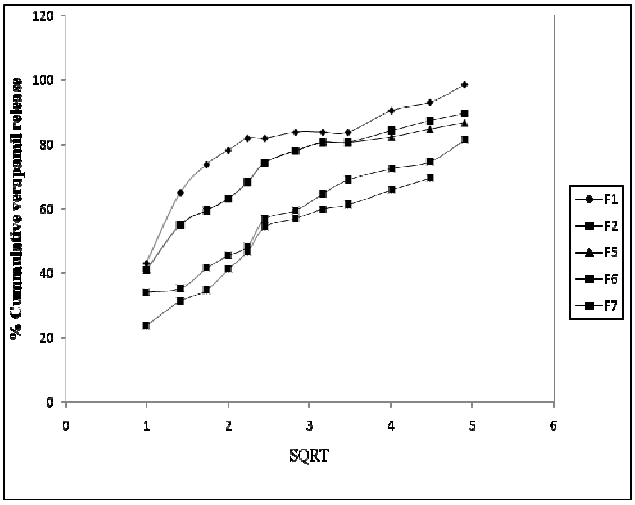

Fig. 10: Higuchi release model of Verapamil hydrochloride loaded PCL /AA hydrogels.

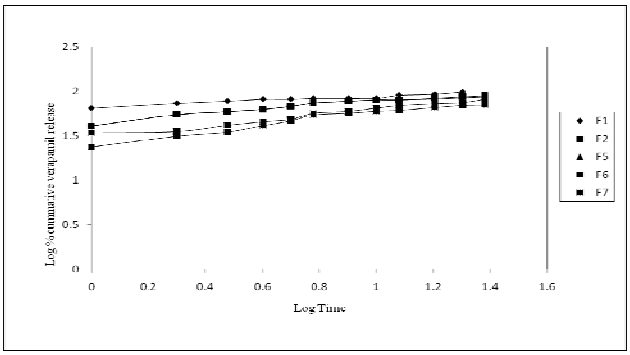

Fig. 11: Korsmeyer and Peppas release model of different PCL/AA verapamil loaded hydrogel.

The presence of the hydrophobic unit of PCL could shield carboxylic acid groups and decreased the dielectric constant near the network chain which might influence the dissociation constant of AA unit (Xiuyu *et al*., 2006). Similar results were also reported by Zhang *et al*. who investigated the swelling and controlled release behavior of hydrophobically modified poly(meth-acrylic acid) hydrogel (Olga *et al*., 1997).

Effect of pH on PCL/AA hydrogels

Fig 2 and 3 showed equilibrium of swelling at lower pH(1.2) and higher pH (6.8). Increased equilibrium swelling was due to ionization of AA and elevated osmotic pressure. The swelling ratio depends upon the available free volume of the expanded polymer matrix, polymer chain relaxation, and availability of ionizable functional groups i.e, carboxylic group. The maximum extant of swelling at pH 6.8 was due to the complete dissociation of the acidic group of AA (Kostum *et al*., 1961). Table 3 showed the swelling ratio at pH 1.2, 4.5 and 6.8. At pH 1.2 carboxylic groups were collapsed and the swelling was low due to low pH than pKa. Increased pH from 4.5 to 6.8 the electrostatic repulsion of ionized carboxyl groups weakened the hydrophobic interaction between PCL and increased the swelling ratio. Similar finding were reported by Safaa *et al*., who find the swelling- release behavior of polyvinyl pyrrlidone (PVP) and acrylic acid (AA) copolymer hydrogels increased by increasing concentration of AA when hydrogels prepared by gamma irradiation (Safaa *et al*., 2007).

Effect of degree of cross linking agent on PCL/AA hydrogels

Flory equation reported the inverse relation of swelling and cross linker (C_c). Water absorbency ratio also decreased with increased cross-linker concentration. The known relationship between the swelling and cross-linking agent is stated as equation

$$S = KC_c^{-n} \qquad (10)$$

Where k and n are constant values of the individual hydrogels. As reported by Regian da Silva *et al*. they prepared hydrogels by using of poly(N-isopropylacrylamide)-co-polymerized with acrylic acid and NNMBisAm used as crosslinking agent. They reported that the crosslinking agents had the inverse effect on swelling ratio (Yu-Yang *et al*., 2007).

Mechanism of swelling kinetics and diffusion coefficient

It was observed that the diffusion coefficient values from F1-F3 (0.2780 to 0.09589) were decreased with the decreasing concentration of AA moreover inverse response was observed in case of F7-F9 (0.2013-0.3931) and F4-F6 (0.0497-0.1342) when concentration of PCL and NNMBisAm increased respectively. These result implied that hydrogels has high concentration of AA swelled more as compare to hydrogels having high concentration of PCL and. The diffusion coefficient of PCL/AA hydrogel were calculated from equation 5 (Kaplan and Guner, 2000).

Analytical techniques;

The congested and rough structure of hydrogel showed much smaller pore diameter (Pourjavadi *et al*., 2007). The porous structures have spherical and spongy like shapes at 50 μm, due to high concentration of cross-linking agent [NNMBisAm] as shown in fig 4a. Dense structure was due to dry gels. Similar network structure was observed by Regiane da Silva *et al*. (Park and Hoffman, 1994).

Pore size increased with the increased concentration of AA due to hydrophilic nature, and having more water accessibility in polymer matrix. PCL decreased the pore size because of hydrophobic structure, which did not allow fast water penetration (Yu-Yang *et al*., 2007). Verapamil drug particals was also seen on the surface of PCL/AA hydrogels when observed the drug loaded cylinders at 30 μm in fig.4b.

Thermogravimatric analysis (TGA)

Thermal decomposition of the hydrogels based on either pure polymers or PCL/AA. PCL showed higher T_{max} (555.34^{o}C) due to long polymer chain than AA(272.21^{o}C) as shown in table 5. Increasing T_{max} from F1(235.12^{o}C) to F4(296.12^{o}C) than F7(280.45^{o}C) was due to increased concentration of PCL and decreased concentration of AA respectively. Continuous TGA curve indicated the formation of interpolymeric matrix (Pitt *et al*., 1981). Safaa G *et al*., also observed the Structure and swelling-release behaviour of poly (vinyl pyrrolidone) (PVP) and acrylic acid (AA) copolymer hydrogels prepared by gamma irradiation (Safaa *et al*., 2007) and decreased thermostbility of higher AA concentration. Similar studies were performed by Burugapalli *et al*., by using acrylic acid and gelatin hydrogels and explained that continuous thermostability showed the formation of interpenetrating polymeric net work (Burugapalli *et al*., 2001).

Verapamil Release studies

Overall curve fitting showed that the drug release from interpolymeric crosslinking gels followed first order release model (r^2 = 0.966) and Korsmeyer & Peppas model (n<0.5) with Fickian diffusion as shown in table 6. This was further supported by the fact that the combinations of polymer hydration, drug dissolution and polymer relaxation mechanism are dominant during gel formed phase (Chopra *et al*., 2006; Pourjavadi *et al*., 2007). Chong-Su Cho *et al* in 1999 performed the relaese studies of clonazepam from polycaprolactone and poly ethylene glycol hydrogels and reported that hydrophobic drugs had the slow release pattern due to higher concentration of hydrophobic components and reverse in hydrophilic components (Pham and Lee, 1994). All percentages of Verapamil release and their kinetics are shown in figs. 7-11.

CONCLUSION

Orally controlled release polymeric network of polycaprolactone and acrylic acid hydrogel for water soluble drugs was successfully established and loaded with Verapamil hydrochloride. Swelling ratio was directly proportional to AA content and pH of the surrounding media was inversely proportional to PCL and NNMBisAm content. The presence of AA and PCL in hydrogel was confirmed by FTIR spectroscopy and SEM revealed the surface with large, open, spongy like appearance. Verapamil released showed diffusion relaxation of polymer was dominant during gel state. Further work can be performed by using same polymer, monomer and EGDMA as a cross-linking agent and comparison can be made with reported hydrogels.

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