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Carboxymethyl cellulose (CMC) based semi-IPNs as carriers for controlled release of ciprofloxacine: an in-vitro dynamic study

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Abstract Semi-interpenetrating polymer networks (IPNs) of carboxymethyl cellulose (CMC) and polyacrylic acid were prepared and its potential for controlled release of ciprofloxacine (Cfx) was assessed. The IPNs were characterized by IR spectral analysis and Environmental scanning electron microscopy (ESEM). The entrapped drug was examined for its antibacterial activity and chemical stability. The effects of experimental parameters such as varying chemical composition of the IPNs, percent loading of Cfx, pH and temperature of release medium and presence of salt ions in outer solution were examined on the release profile of the drug. On the basis of Fick's power law equations, the diffusion exponents (n) and diffusion constant (D) were evaluated for different IPNs compositions. From the kinetic parameter data, an attempt was made to resolve the mechanism of the release process of Cfx.

Introduction

Hydrogels are of special interest in controlled drug delivery applications. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body [1]. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability [2]. A controlled drug delivery is delivery of drug at a rate or at a location determined by needs of body or disease spread over a specified period of time. Ideally two main objectives exist for these systems. These are spatial delivery which is related to control over the location of drug release and temporal drug delivery in which drug is delivered over an extended time period during treatment.

Ciprofloxacine hydrochloride (Cfx), also called 1-cyclopropyl-6-fluoro-1,4 dihydro-4-oxo 7-(1-piperazinyl)-3-quinoline carboxylic acid hydrochloride monohydrate, has been used in clinical medicine to kill green pus bacillus, large intestine bacillus, strain coccus, streptococcus and gold grape coccus that can result in some type of infection such as respiration, urethra alimentary canal, etc. [3]. Ciprofloxacine is a leader among the third generation fluoroquinolones with a broad spectrum of antibacterial activity and good penetration in most tissues [4–6]. Fluoroquinolones such as Cfx are considered to be an appropriate choice for the prevention and treatment in infections in bone and soft tissues [7, 8]. A local delivery system containing Cfx is of great interest for this purpose and several previous studies have been carried out to characterize Cfx delivery from different carriers [9, 10].

There is a considerable interest in developing controlled drug delivery systems using natural polymers due to their non-toxicity, biodegradability and biocompatibility [11]. One of such naturally occurring polymers is cellulose, which is one of the richest and environment friendly materials because of its non-toxic, biodegradable, biocompatible, hydrophilic, chiral and semi-rigid nature [12]. A modified form of cellulose is carboxymethyl cellulose (CMC), which represents the most important ionic cellulose ether and has found ample scientific attention, especially due to its character as a polyelectrolyte. Polyacrylic acid is a hydrophilic polymer with a carboxylic acid content between 56% and 68% (w/w) having diverse applications in biomedical science [13]. Thus, being motivated by the vital

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role of cellulosic polymers in pharmaceutical fields, the present communication aims at studying in-vitro controlled drug delivery of Cfx from a semi-IPNs composed of carboxymethyl cellulose (CMC) and crosslinked polyacrylic acid which because of ionic nature of constituent chains could prove a pH-sensitive drug carrier.

Experimental

Materials

Sodium salt of carboxymethyl cellulose (CMC) (Molecular wt. 90,000, viscosity of 4% solution at 25 °C is 10.5 cps) was purchased from Sigma Aldrich Co., USA and used without any pretreatment. Acrylic acid was purchased from Research Lab, Mumbai, INDIA and freed from the inhibitor by vacuum distillation. N,N′-methylene bis acrylamide (MBA) (Central Drug House, Mumbai, INDIA) was employed as a crosslinking agent and used as received. Potassium persulphate (KPS) was obtained from Wilson Laboratories, Mumbai, INDIA and used as a polymerization initiator. Ciprofloxacine tablets (Ahlcon Parenterals Ltd., Bhiwadi, INDIA) were purchased from local market.

All other chemicals used were of analytical grade and bidistilled water was used throughout the experiment.

Preparation of IPNs

The semi-IPNs were prepared by a free radical polymerization method as described in our earlier communications [14]. In a typical experiment, 1.5 g of CMC was dispersed into 20 ml of distilled water with constant stirring for 2 h and to this suspension was added 14.5 mM of acrylic acid, 0.129 mM of MBA and 0.73 mM of KPS. The homogenised mixture was transferred into a petridish (diam. 7.0 cm, Corning glass) and kept at 50 °C for 24 h so that the whole mass solidified into a thin semitransparent film. The IPNs so prepared were equilibrated with distilled water for 72 h so that the unreacted monomer and chemicals were leached out. The fully swollen IPNs were cut into smaller discs (diam. 0.4 cm), dried at room temperature for a week and stored in airtight polyethylene bags.

Loading of drug

Loading of drug onto a carrier is normally performed by two general methods. In one method, the drug is mixed with the hydrogel monomer, an initiator with or without crosslinking agent and allowed to polymerize entrapping the drug within the matrix. In the second approach, the gel is allowed to swell in the drug solution till equilibrium and then dried to obtain the release device. The latter method has some advantages over the first method as polymerization conditions may have deleterious effects on drug properties and difficulties in device purification after loading the polymerization often remains.

In the present work, the latter method of loading was followed which involved swelling of preweighed pieces of IPNs into the Cfx solution of known concentration and then taking out and drying them at room temperature for a weak. The following equation was used to calculate the percent loading:

$$\text{Percent loading} = \frac{W_d - W_o}{W_o} \times 100 \quad (1)$$

where, W_d and W_o are the dry weights of Cfx- loaded and unloaded hydrogel discs, respectively. It is worth mentioning here that no leaching of polyacrylic acid was detected in the outer drug solution which clearly suggest for hydrolytic stability of the prepared polymer matrix.

Release experiments

Absorbance of Cfx solutions of different concentrations viz. 0.01, 0.02, 0.03–0.1 was read at 273 nm by UV-Vis double beam spectrophotometer (Systronics-2201,Ahamadabad, Gujarat, India). A calibration curve of absorbance vs. concentration was drawn, which obey Beer-Lambert's low.

The dried and loaded IPNs were placed in a fixed volume (5 ml) of phosphate buffer solution (PBS) as a release medium. The IPNs were repeatedly removed and transferred into fresh PBS at predetermined time intervals. PBS is used as reference and the amount of released Cfx was assayed by UV-Vis double beam spectrophotometer for 3 h. In order to have mechanistic insights into the drug transport processes the kinetic data of the swelling process were fitted into various equations which are basically derived from the Ficks law. The first equation is the Ficks power law equation [15],

$$\frac{W_t}{W_\infty} = Kt^n \quad (2)$$

where k is a constant incorporating structural and geometric characteristics of the device, n is diffusional exponent and W_t and W_∞ are the amounts of drug released at time t and equilibrium time, respectively. For $n > 0.5$, non-Fickian diffusion is observed, while $n = 0.5$ represents a Fickian diffusion mechanism. The value of $n = 1$ provides Case II transport mechanism in which drug releasing from hydrogel of slab geometry will be of zero order. It is notable here that Eq. (2) is based on the assumption that

release occurs as soon as the matrix is placed in contact with the fluid.

For calculating diffusion constant of the drug, the following Fickian diffusion equation can be used,

$$\frac{W_t}{W_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left\{\frac{-D(2n+1)^2\pi^2}{l^2}\right\} \quad (3)$$

The above equation is further simplified to the following early-time approximation,

$$\frac{W_t}{W_\infty} = 4\left[\frac{Dt}{\pi l^2}\right]^{0.5} \quad (4)$$

where D is the diffusion constant of the drug ($cm^2\ S^{-1}$) and l is thickness of the dry and drug-loaded IPN slab. Equation (4) clearly implies that from the early-time slope of the plot drawn between W_t/W_∞ and $(t)^{0.5}$, the value of D can easily be calculated for any fractional release vs. $(time)^{0.5}$ curve. The diffusion behavior of various drug releasing systems has been largely investigated and cited in literature [16].

Characterization of IPNs

The IPNs prepared as above were characterized by techniques such as FTIR and ESEM as discussed below:

FTIR spectra

The structural characterization of unloaded and Cfx loaded IPNs were performed by recording transmittance FTIR spectra on a Parkin Elmer spectrophotometer (Paragon 1000, FTIR).

Environmental scanning electron microscopy

Morphological features of Cfx loaded and unloaded IPNs were examined by using an Environmental Scanning Electron Microscope (Philips 515).

Drug activity

In order to demonstrate that the biological and chemical activities of the entrapped Cfx are not lost during the device preparation, the following two tests were performed.

(i)Antibacterial activity

Antibacterial activity of the loaded IPNs has been demonstrated by disk-diffusion (Kirby–Bauer) method. The standardization disk diffusion procedure of Bauer et al. [17] has been widely accepted for testing bacterial susceptibility to antimicrobial agents. Several minor modifications have been introduced by the National committee for Clinical Laboratory Standards (NCCLS) in an effort to maintain current and updated standards [18]

(ii) UV-spectral study

Structural stability of entrapped Cfx drug was investigated by a UV-spectral study.

Results and discussion

Characterization of network

FTIR spectra

The FTIR spectra of hydrogel and Cfx loaded hydrogels are depicted in Fig. 1 as (a) and (b), respectively.

The spectra of both the unloaded (a) and the Cfx loaded carriers (b) show a broad band around 3,500 cm^{-1} which is typical of hydrogen bonded O–H stretch of CMC and polyacrylic acid and bonded water in hydrogel matrices. The observed band also implies for N–H stretching due to the MBA (crosslinker). The same band shows N–H stretching of piperzine moiety in Cfx. The methylene groups of polyacrylic acid and cyclopropane of cfx are quite evident at 2,971 cm^{-1}. In the spectra (a) two prominent peaks at 1,653 and 1,391 cm^{-1} are observed from the asymmetrical and symmetrical stretching of COO^- groups of CMC while the peaks at 1,683 and 1,362 in spectra (b) also appear for the stretching vibrations of carboxylate ion in Cfx. A sharp band in the spectra (a) appears at 2366 cm^{-1} due to sodium salt of CMC while this band shifted at lower wave number, i.e. at 2207 cm^{-1} in the spectra (b) that may be due to interaction of cfx with hydrogel.

In the spectra (b), a sharp peak appears at 1830 cm^{-1} for C = O stretching of Cfx conjugated with double bonds. A

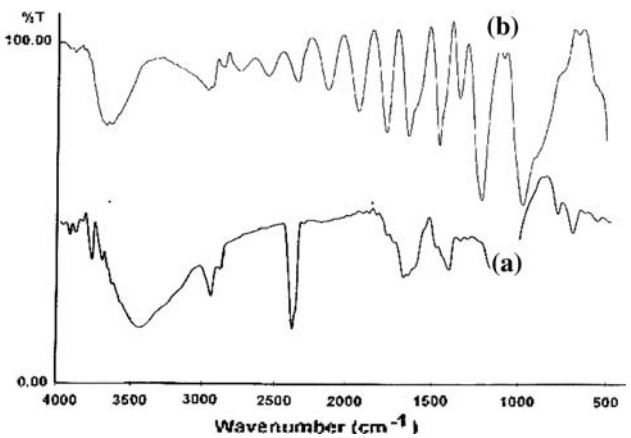

Fig. 1 IR spectra of unloaded (**a**) and cfx loaded (**b**) IPNs

medium peak at 1489 cm^{-1} appears due to stretching vibration of C–C and C–N bond in the quinolone ring [19]. A sharp peak at 1210 cm^{-1} appears due to C–O of COOH. The spectrum (b) also shows a band at 950 due to C–F stretching in Cfx. In spectra (b) several uncommon but minor peaks also appear which could be due to the overtones, however, the absorption band at 2750 cm^{-1} may be due to the presence of C–CH_3 group.

Environmental scanning electron microscopy

In order to gain insights into the morphology of the prepared hydrogels the scanning electron micrograph (ESEM) images of the unloaded and Cfx loaded semi-IPNs were recorded as shown in Fig. 2(a, b), respectively. Fig. 2(a) clearly indicates that the surface of the gel is slightly heterogeneous, and has long cavities with average dimensions of 344 μm × 206 μm. Moreover, on the surfaces of the gel some unevenly scattered needle shaped crystallites of PAA are also present. The crystalline nature of gel is further confirmed by DSC studies as discussed in the previous para. The image also depicts rope like structures on the surface, which could be assigned to the aggregated fibrous bundles of CMC.

The ESEM image (b) of Cfx loaded gel is very much different from the unloaded image (b). It is clear from the image (b) that the surface of the loaded gel becomes more heterogeneous and contains minor pits varying in dimension of 50–100 μm. Moreover, a significant change is that the needle shaped crystallites of PAA get almost disappeared in the loaded gel. The obtained micrograph clearly indicates for strong drug-polymer interactions, which eventually result in almost, complete loss of crystallites. The inclusion of charged drug molecules in the hydrogel may cause interactions with the charged centers of PAA and CMC, thus enhancing heterogeneity on the loaded gel's surface.

Drug activity

(i) Antibacterial activity

Antibacterial activity of Cfx has been demonstrated in Fig. 3, which exhibits a clear zone around loaded IPNs disk where the growth has been inhibited. This zone is known as zone of inhibition. Cfx inhibits both Topoisomerase II (DNA gyrase) and Topoisomerase IV. Cipro inhibits the formation of Topoisomerase II, which allows the replication of the bacterial DNA by unwinding the double helix and prevention of supercoiling. Topoisomerase IV equally splits up the chromosomal ring of DNA to new daughter cells. These inhibitions results stop of replication and death of the bacterial cell [20–21]. Formation of zone of inhibition shows that Cfx can easily diffuse into the agar media from loaded IPNs and its antibacterial activity remain unchanged after loading into the IPNs. It was also noticed that no inhibition zone was formed with unloaded IPNs, which also favors antibacterial activity of Cfx.

(ii) UV spectral study

The UV spectra of pure Cfx in solution and released Cfx in the released medium were scanned by UV-Vis double beam spectrophotometer (systronics-2201) in the range 220–330 nm as shown in Fig. 4. The two spectra clearly show that there is almost no change in the absorption pattern of the spectra, thus clearly indicating that the chemical activity of the drug is also retained during the loaded and drying processes.

Effect of percent loading on released Cfx

Analysis of drug release behavior requires an understanding of the factors influencing the drug loading into each sample. As the drug concentration is an important factor in the observed release rates, the incorporation efficiency of the IPNs was evaluated for three different loadings of Cfx in the IPNs. Three drug loadings of 2, 4 and 6% were

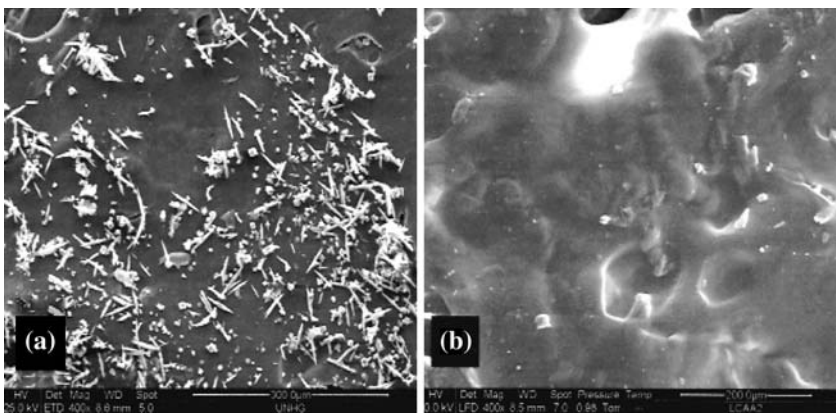

Fig. 2 Scanning electron micrograph of unloaded (**a**) and cfx loaded (**b**) IPNs

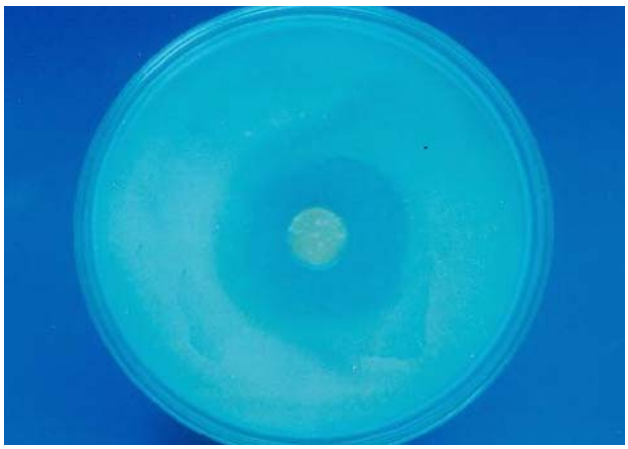

Fig. 3 Photograph depicting the evidence of antibacterial activity of released cfx

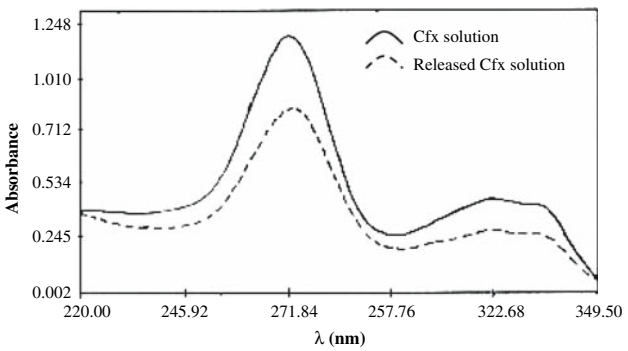

Fig. 4 UV spectra of pure Cfx in solution and released Cfx in released medium

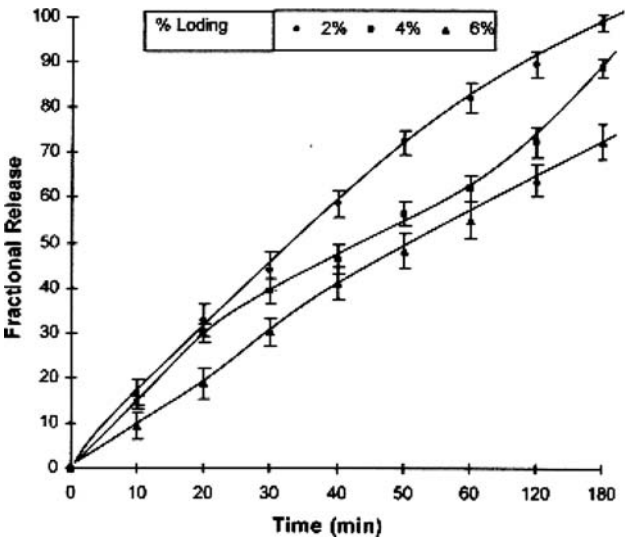

Fig. 5 Effect of percent loading of cfx on its release through an IPNs of [CMC] = 1.5 g, [Acrylic acid] = 14.5 mM, [MBA] = 0.129 mM, [KPS] = 0.073 mM, Temp. = 23 ± 0.2 °C

investigated in this study and the results are depicted in Fig. 5, which shows a decrease with increase in percent loading.

The observed decrease in the release rate with increasing percent loading may be attributed to the fact that with increasing percent loading the pore size of IPNs become smaller due to accumulation of drug molecule within the IPNs and this restrains the diffusion of release medium into the loaded IPNs. This obviously results in a lower release of Cfx.

Another factor of concern is the potential interaction between polymer and drug, which could affect drug diffusion through the matrix due to attraction or repulsion forces. Recently, it has been demonstrated that release of acetyl-salicylic acid was slower from carboxylated cross-linked high amylose starch when the drug loading increased [22] which was attributed to the physical interaction between carboxylic groups of the polymer. In the present study also, a similar type of interaction between Cfx and IPNs may not be ruled out.

Effect of CMC

It is an established fact [23] that the drug-polymer ratio is one of the important factors that significantly influence the release of a drug from polymer matrices. Thus, it can be said that the drug release profiles are sensitive to chemical architecture of the carrier. In the present study too, the morphology of semi-IPN is greatly dependent upon the concentration of CMC.

The effect of CMC on the release of Cfx has been investigated by varying its concentration in the range 1–2.5 g in the feed mixture of the IPNs and observing the maximum fractional release of the drug by determining the amount of released Cfx after 24 h. As the pore sizes of the matrix could affect the release rate of the drug, in place of release rate the maximum fractional release was determined for each composition of the gel. The results are depicted in Table 1 which indicate that the release of Cfx increases up to 1.5 g of CMC while beyond it a fall in the released amount is observed. The above results can be explained on the basis of the increase in polyelectrolyte nature of the CMC molecule and, therefore, a greater force of repulsion operates within the hydrogel network. This obviously produces a faster relaxation in the macromolecular chains and causes a greater release of Cfx into the release medium. However, beyond 1.5 g concentration of CMC, the observed decrease in released amount of Cfx may be attributed to a greater charge density of the network which permits less number of H_2O molecules into the gel, thus bringing about a fall in the released amount of Cfx.

Table 1 Data showing variation in maximum fractional Release with different compositions

CMC (g)	AA (mM)	KPS (mM)	MBA (mM)	Maximum%Fractional release[a]
1	14.5	0.073	0.129	79.3 ± 2.12
1.5	14.5	0.073	0.129	98.6 ± 4.08
2.0	14.5	0.073	0.129	74.1 ± 1.88
2.5	14.5	0.073	0.129	70.9 ± 2.46
1.5	7.3	0.073	0.129	80.4 ± 3.86
1.5	14.5	0.073	0.129	98.6 ± 4.22
1.5	21.6	0.073	0.129	73.7 ± 2.24
1.5	36.4	0.073	0.129	66.1 ± 1.12
1.5	14.5	0.073	0.129	98.6 ± 3.83
1.5	14.5	0.110	0.129	68.6 ± 2.02
1.5	14.5	0.147	0.129	64.5 ± 1.98
1.5	14.5	0.184	0.129	61.2 ± 1.29
1.5	14.5	0.073	0.064	74.1 ± 3.97
1.5	14.5	0.073	0.129	98.6 ± 4.19
1.5	14.5	0.073	0.194	83.7 ± 3.33
1.5	14.5	0.073	0.259	76.4 ± 3.26

[a] The values represent mean ± S.D.of at least four independent determinations

Effect of AA

The swelling ratio (Q) of a hydrogel can be best quantified by the following Flory's equation [24]:

$$Q^{5/3} = [i/2V_uS^{1/2} + (1/2 - X_1)/V_1] \Big/ (V_e/V_o) \qquad (5)$$

where i/V_u is the concentration of fixed charges referred to the unswollen IPNs, S the ionic concentration in the external solution, $(½ - x_1)/V_1$ the affinity of the hydrogel with water; and (V_e/V_o), the crosslinked density of the hydrogel. Thus, Q is a function of the ionic osmotic pressure, crosslinked density and affinity of the hydrogel with water.In the present study, the effect of ionic monomer on the release of Cfx has been investigated by varying the concentration in the range 7.3–36.4 mM in the feed mixture of the IPNs. The results are displayed in Table 1, which indicate that release of Cfx increases from 7.3 mM to 14.5 mM of AA while a constant fall is observed beyond 14.5 mM.

The results may be attributed to the reason that with increasing acrylic acid concentration in the IPNs, the magnitude of fixed charges, i.e. i/V_u increases within the gel and as predicted from the above equation, the swelling ratio increases which consequently increases the released amount of Cfx. It can be also explaine by the fact that with increasing number of carboxylate ion (COO^-) along the crosslinked polyacrylic acid chains, the electrostatic repulsion among the COO^- group becomes operative and result in a loosening of the network chains and enhance sorption, and as well as release.

However, beyond 14.5 mM concentration of AA, the number of polyacrylic acid chains becomes so great that the IPNs becomes densely packed resulting in a reduction in mesh size of the network. This obviously lowers the diffusion of solvent molecule into the IPNs and thus decreases water sorption, which leads to a low release of the entrapped drug.

Effect of crosslinker

One of the most effective ways of modifying both water imbibing capacity and release characteristics of hydrogels is to bring about a change in the crosslink density of the network by employing varying amounts of crosslinker in the feed mixture of the hydrogel [25]. In the present investigation, it has been achieved by employing varying concentration of the MBA in the feed mixture in the range 0.064–0.259 mM. The results are shown in Table 1, which clearly reveal that the release rate of Cfx increases with increasing concentration of MBA from 0.064 mM to 0.128 mM while beyond 0.128 mM a significant fall is noticed.

The observed results may be explained by the fact that with increasing MBA, the hydrophilicity of the network slightly increases which as a result enhances both water sorption and subsequently the release rate. The observed fall in the release rate beyond 0.128 mM of MBA may be explained due to the reason that with increasing MBA content in the IPNs the crosslink density of the IPNs increases which results in narrow mesh sizes of the network. This obviously slows down the solvent (water) diffusion and subsequent relaxation rate of gel and consequently the release of Cfx molecule decrease.

Effect of initiator

In free radical polymerization, the concentration of initiator has a direct impact on the molecular weight of polymer [26]. In the present study, potassium persulphate has been used as polymerization initiator and its concentration has been varied in the range 0.073–0.180 mM in the feed mixture of the IPNs. The results are displayed in Table 1, which clearly indicates that the released amount of Cfx constantly decreases with increasing concentration of (KPS) initiators. The results are explained by the fact that the increased initiator concentration results in a lower molecular weight of the polymer, which, in turn, produces network of small mesh sizes. In other words, free volumes will have low swelling ratio and this consequently lowers the release of Cfx.

Effect of pH on released Cfx

In the present investigation, the release dynamics of Cfx has been studied by varying the pH of the release medium in the range 1.5–9.0 as found in GI tract (e.g. stomach, gastric juice 1–2, and small intestines 7.5–8.6). The wide range of pH allows a specific drug to be delivered to a targeted site only. For example, the pH in the stomach (<3) is quite different and could be used to prevent release of foul testing drug in the neutral pH environment of the mouth while using polycationic hydrogels as drug carrier [27]. Similarly, a polyanionic hydrogel which shows a minimal swelling at acidic pH (such as stomach) could be of potential use to deliver drug to the intestinal tract due to increase in pH leading to ionization of the carboxylic group.

In the present study the release profile of Cfx are shown in Fig. 6, which indicate that the release rate increases with increasing pH of the medium in the range 1.5–7.4 while beyond 7.4, a fall is observed.

The results can be explained by the fact that when pH of the release medium rises, the number of carboxylate ions (COO^-) also rises and thus, as a result, H-bonds are broken, thereby relaxing the network chains. This obviously leads to a faster diffusion of water molecules into the network and the release of Cfx increases. It is also likely that because of the repulsion operating between the carboxylate anionic groups, the network chains get relaxed and release of Cfx increases. When the pH exceeds 7.4, the number of carboxylate anions reaches at maximum and produce greater repulsion within the IPNs matrix. This obviously results in much greater relaxation of macromolecular chains of the IPNs, which causes expulsion of water molecules from within the IPNs into the release medium due to weakening of H-bonds established between water molecules and IPNs chains.

Effect of temperature on released Cfx

The influence of temperature on the release of drug from a hydrogel is of much significant because it directly controls the diffusion of water molecules into the gel, segmental mobility of the network chains and water polymer interaction. In the present study, the effect of temperature of release medium has been investigated by varying the temperature in the range 5–35 °C and the results are depicted in the Fig. 7. The observed results can be explained by the fact that on increasing temperature, the segmental mobility and diffusion of water molecules increase and this obviously favors a rapid swelling of hydrogel which results in a greater release.

Effect of salts on released Cfx

The influence of the presence of salts in the swelling medium of a hydrogel is of importance in agriculture and biomedical application, viz. water reservoir in agriculture and hydrogels as implants for drug release applications [28]. In principle, changes in swelling behavior due to the presence of salt can affect the mechanical properties of the material [29] as well as the torturity of the matrix which gives rise to different diffusion coefficient of drug release [30]. Hydrophilic polymers can be categorized into two types with regard to their behavior in salt solution (a) undissociable polymers in water, and (b) dissociated polymers in water. Considering polymers of type (a) the presence of salt ion may enhance polymer/water mixing conditions (salting–in) or may impair them (salting–out). Partial effects such as electrostatic ones, water structuring due to micro-solutes (salt can be structure makers), association of the hydrophilic sites of the macromolecule and formation of the complexes between polymers and ion contributes to the overall effect. Polymers of type b (i.e. acid derivatives) exhibit the so-called polyelectrolyte behaviors characterized by a marked deswelling in salt solution [31].

Effect of anions

In the present study, chloride, sulphate and phosphate salts of potassium have been added into the release medium and their effects on swelling ratio have been noticed. The results are shown in Fig. 8 and which clearly indicate that the release of Cfx increases with increasing ionic concentration and the added anion obey the following order of Cfx release.

$$Cl^- < SO_4^{2-} < PO_4^{3-}$$

The observed results can be explained by the fact that anions are adsorbed onto the polymer molecules, thus,

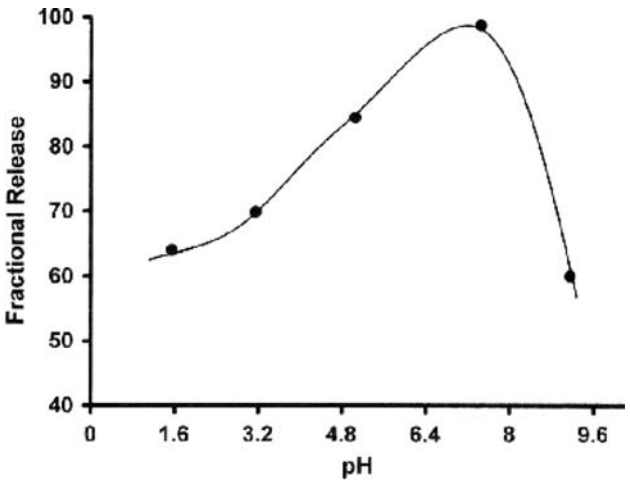

Fig. 6 Effect of pH of the release medium on the release of cfx through the IPNs of fixed composition [CMC] = 1.5 g, [Acrylic acid] = 14.5 mM, [MBA] = 0.129 mM, [KPS] = 0.073 mM, Temp. = 23 ± 0.2 °C

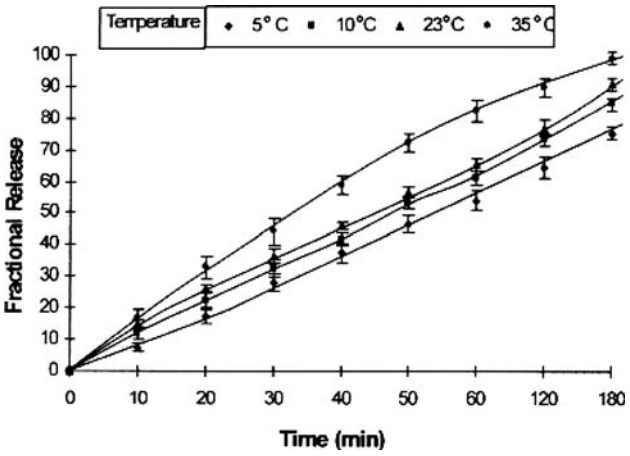

Fig. 7 Effect of temperature of the release medium on the release of cfx through the IPNs of fixed composition [CMC] = 1.5 g, [Acrylic acid] = 14.5 mM, [MBA] = 0.129 mM, [KPS] = 0.073 mM, Temp. = 23 ± 0.2 °C

charging them negatively producing repulsion between like-charges resulting in chain expansion and subsequent increase in water uptake. The further effect of this partial negative charge of the polymer are (i) reduction of hydrophobic character of the polymer chains, (ii) reduction of the association of hydrophobic groups, and (iii) electrostatic attraction of cations and their hydration layers. The overall effect is, therefore, an increase in swelling which also increases the Cfx release.

Effect of cations

For investigating the influence of cations on the release of cfx, chlorides of K^+, Ca^{2+} and Al^{3+} were added in the

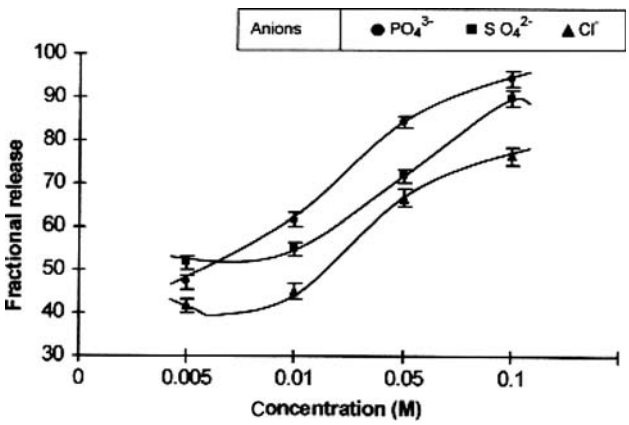

Fig. 8 Effect of addition of anions of potassium on the release of cfx through the IPNs of fixed composition [CMC] = 1.5 g, [Acrylic acid] = 14.5 mM, [MBA] = 0.129 mM, [KPS] = 0.073 mM, Temp. = 23 ± 0.2 °C

concentration range 0.005–0.1 M and observed findings are shown in Fig. 9, which clearly indicate that the release of Cfx increases with increase in salt concentration and the added cations obey the following order of increasing Cfx release

$$Al^{3+} < Ca^{2+} < K^+$$

The results may be explained by the fact that the added ions diffuse into the interior of the IPNs and may increase the ionic concentration, thus, resulting in an increase of Cfx release. The order of effectiveness of the added cations in affecting Cfx release may be explained by the fact that positively charged cations get attracted to COO^- ions and decrease the number of COO^- ions in IPNs. These results a decrease in inter-ionic repulsion and hence network expansion also.

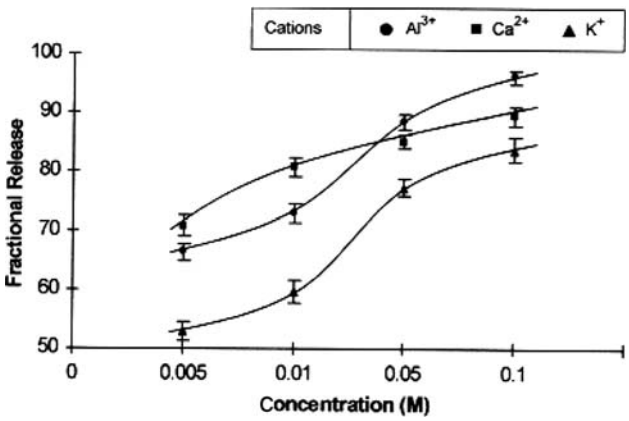

Fig. 9 Effect of addition of cations of chloride on the release of cfx through the IPNs of fixed composition [CMC] = 1.5 g, [Acrylic acid] = 14.5 mM, [MBA] = 0.129 mM, [KPS] = 0.073 mM, Temp. = 23 ± 0.2 °C

Table 2 Data showing the variation of diffusional (release) exponents and diffusion constant with varying composition and temperature

CMC (g)	AA (mM)	KPS (mM)	MBA (mM)	Temp. (°C)	D ($\times 10^6$)	n	Release Mechanism
1	14.5	0.073	0.129	35	3.71	0.72	Anomalous
1.5	14.5	0.073	0.129	35	3.44	1	Case II
2.0	14.5	0.073	0.129	35	3.28	0.74	Anomalous
2.5	14.5	0.073	0.129	35	2.46	0.85	Anomalous
1.5	7.3	0.073	0.129	35	3.97	0.54	Anomalous
1.5	14.5	0.073	0.129	35	3.44	1	Case II
1.5	21.6	0.073	0.129	35	3.71	0.75	Anomalous
1.5	36.4	0.073	0.129	35	0.53	1	Case II
1.5	14.5	0.073	0.129	35	3.44	1	Case II
1.5	14.5	0.110	0.129	35	3.82	0.72	Anomalous
1.5	14.5	0.147	0.129	35	2.97	.87	Anomalous
1.5	14.5	0.184	0.129	35	2.65	0.86	Anomalous
1.5	14.5	0.073	0.064	35	2.44	0.86	Anomalous
1.5	14.5	0.073	0.129	35	3.44	1	Case II
1.5	14.5	0.073	0.194	35	3.60	0.63	Anomalous
1.5	14.5	0.073	0.259	35	3.82	0.54	Anomalous
1.5	14.5	0.073	0.129	5	2.82	1.2	Super Case II
1.5	14.5	0.073	0.129	10	4.08	0.71	Anomalous
1.5	14.5	0.073	0.129	23	7.21	0.73	Anomalous
1.5	14.5	0.073	0.129	35	3.44	1	Case II

Analysis of kinetic release data

Release of a water-soluble drug entrapped in a hydrogel occurs only after water penetrates the network to swell the polymer and dissolves the drug followed by its diffusion along aqueous pathway to the surface of the device. In the present study the release data have been treated with equations (2) and (4) and the evaluated kinetic constants such as diffusion constant D and diffusional exponent n have been shown in Table 2 may be analyzed to provide some information about the mechanism of the release process as explained below.

It is clear from the Table that for IPNs compositions prepared at varying concentrations of CMC, AA, MBA and KPS, the value of 'n' fluctuates between 0.5 and 1, thus, suggesting an anomalous type of release that is characterized by almost equal rates of solvent diffusion and chain relaxation (R_{diff}–R_{relax}). However, for control set (1.5 g CMC, 14.5 mM AA, 0.129 mM MBA, 0.073 mM KPS) the value of n becomes almost unity, thus, indicating a case II (zero order release) transport process, the most desirable condition in pharmacokinetics. (Table 2).

Conclusions

Interpenetrating polymer networks (IPNs) of CMC and crosslinked polyacrylic acid from highly hydrophilic, ionizable and pH sensitive matrices, which show potential to act as a vehicle for the controlled delivery of Cfx. It is observed that the release of cfx decreases with increasing percent loading of the drug onto the IPNs. The release profile of Cfx is greatly influenced by the chemical architecture of the IPN.

The prepared IPNs shows pH dependence of Cfx release and exhibits an enhanced release with increasing temperature. The release profiles are also greatly influenced by salt ion concentrations.

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