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Research Paper

Preparation, Characterization, Water sorption and Drug Release study of 2-acrylamido-2-methylpropane sulfonic acid (AMPS) based hydrogel

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Abstract: *A novel biodegradable hydrogel composed of starch, 2-acrylamido-2-methylpropane sulfonic acid (AMPS) and acryl amide(AM) have been prepared by free radical polymerization method using N,N^{I}-methylenebisacrylamide(MBA) as cross-linking agent. The structure, morphology, and thermal nature of hydrogel is investigated by Fourier Transform Infrared (FT-IR) spectroscopy, Scanning Electron Microscopy (SEM) and Thermogravimetric Analysis (TGA) respectively. The swelling and tetracycline release profile of hydrogel is investigated under different parameters. The Swelling study shows that the water uptake property of the hydrogel is dependent on composition of polymer, pH and ionic concentration of the medium. The results of in-vitro drug release experiments shows that the hydrogel has sustained release properties and the release rate depends on the equilibrium swelling ratio of the hydrogels and pH of the medium. The diffusion exponent calculated from empirical equation indicated that the water transport mechanism followed non-Fickian.*

Keywords: Acryl amide (AM), Hydrogel, N N'-methylenebisacrylamide (MBA), Tetracycline, Water sorption

Introduction

Hydrogels have been successfully used as super absorbent materials and in drug delivery, cell encapsulation and tissue repair due to their high water content and consequent biocompatibility. Considering the fact that water retention in the hydrogels provides a suitable drug diffusion pathway, many hydrogel-based networks have been designed and fabricated as intelligent carriers of drugs. Due to unique properties, hydrogels has a wide application in drug delivery [1-4], wound dressing [5-7], contact lens [8-10], tissue engineering [11-14]. Many synthetic and naturally derived materials have been reported to form well characterized hydrogels. Since natural polymers possess better biocompatibility, biodegradability, non toxicity and easily modified ability than various synthetic materials, more and more researches have focused on natural polymer based hydrogels using polysaccharides, cellulose derivative and proteins as drug carrier [15, 16].

Among natural polymers, starch is an attractive candidate as starting material for the preparation of hydrogel because of low cost, large scale production, biodegradability, and biocompatibility, renew ability and no toxicity. But the application of starch is limited due to brittleness and solubility in hot and cold water [17]. However the mechanical properties of the starch can be improved by incorporating other polysaccharide or vinyl monomer like collagen [18], polyvinyl alcohol [19], gelatine [20, 21], acrylic acid etc through grafted copolymerization [22]. Starch and its derivatives have been utilized in many industrial applications such as food, medicine and cosmetics [23-25]. Another monomer chosen for the preparation of hydrogels is acryl amide (AM) and 2-acrylamide-2-methylpropane sulfonic acid (AMPS). Both AM and AMPS have large application in medical application as well as other applications [26].

AMPS have attractive application as wound dressing material [27, 28] since it adheres to healthy skin but not to the wound surface and is easily replaceable

without any damage to the healing wound. The drug used to observe the release behaviour of the hydrogel is Tetracycline (TC), one of the most well known antibiotics and is very effective against many anaerobic microbes associated with various periodontal disease involving both adult and juvenile periodontitis patients [29].

In this study, a new hydrogel composed of starch, AMPS-Na and AM is prepared by free radical polymerization method using MBA as the cross-linking agent. The hydrogel is characterized by FT-IR, SEM and TGA techniques. Swelling and in vitro release studies have been reported here. Diffusion mechanism of the hydrogel is also reported.

Material and Methods

Acrylamido-2-methyl-1-propane sulfonic acid (AMPS) was purchased from Merck, India and its sodium salt (AMPS-Na) was prepared by neutralising with 1 mole of NaOH solution. Acryl amide (AM) (Merck, India) was purified twice by recrystalling with ethanol. Starch, potassium peroxodisulfate (KPS), NaOH, KCl, $CaCl_2$ were purchased from Merck, India. N,N^{I}-methylenebisacrylamide (MBA) was obtained from central drug House (P) Ltd. India. Tetracycline was purchased from Merck, India.

Preparation of hydrogel

The hydrogel were prepared by free radical polymerisation method. 0.5 g of starch was dissolved in 5ml of boiled double distilled water and prepared a clear solution. To this solution 7.02 mM AM, 14.06 mM AMPS-Na, 0.073 mM initiator (KPS) and 0.12mM cross linker (MBA) were added and mixed with continuous stirring. The whole mixture was transferred into PVC straw and the polymerization was carried out at 60^0 C for 30 minutes. After complete polymerisation, the gel was dried at 50^0 C for 8 hours. The polymer was then cut into small pieces and allowed to equilibrate for 10 days by changing the swelling medium every day. After 10 days the hydrogel were taken out from swelling medium and dried in air.

Characterisation of hydrogel

IR-spectra of the monomers, drug, hydrogel and drug loaded hydrogel were recorded in Shimadzu-8400s Ft-IR spectrophotometer. The morphology of the hydrogel was investigated by using Scanning electron microscope (SEM) (Carlzeissieo Leo 1430VP). The thermal property of the gel was investigated by thermo gravimetric analysis (TGA) (Perkin Elmer 4000).

Swelling study

The progress of swelling was monitored gravimetrically as described by other workers [30]. 40 mg of dry hydrogel was immersed in 100 ml of double distilled water. After every 30 minutes interval of time the hydrogel was taken out and excess surface adhered water was removed by blotting and the weights of swollen gels were recorded. The swelling ratio was calculated by following equation.

$$\text{Swelling ratio} = \frac{\text{Weight of swellen gel}}{\text{Weight of dry gel}} \quad \text{.....(1)}$$

To understand the effect of monomer composition and external environment on the swelling, the swelling experiment is carried out by varying monomer composition, and pH and electrolyte concentration of the swelling medium.

Drug loading

Drug loading was carried out by allowing a dry preweighed piece (40 mg) of hydrogel to equilibrate in a tetracycline solution of (5 mg/ml) for 24 hours. After 24 hours, the hydrogel was taken out, dried in air and reweighed. The percentage (%) of drug loading is calculated by following equation.

$$\text{Percent of Loading} = \frac{W_2 - W_1}{W_1} \times 100 \quad \text{.....(2)}$$

Where W_2 and W_1 are weights of drug loaded and dry hydrogel respectively.

In-vitro release studies

Drug release from the hydrogels with different monomer composition, different pH (2 to 9) was investigated at 30^0C. These experiments were performed using UV-visible spectrophotometer (Shimadzu-1700). A piece of drug loaded dry hydrogel was immersed in 50 ml of distilled water (pH 7) at 30^0C. At scheduled time intervals, 5ml solution was withdrawn, the absorbance was recorded at a wave length of 420 nm in a UV-visible spectrophotometer (Shimadzu 1700) and returned back to the medium. The experiments were repeated in triplets and the data represented in the graph were mean value of three experiments.

Results and Discussion

FT-IR analysis

The IR spectra of pure AM, Na-AMPS, starch and prepared hydrogel are depicted in fig 1 (a-d). The IR spectra of the gel in Figure 1(d) clearly shows combined spectral feature of various functional groups of AM, Na-AMPS, and starch. The peak at 3661 cm^{-1} is due to the overlapping peaks of N-H and O-H groups of AM, Na-AMPS, starch. The C-H (symmetric and asymmetric) stretching is observed at 2779 to 3063 cm^{-1}. The N-H bending, N-C and C=O stretching of AM and Na-AMPS are observed at 1527, 1228 and 1693 cm^{-1} respectively. The characteristic peak of Na-AMPS units can be seen at 1049 cm^{-1} due to SO group.

To understand stability of the drug within the polymer matrix, IR spectra of tetracycline, drug loaded gel and blank composite gel were compared in fig 2(a-c). In IR spectra of drug loaded hydrogel, all the peaks of blank composite gel are present but the peaks of Tetracycline are hard to detect. The peaks 3661, 2948 and 1693cm^{-1} of the blank composite hydrogel is slightly shifted to lower wave number than that of the drug loaded gel. This may be due to intermolecular interaction of Tetracycline with the gel network. No new peaks are observed in IR spectra of drug loaded composite gel, this indicates that there is no chemical interaction between Tetracycline and gel. The entrapment of drug is only physical in nature. From this observation it can be said that the activity of the drug, Tetracycline is not lost after loading.

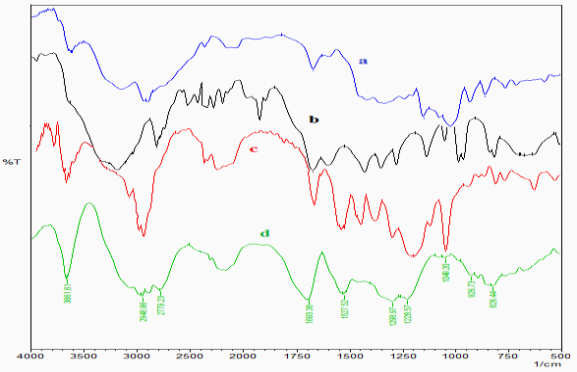

Figure 1: IR spectra of (a) starch (b) AM, (C) AMPS and (d) hydrogel

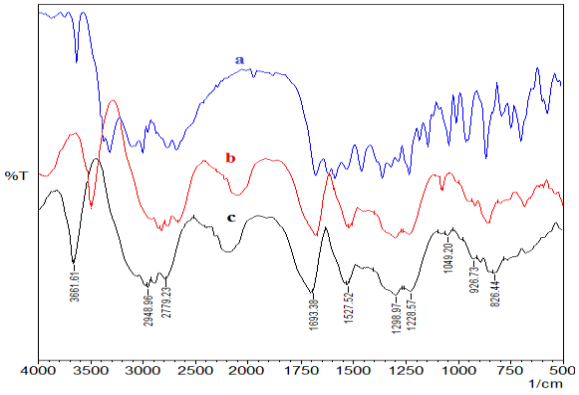

Figure 2: IR spectra of (a) TC, (b) drug composite and (c) Blank composite hydrogel Method validation

SEM study of hydrogel

The morphological surface of the hydrogel is found to be heterogeneous in nature having some pores as shown by SEM image of the hydrogel in Figure 3.

TGA study of hydrogel

The thermo gravimetric analysis (TGA) of hydrogel is depicted in fig 4. The thermogram shows that the hydrogel is thermally stable and the decomposition takes place in four steps. The first step of degradation due to dehydration is observed up to 237^{0}C with 13.178 % weight loss. Second step of degradation is observed from 237-366^{0}C with 31.17% weight loss and third step from 366-489^0 C with 16.782% weight loss due to degradation of functional groups of hydrogel. The final degradation of hydrogel is observed at 489-810^{0}C with 29.770% weight loss.

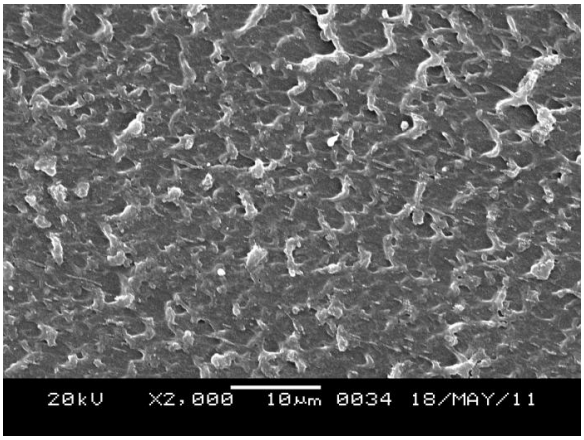

Figure 3: SEM image of hydrogel

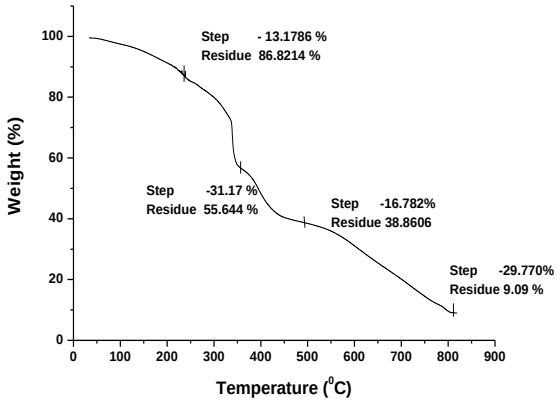

Figure 4: TGA of hydrogel

Swelling study

The equilibrium swelling ratio data of hydrogel presented in the table1 indicate that as the amount of AMPS-Na content in the matrix increased from 3.51 mM to 9.36 mM, the equilibrium swelling ratio initially increased from 17.35 to 26.55 and then decreased to 15.675, which is shown in fig 5. Similarly, when AM content increase from 7.03 to 21.1 mM the Swelling Ratio initially increased from 33.45 to 39.05 and then decreased to 21.66, shown in fig 6. The initial rise in equilibrium swelling ratio is due to greater hydration with higher hydrophilic content in the polymer chain, which occurs to a certain limits.

However, further rise in the concentration, formation of dense network structure take place, which prevents the water molecule penetration inside the network. This leads to decrease in the swelling ratio. The equilibrium swelling ratio decreases as the starch content in the matrix increased as shown in figure 7. The reduction of equilibrium swelling ratio from 38.225 to 26 were due to the formation of tight network structure in the high content of starch respectively, which hinders the mobility of the polymer chains and reduces water penetration into the gel.

Environmental pH value has large effect on the Swelling ratio especially for the hydrogel composed of ionic networks and containing large pendant groups [31] like these hydrogels. The swelling experiment is carried out a pH range of 2-9 by adjusting pH with NaOH and HCl solution.

The results in fig 8 indicate that the hydrogel is sensitive to pH and optimum swelling is observed around pH 7. At low pH pendant groups of the polymer ionizes and forms anionic centres along the polymeric chains. Thus, polymer – polymer interaction predominates over the polymer – water interactions. Again, at high pH ionization of sulfonic group and complete deprotonation of amine group take place. This results in formation of new cross linked segments by hydrogen bond. These electrostatic interactions between the functional groups make the macromolecular chain arrangement compact and less chain relaxation and ultimately result in low swelling.

Table 1: Composition of hydrogels, equilibrium swelling ratios at 30ºC and n values

Samples	AMPS-Na(mM)	AM(mM)	Starch(g)	MBA(mM)	Equilibrium Swelling Ratio	n
S1	3.51	14.06	0.5	0.12	17.35	0.5
S2	4.68	14.06	0.5	0.12	27.225	0.61
S3	5.85	14.06	0.5	0.12	26.98	0.62
S4	7.02	14.06	0.45	0.12	38.225	0.63
S5	9.36	14.06	0.5	0.12	15.675	0.61
S6	7.02	10.55	0.5	0.12	39.05	0.50
S7	7.02	17.6	0.5	0.12	25.25	0.73
S8	7.02	21.1	0.5	0.12	21.66	0.63
S9	7.02	14.06	0.5	0.12	26.55	0.62
S10	7.02	14.06	0.55	0.12	26	0.62

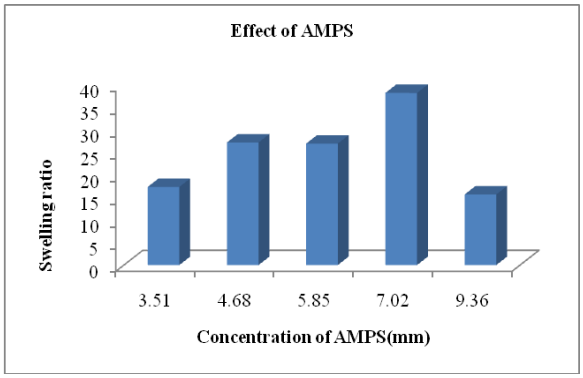

Figure 4: Effect of AMPS on swelling ratio

A remarkable change in the equilibrium swelling ratio is observed at different salts concentration. The reduction in equilibrium Swelling Ratio (Fig 8) from 0.01 M to 1.0 M KCl and $CaCl_2$ solution was due to decrease in the osmotic pressure. Since, there is a balance between the osmotic pressure and the polymer elasticity, which sets the physical dimensions of the hydrogels [32]. The osmotic pressure is results from a net difference in the concentration in the mobile ions between the interior of the gel and the solution. Addition of the ions to the outer medium probably reduces the osmotic pressure and this brings decrease in the swelling ratio at high salt concentration. However, comparatively lower values of Swelling Ratio in case of $CaCl_2$ than that of KCl is due to greater number of Cl^- ions in the swelling medium.

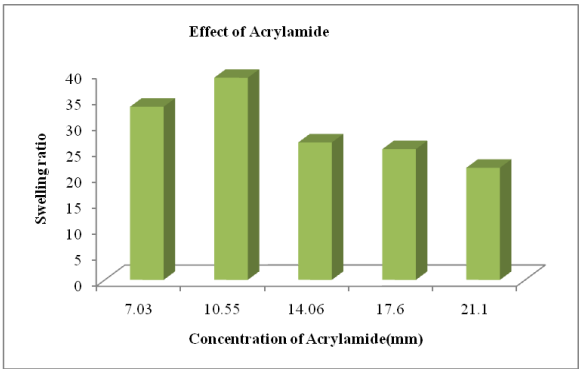

Figure 5: Effect of AM on swelling ratio

The water transport mechanism through the hydrogel was determined by several key factors such as the equilibrium water content, chemical architecture of the gel and relative rate of diffusion of water and relaxation of macromolecular chains [33]. Dynamic swelling data of all samples have been fitted to an empirical equation [34, 35] given below.

$$\frac{W_t}{W_\infty} = k t^n \quad \text{----------} \quad (3)$$

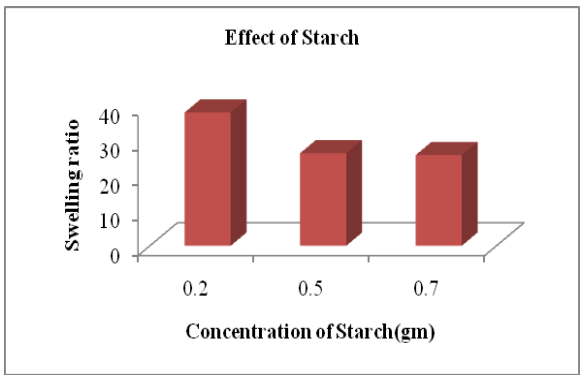

Figure 6: Effect of starch on swelling ratio

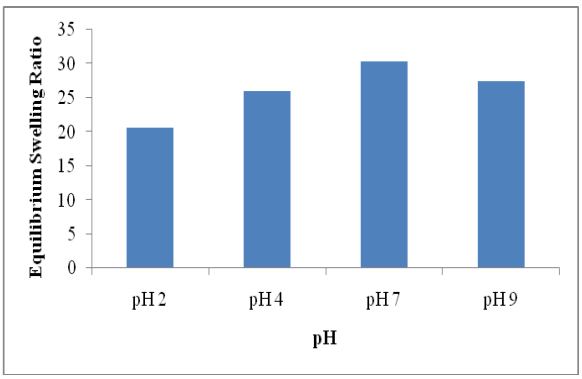

Figure 7: Effect of pH on equilibrium swelling ratio

Where n is the swelling exponent, k is the swelling rate front factor and W_t and W_∞ are the water intakes by the swollen hydrogel at time t and equilibrium time ∞ respectively. A double log plot drown between W_t/ W_∞ and time t provides the value of n, which determined the nature of the solvent diffusion process, that is Fickian (n= 0.5) or non-Fickian (n= 0.5 to 1.0) diffusion. The calculated n values of hydrogels are given in the table 1. It is observed that the swelling exponent (n) values shift from Fickian to non-Fickian when AMPS-Na and AM concentration of hydrogel increased due to the formation of compact arrangement of macromolecular chain, the relaxation rate slowed down and became identical to water diffusion rate. This obviously results in a non-Fickian type of water transport mechanism. Starch does not have any effect on water transport mechanism in the study range.

In vitro release studies

The release profile of different hydrogel formulation with varying amount of AMPS-Na, AM and starch in buffer of pH 7 at 30^0C as a function of time are given in fig 9. The influence of Na-AMPS on the % of cumulative release is investigated by varying AMPS-Na at a range from 3.51 mM to 9.36 mM in the feed mixture. It was observed that the % of cumulative release gradually decreased with increasing AMPS-Na concentration. The gradual decrease of % of cumulative release is due to the formation of compact network structure of macromolecular chain at high content of Na-AMPS, which led to decreased swelling and % of cumulative release.

The effect of AM on release profile is investigated and shown in figure10. The % of cumulative release increased with increasing concentration AM from 10.55 mM to 21.12 mM. This observation is due to the hydrophilic nature of AM. Increasing hydrophilic segments on polymer enhances greater hydration which obviously increased in the % of cumulative release.

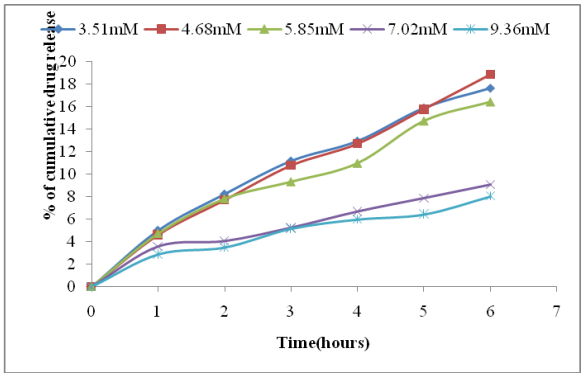

Figure 9: Effect of AMPS-Na on drug release

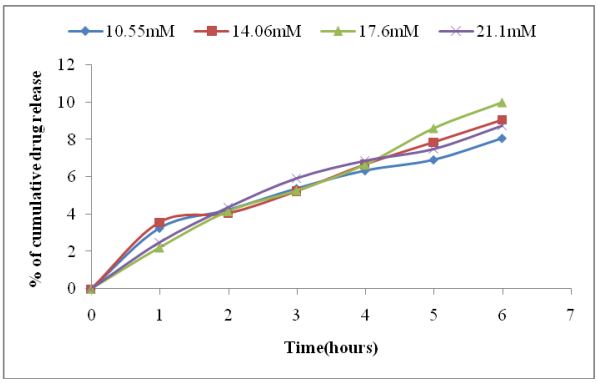

Figure 10: Effect of AM on drug release

The effect of starch on release profile is investigated and shown in fig11. The % of cumulative release increased with increasing concentration of starch from 0.45g to 0.55g. This observation is due to the hydrophilic nature of starch.

The release profiles of TC at different pH (2 to 9) are shown in fig 12. Compared to the release profile at pH 2, 4 and 9, TC is released more rapidly at pH 7. These results indicated that the TC release profile is pH sensitive. The optimum release at pH 7 is due to the optimum swelling of the hydrogel (fig.7) as the drug releases only after water molecule penetrate into polymer matrix.

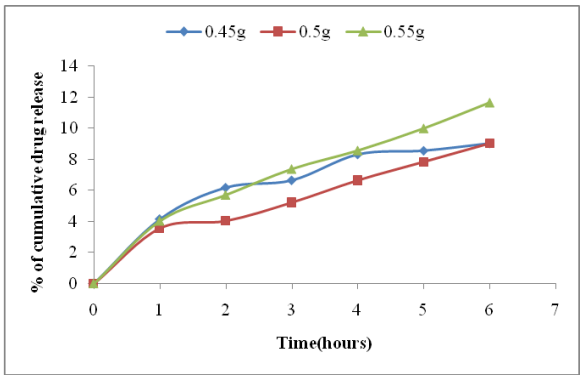

Figure 11: Effect of starch on drug release

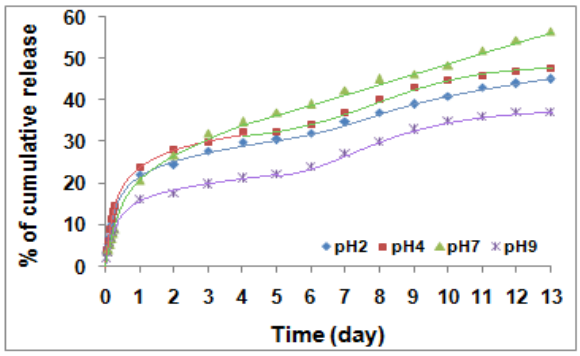

Figure 12: Effect of pH on % of cumulative release

Conclusion

In this work we have synthesized starch containing hydrogel by free radical polymerization using MBA as a cross linking agent, characterized and studied the swelling and tetracycline release profile at different conditions. FT-IR analysis reveals that the activity of drug does not change inside the cross linking structure of the polymer. FT-IR analysis also shows that existence of drug inside the hydrogel is only physical in nature and it is believed that the activity of drug does not change The Swelling study shows that the water uptake property of the hydrogel is dependent on composition of polymer, pH and ionic concentration of the medium. The results of in-vitro drug release experiments shows that all the hydrogel has sustained release properties and the release rate depends on the equilibrium swelling ratio of the hydrogels and the pH value of the medium. The diffusion exponent calculated from empirical equation indicated that the water transport mechanism for all hydrogels followed non-Fickian nature of diffusion. It is believed that this hydrogel could be potentially used for localized drug delivery system.

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