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Molecular Imprinted Polymers for use as Drug Delivery Devices: Preliminary Evaluation

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In view of technological significance of molecular imprinting polymers in drug delivery, the present study is an attempt to synthesize 2-hydroxyethylmetacrylate (HEMA) and acrylic acid (AAc) based hydrogels imprinted with model drug glucose. Both molecular imprinted polymers (MIPs) and non-imprinted polymers (NIPs) have been synthesized and have been used to study their binding affinity, swelling and *in vitro* release dynamics of the drug. It has been observed from this study that the template formed in MIPs has increased the absorption percentage of the drug and has improved the release profile of the drug from these polymers.

Keywords: drug delivery devices; hydrogels; molecular imprinted polymers; release dynamics; swelling kinetics

1. Introduction

Recently, there has been rapid growth in the area of drug discovery, facilitated by novel technologies, which has resulted in a more urgent focus on developing novel techniques to deliver these drugs more effectively and efficiently. In conventional drug administration, drug concentration in blood increases immediately after the drug is taken, and then declines with time. Sustained release dosage forms extend the duration time of drug therapy, reduce side-effects and increase safety and patient compliance by reducing the frequency of dosing. An optimum plasma drug concentration is required for its therapeutic response, above which it is toxic and below which it is ineffective. Self-regulated release from the delivery vehicle may enhance drug potency with a sustained action (1, 2). Hydrogels are frequently chosen as a material to allow controlled delivery of drugs (3, 4). There is an ongoing interest to identify additional tools to modify the release profile of a drug from a polymer matrix, and molecular imprinting has been suggested as one of those tools. The applications of polymer gels have been reported in the areas of controlled release and various systems have been designed for intelligent modulated delivery (5, 6). Recently, researchers have applied the molecular recognition properties of imprinted polymers to enhance control in the release of pharmaceutical compounds. Peppas and coworkers have utilized the technique of molecular imprinting in the controlled delivery of proteins. The ability of imprinted polymers to bind a template molecule with high affinity lends to their application as excipients for sustained drug delivery (7). The molecular imprinted polymers have been exploited for the controlled release of template molecule such as propanolol (8), tetracycline (9), sulfasalazine (10), pyrazinamide (11), Ibuprofen (12) and theophylline by the various researchers.

The molecularly imprinted polymer is prepared by mixing the template molecule with functional monomers, crosslinking agents and radical initiator in a proper solvent. After polymerization, the template is removed, leaving well-defined three-dimensional cavities possessing size, shape and functional group orientation, which are complementary to the target molecule. The free-radical polymerization mechanism is mostly used in these systems with several advantages (13). Beside the use of MIPs in the drug delivery systems, these have also been applied in a wide range of other technologically important applications such as in catalysis (14), separation and purification (15, 16) and in developing biomimic sensors (17) because of their stability, predesigned selectivity and easy preparation.

Keeping in view the technological significance of molecular imprinting polymers in drug delivery, the present study is an attempt to synthesize 2-hydroxyethylmetacrylate (HEMA) and acrylic acid (AAc) based hydrogels imprinted with model drug glucose. For the synthesis of these hydrogels, N,N-methylenebisacrylamide (N,N-MBAAm) has been used as a crosslinker, ammonium persulfate (APS) as an initiator,

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N,N,N′,N′ tetramethylethylenediamine (TEMED) as accelerator. Both MIPs and non-imprinted polymers (NIPs) were synthesized with a different concentration of drug, and without drug, and have been used to study their different loading capacity, swelling and *in vitro* release dynamics of the drug.

2. Experimental

2.1 Materials and Method

HEMA and AAc were obtained from Merck-Schuchardt, Germany. Ammonium persulphate (APS), and N,N′-methylenebisacrylamide (N,N-MBAAm) were obtained from S.D. Fine, Mumbai, India and were used as received. TEMED was obtained from the Sisco Research Lab. Pvt. Ltd. Glucose was obtained from Qualigens Fine Chemicals Mumbai, India.

2.2 Synthesis of Poly(HEMA-cl-AAc)

Synthesis of molecular imprinted hydrogels was carried out with 4.38×10^{-2} mols/L of APS, 7.68×10^{-1} mols/L of HEMA, 13.88×10^{-1} mol/L of AAc, 3.89×10^{-2} mols/L of N,N-MBAAm and 1.72×10^{-1} mol/L of TEMED in the aqueous solution of model drug (glucose) at 37°C temperature for half an hour. The hydrogels thus formed were washed with distilled water and thereafter named as poly(HEMA-*cl*-AAc). Synthesis of non-imprinted hydrogels was carried without drug under similar conditions. Both MIPs and NIPs have been synthesized in triplicate. The MIPs were synthesized with two different concentrations of the drug (2 mg/mL and 4 mg/mL) to observe the effect of the number of recognition sites in the imprinted polymers on the entrapment of drug and on the release pattern of the drug. Glucose imprinted in hydrogels is shown in Plate 1. The interaction between the glucose and, HEMA, AAC and N′N′-MBAAm are expected to be hydrogen bonding with the functional moieties present in the monomers and crosslinker. The MIPs loaded with 4 mg/ml and 2 mg/ml of glucose have been named as MIPs-4 and MIPs-2, respectively and polymers without drug were named as non-imprinted polymers (NIPs). All the polymers were synthesized in triplicate and were used to study the release dynamics of the drug immediately after synthesis. After removal of the template from the MIPs, these were dried at 37°C in an oven and reloaded in a definite concentration of the template molecules (drug) in the aqueous solution. Reloading of MIPs and NIPs has been carried out with same concentration of the drug (10 mg/mL). The MIPs and NIPs thus obtained were subjected to swelling studies and drug release studies.

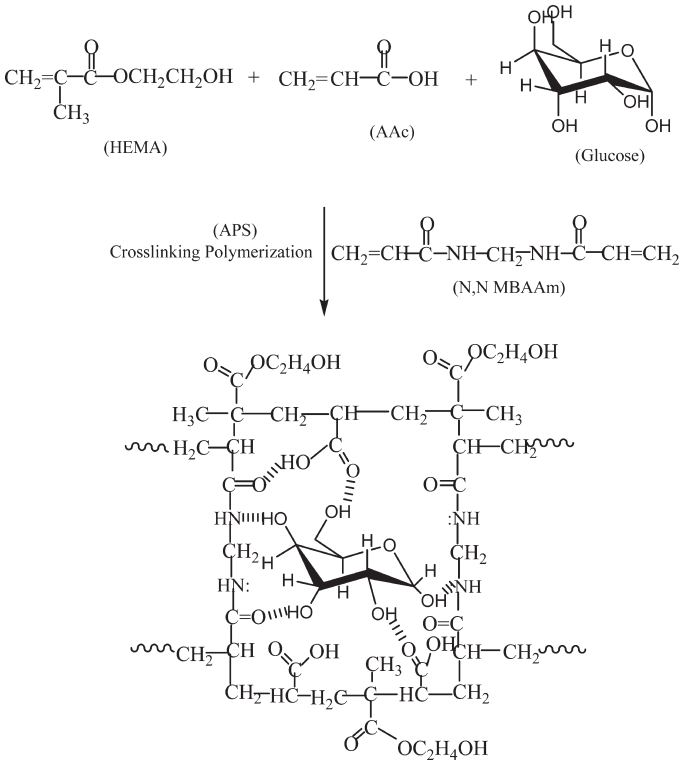

Plate 1. Glucose imprinted in poly (HEMA-*cl*-AAc) based hydrogels.

2.3 Characterization

Polymers were characterized by FTIR spectroscopy and swelling studies. FTIR spectra of polymers were recorded in KBr pellets on Nicolet 5700FTIR THERMO. Swelling kinetics of the polymers were carried out in distilled water by a gravimetric method. The known weight of polymers were taken and immersed in an excess of solvent for different time intervals at 37°C and then polymers were removed after 30 min, wiped with tissue paper to remove the excess solvent, and weighed immediately. The difference in weight has given the gain in weight at different time intervals. The equilibrium swelling was taken after 48 h.

2.4 Release Dynamics of Drug from Poly(HEMA-cl-AAc)

2.4.1 Preparation Calibration Curves

In this procedure, the absorbance of a number of standard solutions of the reference substance at concentrations encompassing the sample concentrations were measured on the UV Visible Spectrophotometer (Cary 100 Bio, Varian) and calibration graph was constructed. The concentration of the drug in the sample solution was read from the graph as the concentration corresponding to the absorbance of the solution. The calibration graph of glucose was made to determine the amount of glucose release from the drug loaded MIPs at wavelength 490 nm by using DNS method (18).

2.4.2 Drug Release from MIPs

In vitro release studies of the drug were carried out by placing a dried and loaded sample in 20 mL distilled water taken in a

beaker at 37°C. After every 30 min, the drug loaded polymer was removed from the first beaker and transferred to the next beaker containing 20 mL distilled water at 37°C. The solution of the first beaker was made 20 mL by adding distilled water because some of the solution was taken up by the hydrogel. The amount of drug released was assayed spectrophotometrically after each 30 min. The absorbance of the solution was measured at a wavelength of 490.0 in each case (18). Ten readings were taken up to 300 min in a similar manner and then a final reading was taken after 48 h. The amount of drug release after each 30 min was calculated and a cumulative addition was made after each 30 min, which corresponded to the M_t of Equation (2). The amount of drug release after 48 h was considered as M_∞ of Equation (2). The polymers used in the above study were cylindrical in shape. The thickness of the MIP-4 was (0.744 ± 0.003) cm, MIP-2 was (0. 742 ± 0.003) cm and NIP was (0.742 ± 0.003) cm.

2.4.3 Drug Reloading to the MIPs or Reloading Capacity of the MIPs and NIPs

After removal of the template from the MIPs, the polymers were dried at 37°C in an oven and reloading of the drug into MIPs and NIPs was carried out by a swelling equilibrium method. The hydrogels were allowed to swell in 20 mL of the drug solution of known concentration (10 mg/mL of glucose solution) for 48 h at 37° and then dried to obtain the release device. Reloading of glucose was carried out in both cases (i.e., MIPs and NIPs) in triplicate to observe the binding affinity of hydrogels for the template.

2.5 Mathematical Modeling for Drug Release from Polymer Matrix

In the hydrogels system, absorption of water from the environment changes the dimensions and physicochemical properties of the system and thus, the drug release kinetics. In the case of water uptake, the weight gain, M_S, is described by the following empirical equations:

$$M_S = kt^n \tag{1}$$

where k and n are constant. Normal Fickian diffusion is characterized by $n = 0.5$, while Case II diffusion by $n = 1.0$. A value of n between 0.5 and 1.0 indicates a mixture of Fickian and Case II diffusion, which is usually called non-Fickian or anomalous diffusion. Ritger and Peppas showed that the above power law expression could be used for the evaluation of drug release from swellable systems (19, 20). In this case, M_t/M_∞ replace Ms in the above equation to give:

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where Mt/M_∞ is the fractional release of drug in time *t, 'k' is* the constant characteristic of the drug-polymer system, and 'n' is the diffusion exponent characteristic of the release mechanism. For cylindrical shaped hydrogels the integral diffusion is given in simple Equation (3).

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi \ell^2}\right)^{0.5} \tag{3}$$

where (M_t/M_∞) is the fractional release and M_t and M_∞ is drug released at time 't' and at equilibrium, respectively, D is the diffusion coefficient and l is the thickness of the sample. In Equation (3), the slope of the linear plot is between (M_t/M_∞) and $t^{1/2}$ yield diffusion coefficient D. Therefore, the initial diffusion coefficient D_i was evaluated from the slope of the plot. The average diffusion coefficient D_A may also be calculated for 50% of the total release by putting $M_t/M_\infty = 0.5$ in Equation (3), which finally yields Equation (4). Where $t^{1/2}$ is the time required for 50% release of drug, late diffusion coefficients were calculated using the late-time approximation as described by Peppas et al. given in Equation (5) (19, 20).

$$D_A = \frac{0.049\ \ell^2}{t^{1/2}} \tag{4}$$

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right)\exp\left[\frac{(-\pi^2 Dt)}{\ell^2}\right] \tag{5}$$

The slope of the plot between $\ln(1 - M_t/M_\infty)$ and t was used for the evaluation of D_L. The values of diffusion coefficients for the swelling kinetics and release dynamics of the drug from the hydrogels have been evaluated and results are presented Tables 1–3.

Table 1. Results of diffusion exponent 'n', gel characteristic constant 'k' and various diffusion coefficients for the release of glucose from the molecularly imprinted polymers (MIP) samples of poly(HEMA-*cl*-AAc) in distilled water at 37°C

Glucose release from polymers	Diffusion exponent 'n'	Gel characteristic constant $k \times 10^2$	Diffusion coefficients (cm^2/min)		
			Initial $D_i \times 10^4$	Average $D_A \times 10^4$	Late time $D_L \times 10^4$
MIP-4	0.6	2.48	24.41	24.93	3.81
MIP-2	0.7	1.54	34.31	25.74	5.30

Table 2. Results of diffusion exponent 'n', gel characteristic constant 'k' and various diffusion coefficients for the swelling kinetics of the molecularly imprinted polymers (MIP) and non imprinted polymers (NIP) poly(HEMA-*cl*-AAc) hydrogels in distilled water at 37°C

Different polymers	Diffusion exponent 'n'	Gel characteristic constant 'k' $\times 10^2$	Diffusion coefficients (cm^2/min)		
			Initial $D_i \times 10^4$	Average $D_A \times 10^4$	Late time $D_L \times 10^4$
MIP-4	0.7	0.76	6.33	12.48	1.11
MIP-2	0.8	0.51	10.59	14.38	1.44
NIP	0.8	0.44	7.27	12.82	1.17

Table 3. Results of diffusion exponent 'n', gel characteristic constant 'k' and various diffusion coefficients for the release of glucose from the molecularly imprinted polymers (MIPs) and non imprinted polymers (NIP) poly(HEMA-*cl*-AAc) hydrogels in distilled water at 37°C

Glucose release from polymers	Diffusion exponent 'n'	Gel characteristic constant 'k' $\times 10^2$	Diffusion coefficients (cm^2/min)		
			Initial $D_i \times 10^4$	Average $D_A \times 10^4$	Late time $D_L \times 10^4$
MIP-4	0.8	0.50	17.60	17.65	2.14
MIP-2	0.9	0.40	16.73	17.04	2.00
NIP	0.8	0.82	19.09	19.58	2.34

3. Results and Discussion

3.1 Characterization

Poly(HEMA-*cl*-AAc) hydrogels were characterized by FTIR and swelling studies.

3.1.1 Fourier Transform Infrared Spectroscopy

FTIR spectra of poly(HEMA-*cl*-AAc) was recorded and is presented in Figure 1. The broad absorption bands at 3430.9 cm^{-1} is due to -OH stretching, indicating the strong association in this polymer. The IR absorption bands at 1726.4 cm^{-1} due to C═O stretching of the ester and at 1260.6 cm^{-1} due to the C-O stretching of esters and at 1666 cm^{-1} due to C═O stretching of the acid were observed in the poly(HEMA-*cl*-AAc). The CH_2 asymmetric stretching vibration at 2926 $cm^{-1}$and the symmetric CH_2 absorption at 2856 cm^{-1} along with the -CH deformation mode around 1457.5 cm^{-1} have been observed in the spectra.

3.2 Release Dynamics of Drug

The release profile of drug from the drug-imprinted poly(HEMA-*cl*-AAc) hydrogels is shown in Figure 2. It has been observed from the figure that the release of drug from the drug imprinted poly(HEMA-*cl*-AAc) hydrogels loaded with 4 mg/ml of the drug is higher, compared to the hydrogels loaded with the 2 mg/ml in the first 300 min of release. Total amount drug released from MIPs-4, MIPs-2 has been observed (46.23 ± 0.46) mg/20 ml/g of gel, and ($29.79 + 0.11$) mg/20 ml/g of gel, respectively (Figures 3 and 4). The higher release of glucose from the MIPs-4 occurred due to the higher initial loading of the drug in the polymer during synthesis. The values of diffusion exponent 'n' has been observed to be 0.6 and 0.7, respectively for the MIPs-4 and MIPs-2 (Figure 5). As these values are more than 0.5, so non-Fickian type diffusion mechanism has occurred for the diffusion of the drug from these MIPs. After release of drug from these MIPs, the polymers were dried at 37°C in the oven.

3.3 Reloading of the Drug or Binding Affinity of MIPs

As the molecular imprinting is a technique, producing synthetic materials containing highly specific receptor sites, which have an affinity for a target molecule and MIPs can mimic the recognition and binding capabilities of the template molecule. In the present case, it is observed that the binding affinity of the MIPs for the glucose is higher as compared to NIPs when the reloading of drug was carried out by a swelling equilibrium method by keeping both the MIPs (MIPs-4 and MIPs-2) and NIPs in 10 mg/ml solution of glucose for 48 h at 37°C. Then, polymers were dried to obtain the release device for further study. The results are presented in Figure 6. It is observed from the figure that the MIPs which were initially loaded with 4 mg/ml of glucose have entrapped higher amount of the drug (98.16 ± 1.74 mg/g of gel) as compared to MIPs loaded with 2 mg/ml of glucose (70.21 ± 2.58 mg/g of gel) and NIPs (55.50 ± 0.63 mg/g of gel). It may due to the fact that in the MIPs-4, the copolymerization is disturbed by the high amount of glucose, resulting from a low crosslinker concentration of the MIPs-4, as compared to the MIPs-2, which is made with a smaller concentration of glucose. Because of this lower crosslinked concentration of the polymer, the MIPs-4 can absorb a higher amount of glucose than the MIPs-2.

3.4 Swelling and Release Dynamics of the Drug from the MIPs and NIPs after Reloading

After reloading of the drug, the MIPs and NIPs were dried at room temperature and then were used to study the swelling of

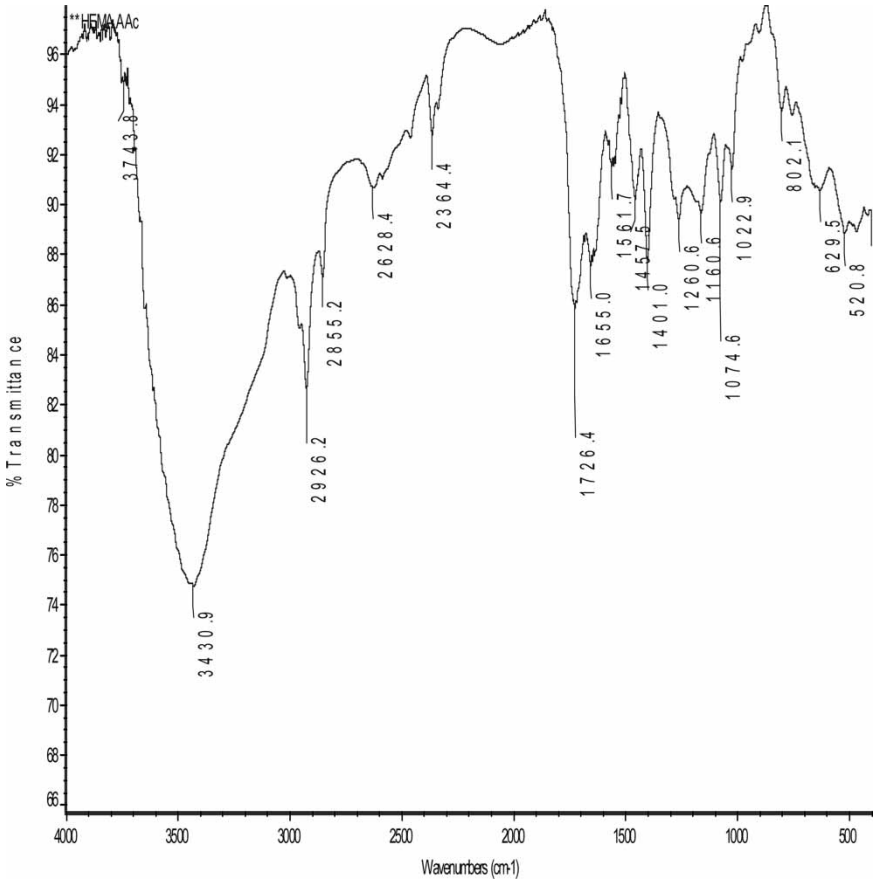

Fig. 1. FTIR spectra of poly(HEMA-*cl*-AAc).

the poly(HEMA-*cl*-AAc) hydrogels and release dynamics of the drug from these hydrogels.

3.4.1 Swelling Kinetics

The swelling of the MIPs and NIPs is presented in Figure 7. The swelling of the MIPs has been observed to be higher as compared to NIPs. It is also clear from the figure that the MIPs, which were initially loaded with the 4 mg/ml of the glucose (MIPs-4), have shown more swelling as compared to the MIPs initially loaded with 2 mg/ml of the glucose (MIPs-2) and NIPs. Total amount of water taken by MIP-4, MIP-2 and NIPs has been observed (8.20 ± 0.08, 5.88 ± 0.08 and 3.49 ± 0.07 g/g of gel), respectively (Figure 8). It may due to the same reasons as mentioned above that in the MIPs-4 the copolymerization is disturbed by the high amount of glucose, resulting in a low crosslinker concentration of the MIPs-4, as compared to the MIPs-2, which is made with a smaller concentration of glucose. Because of this lower crosslinked concentration of the polymer, the MIPs-4 have absorbed a higher amount of water than the MIPs-2 and NIPs. 50% of the total swelling occurred in 412.19 min, 315.94 min, and 442.26 min, respectively for the MIP-4, MIP-2 and NIPs (Figure 9). It shows that the rate of swelling is higher in MIPs as compared to NIPs. The values of diffusion exponent 'n' and gel characteristics

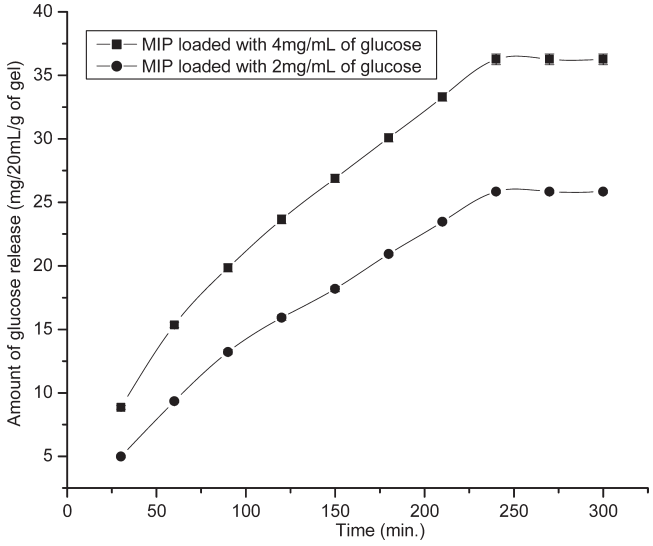

Fig. 2. Release profile of glucose from MIPs of poly(HEMA-*cl*-AAc) hydrogels loaded with different glucose concentration in distilled water at 37°C. (Reaction time = 30 min, reaction temperature = 37°C, [HEMA] = 7.68×10^{-1} mol/L, [AAc] = 13.88×10^{-1} mol/L, [APS] = 0.438×10^{-1} mol/L, [N,N-MBAAm] = 3.89×10^{-2} mol/L and [TEMED] = 1.72×10^{-1} mol/L).

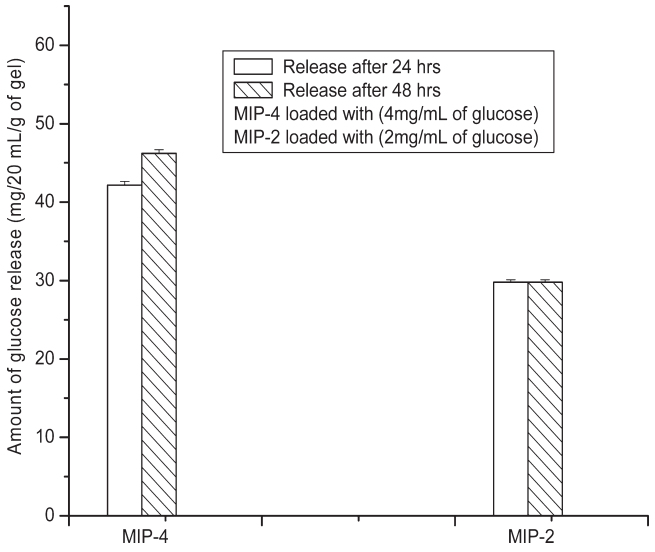

Fig. 3. Release pattern of glucose from MIPs of poly(HEMA-*cl*-AAc) hydrogels after 24 h and 48 h in distilled water at 37°C.

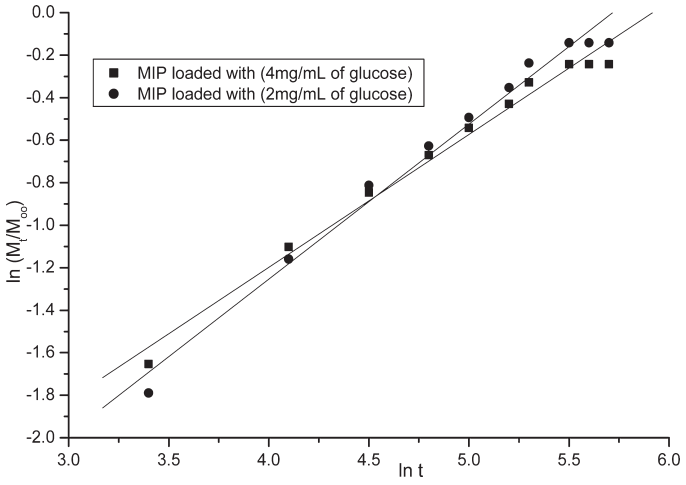

Fig. 5. Plot for the evaluation of diffusion exponent '*n*' and gel characteristic constant '*k*' of glucose from MIPs of poly(HEMA-*cl*-AAc) hydrogels loaded with different glucose concentration in distilled water at 37°C.

constant '*k*' have been evaluated from Figure 10 and results are presented in Table 2. It is clear from the Table that the value of '*n*' for MIP-4, MIP-2 and NIPs are 0.7, 0.8, and 0.8 respectively, which indicates that non-Fickian or anomalous type diffusion mechanism has occurred in all three polymers. The values of the diffusion coefficients have been shown in Table 2. It is clear from the table that the values obtained for the average diffusion coefficient (D_A) were higher than the initial (D_i) and late diffusion coefficient (D_L). It shows that in the beginning and the later stages of the swelling; the diffusion of water molecules into the hydrogels was slow. From the above discussion, it has been concluded that the imprinted gel swelled at faster rates than non-imprinted ones.

3.4.2 *Release Dynamics of the Drug*

The release profile of the drug from the per gram of the MIPs and NIPs is presented in Figure 11. It is observed from the figure that the amount of drug released from the MIP-4 is higher as compared to the NIPs. The total (78.5 ± 0.26), (62.30 ± 0.21) and (42.94 ± 0.16) mg/20 ml/g of gel have been released after 48 h, respectively from the MIPs-4,MIPs-2 and NIPs (Figure 12). The 50% of the total release occurred faster in the case of NIPs as compared to MIPs. Drug from the MIPs released in a controlled manner. The rate of drug release from the NIPs was higher than the MIPs (Figure 13). The values of diffusion exponent '*n*' and gel characteristic constant '*k*' for the release of drug in

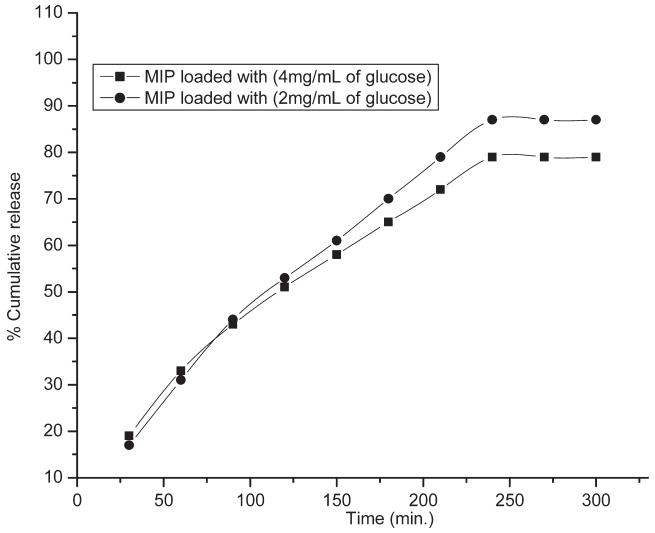

Fig. 4. % Cumulative release of glucose from MIPs of poly (HEMA-*cl*-AAc) hydrogels loaded with different drug concentration in distilled water at 37°C.

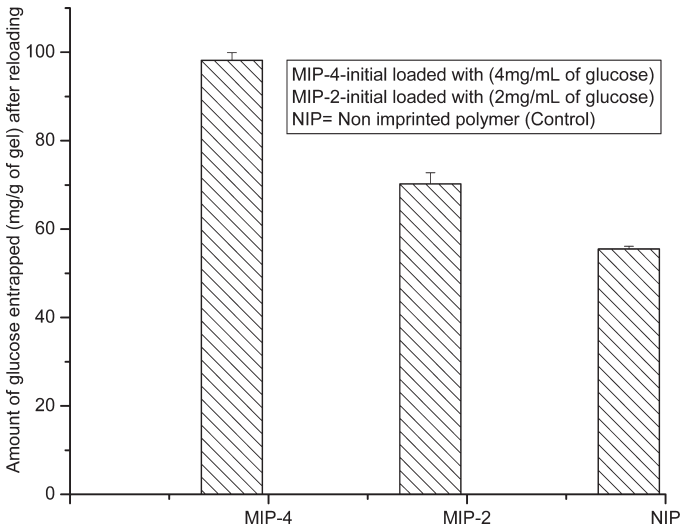

Fig. 6. Total amount of glucose entrapped by reloaded MIPs and NIPs of poly(HEMA-*cl*-AAc) after 24 h in distilled water at 37°C. (Stock concentration = 10 mg/mL).

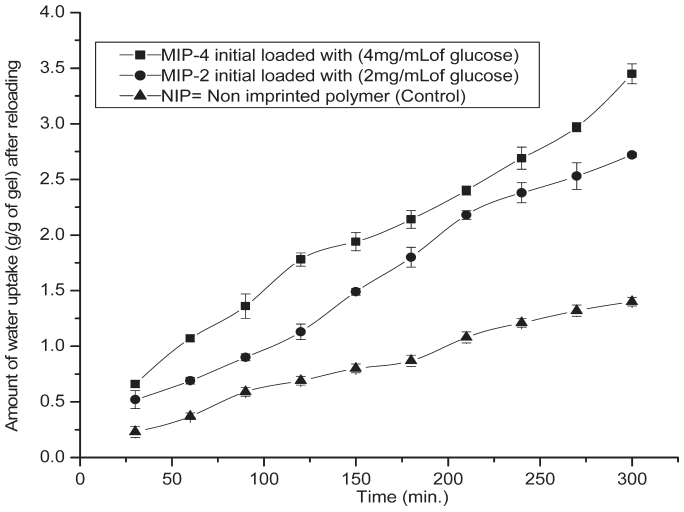

Fig. 7. Swelling kinetics of reloaded MIPs and NIPs of poly (HEMA-*cl*-AAc) hydrogels in distilled water at 37°C.

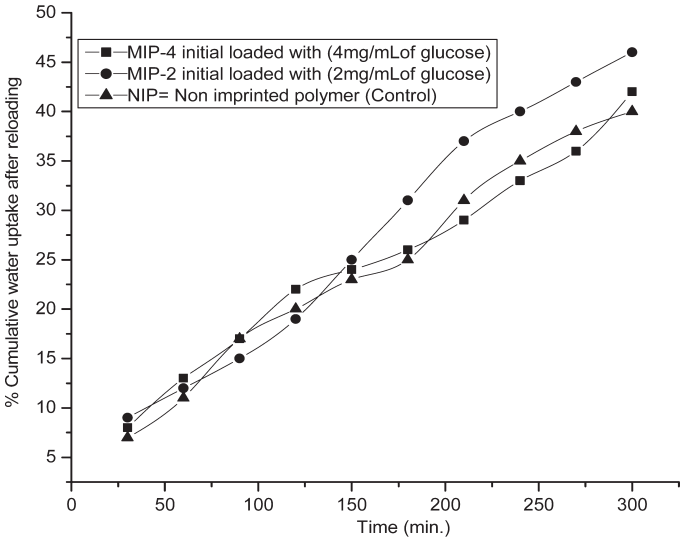

Fig. 9. % Cumulative water uptake of reloaded MIPs and NIPs of poly(HEMA-*cl*-AAc) hydrogels in distilled water at 37°C.

distilled water have been evaluated from the slope and intercept of the plot ln M_t/M_∞ vs. ln t (Figure 14) and the results are presented in Table 3. It is clear from the Table that the values of '*n*' are more than 0.5 in each release case, which indicates a non-Fickian type diffusion mechanism for the diffusion of drug from the polymers. In a non-Fickian diffusion mechanism, both diffusion of the drug molecules from the polymers and relaxation times of polymer chains are comparable. The values of diffusion coefficient for the release of drug from these polymers are presented in Table 3. It is observed from the Table that the values obtained for the average diffusion coefficient (D_A) are higher than initial (D_i) and late diffusion coefficient (D_L). It means that in the early and the later stages of the drug release, the rate of diffusion of the drug from the polymers is slow. This observation is also supported by results obtained from the swelling kinetics of these polymers. In the present case, it is important to mention here in the case of NIPs, no release of drug has occurred after 24 h, whereas MIPs samples have shown a release up to 48 h. From this, it is clear that the non-imprinted polymers (NIPs) do not have specific binding cavities where the drug can be entrapped, whereas in MIPs, due to their highly specific network structures, a small amount of drug is still retained, and therefore, shows a very controlled release pattern of drug. This observation shows that the

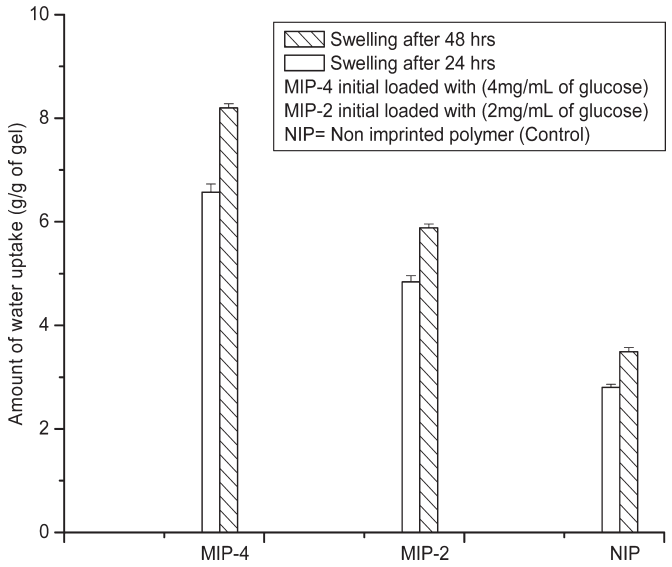

Fig. 8. Swelling pattern of reloaded MIPs and NIPs of poly (HEMA-*cl*-AAc) hydrogels after 24 h, 48 h in distilled water at 37°C.

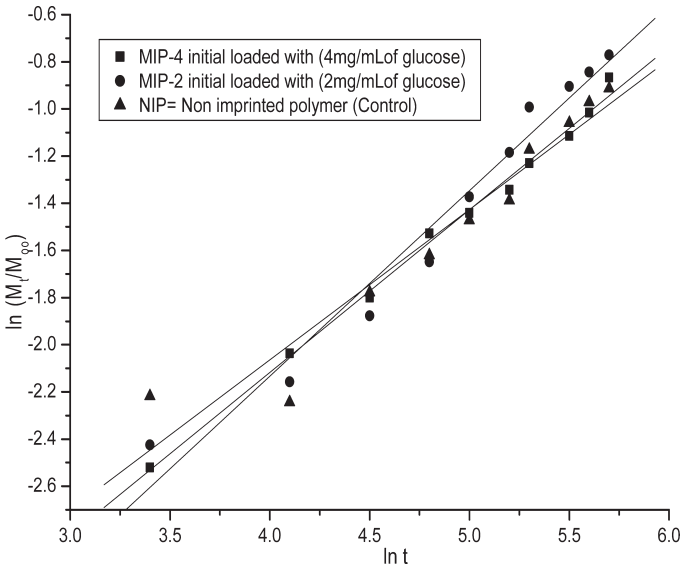

Fig. 10. Plot for the evaluation of diffusion exponent '*n*' and gel characteristic constant '*k*' for the swelling of reloaded MIPs and NIPs of poly(HEMA-*cl*-AAc) hydrogels in distilled water at 37°C.

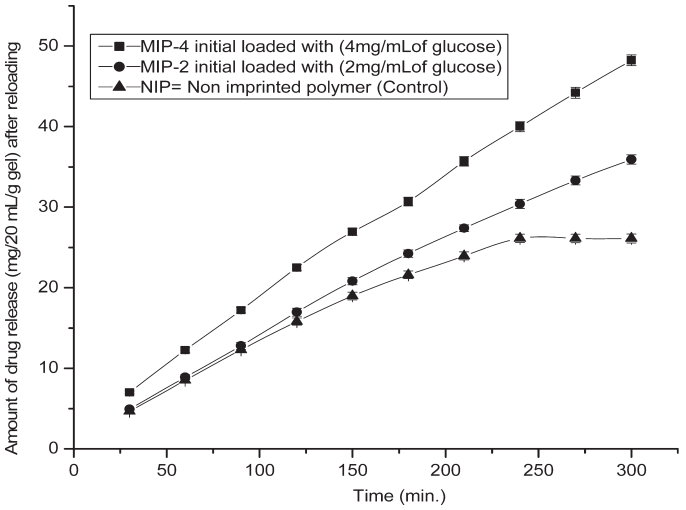

Fig. 11. Release profile of glucose from reloaded MIPs and NIPs of poly(HEMA-*cl*-AAc) hydrogels in distilled water at 37°C. (Reloading concentration of glucose = 10 mg/mL).

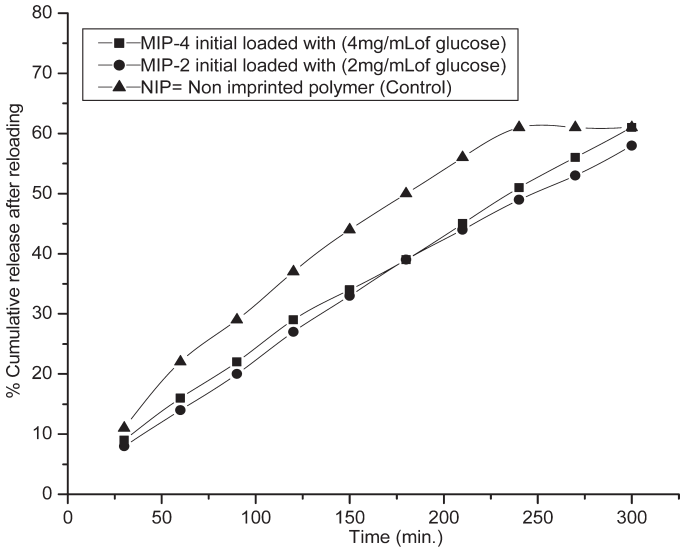

Fig. 13. % Cumulative release of glucose from reloaded MIPs and NIPs of poly(HEMA-*cl*-AAc) hydrogels in distilled water at 37°C. (Reloading concentration of glucose = 10 mg/mL).

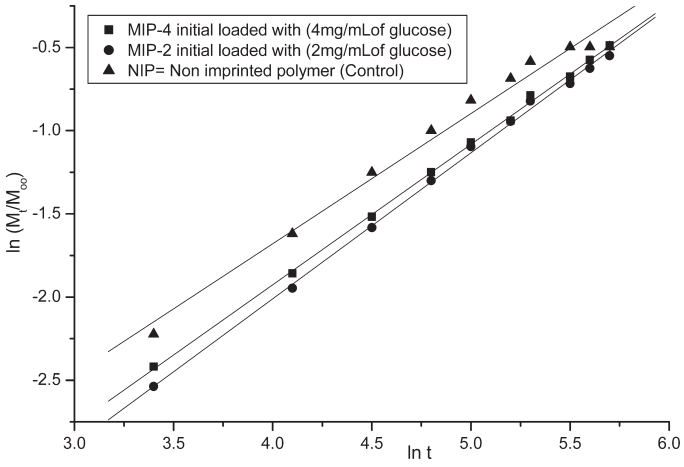

Fig. 14. Plot for the evaluation of diffusion exponent '*n*' and gel characteristic constant '*k*' of glucose from reloaded MIPs and NIPs of poly(HEMA-*cl*-AAc) hydrogels in distilled water at 37°C.

imprinted sites have a stronger interaction with the drug than the non-imprinted sites (21). Hiratani and coworkers (21) have prepared the imprinted hydrogels from N,N-dimethylacrylamide and tris(trimethylsiloxy)silylpropyl methacrylate (DMAA and TRIS; main components), methacrylic acid (MAA; functional monomer), ethylene glycol dimethacrylate (EGDMA; cross-linker), and timolol (template drug) have used these hydrogels for controlled and sustained release. They have concluded that the release rate of timolol from the imprinted hydrogels can be controlled by the affinity of their imprinted cavities. The differences in the timolol

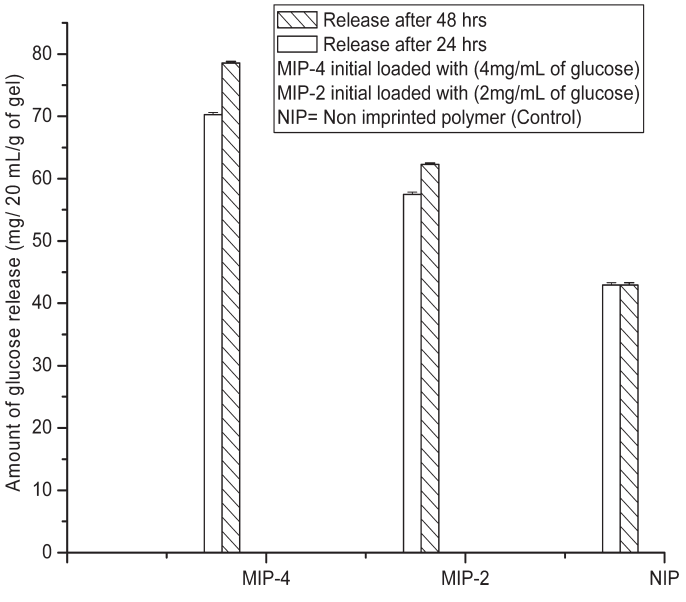

Fig. 12. Release pattern of glucose from reloaded samples of MIPs and NIPs of poly(HEMA-*cl*-AAc)) hydrogels after 24 h and 48 h in distilled water at 37°C. (Reloading concentration = 10 mg/mL).

release rate from the imprinted hydrogels prepared with different amounts of timolol have been related to the affinity between the drug and the imprinted cavities. In addition to the affinity, differences in saturation have also played its role in release of the drug (21).

4. Conclusions

It is concluded from the forgone discussion that the initial drug concentration used for the synthesis of the MIPs affected the reloading of the hydrogels, swelling of the hydrogels and release of the drug from the hydrogels. Hence, the synthetic conditions play a very important role in controlling

the nature of the MIPs. The reloading of the drugs in the MIPs and swelling of the MIPs increases with an increase in the initial drug loading. It is further concluded from the values of diffusion exponent that the release of drug occurred through a non-Fickian type diffusion mechanism from the MIPs. In a non-Fickian diffusion mechanism, both diffusion of the drug molecules from the polymers and relaxation times of polymer chains are comparable.

5. References

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