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Effect of Potassium Chloride and Cationic Drug on Swelling, Erosion and Release from κ-Carrageenan Matrices

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ABSTRACT

The basic objective of this work was to study the effect of model cationic drug metformin HCl on swelling and erosion and, in turn, the release of KCl and drug itself, from the κ-carrageenan matrices. Water uptake by the matrix up to 2 hours was found to increase with KCl concentration from the plain matrix. Erosion was not affected by concentration of KCl. Incorporation of drug favors water uptake, but in presence of KCl it was found to be reduced. Drug-containing matrices have shown higher release of KCl as compared with plain batches. Drug release was retarded as KCl concentration increased up to 5%, above which the reduced cohesivity of the matrix caused increase in drug release.

KEYWORDS: κ-carrageenan, cationic drug, swelling, erosion, KCl

INTRODUCTION

Polymeric matrix systems are most commonly used for controlled release of drug. Hydrophilic and hydrophobic polymers and their different combinations are used to manipulate the drug release. Polymers sensitive to different stimuli such as temperature, pH, enzymes, and ions are used to control site and rate of drug release.[1-4]

Carrageenan, a polymer widely used in food industry has been recently studied for its applications for controlled drug delivery.[3] Carrageenans are hydrophilic, high molecular weight, anionic linear heteropolysaccharides extracted from marine algae *Rhodophyceae*. There are different types of carrageenans but kappa (κ), iota (ι), and lambda (λ) are used for pharmaceutical applications. Carrageenans are sulfate esters of galactose and 3,6-anhydrogalactose copolymers, linked by alternating α-1,3 and β- 1,4 glycosidic linkages. The λ-carrageenan does not contain 3,6-anhydrogalactose and is highly sulphated. It consists of β-(1-3)-D-galactose-4-sulfate and alpha-(1-4)-D-galactose-2,6-disulphate including 3 sulfate groups. The κ-carrageenan consists of a repeating unit composed of the disaccharide, β-(1-3)-D-galactose-4-sulfate, and alpha-(1-4)-3-6-anhydro-D-galactose. The ι-carrageenan possesses 2 sulfate groups in a disaccharide repeat unit; β-(1-3)-D-galactose-4-sulfate and α-(1-4)-3-6-anhydro-D-galactose-2-sulfate. The κ- and ι-carrageenans are very similar except ι-carrageenan is sulfated at carbon 2.[5,6]

Both κ- and ι-carrageenans have the ability to form gels but differ significantly in their rheological properties. Gels of κ type are hard, strong, and brittle, whereas the ι-carrageenan forms are soft and weak.[7-9] Therefore κ-carrageenan is used in sustained release formulations. It has been used in the formulation of tablets,[3,10,11] beads,[12,13] and hydrogels[14] containing ionic as well as nonionic drugs. The κ-carrageenan contains one sulfate group for every monomer. Therefore, its gelation is promoted in the presence of K^+, Ca^{2+}, Cs^+, and Rb^+. These cations neutralize the coulomb repulsion force between the polymer chain in the cross-link point.[7,15]

The κ-carrageenan exists either in the coil or helix confirmation and can undergo a thermal as well as salt-induced helix-coil transformation. This order-disorder transition of κ-carrageenan was found to be dependent on specific types of cations and anions used. A helix-helix aggregation that is responsible for gel formation relies on a specific cation present. Potassium ions have the capacity to induce helix confirmation and promote helix-helix aggregation, thereby facilitating gel formation. Ca^{2+} or K^+ can screen electrostatic repulsive forces between the participating chains, by packing within the aggregate structure. As the level of potassium increases, the structure becomes tightly aggregated, exhibiting increase in gel strength.[16]

The κ-carrageenan has been evaluated for compressional properties and was found to exhibit viscoelastic behavior.[11,17] Due to its gelling property, it has been studied as a release retardant for ionic and nonionic drugs.[11,13] Picker

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studied the effect of added cation on the properties of 2 varieties of κ-carrageenan as well as using theophylline and diclofenac sodium as model drugs.[18] Sjöberg et al studied the effect of κ-carrageenan on the diffusional transport of positively charged drugs in agarose gels. Likewise, changes in the diffusion coefficient during simultaneous diffusion of 2 drugs was also studied.[19]

Because cations play an important role in the properties of the κ-carrageenan matrix, presence of cationic drugs will cause significant changes in its properties. Similarly, the effect of other cations such as K^+ used for gelling, may be significantly altered due to cationic drug. There are very few reports on the application of κ-carrageenan as a carrier for cationic drugs.[13] Therefore, the aim of the present study is to study the effect of KCl and the cationic model drug, metformin HCl, on the water uptake, erosion, and release of drug and potassium ions from the κ-carrageenan matrix.

MATERIALS AND METHODS

Materials

The κ-carrageenan (GP 911 NF) was a generous gift from FMC Corporation, Philadelphia, PA (through Signet Chem, Mumbai, India). Lupin Research Park (Pune, India) provided metformin HCl as a gift sample. All other chemicals were purchased and were of analytical grade.

Methods

Preparation of Plain Matrices

The κ-carrageenan (50 g) was mixed with different amounts of potassium chloride in a laboratory mixer (Seema Enterprises, Pune, India) to obtain the powder mix containing 2.5% to 13.75% wt/wt potassium chloride. The mixture was passed through a 40-mesh screen. Suitable quantity of powder mixture was weighed and compressed at 100 kg/cm^2 for 60 seconds using KBr press (Spectra Lab, Mumbai, India) to obtain compacts, each containing 400 mg κ-carrageenan. Different batches were coded as K0, K2.5, and so on depending on potassium chloride concentration (suffix denotes KCl concentration).

Preparation of Drug-Loaded Matrices

Metformin HCl and κ-carrageenan were mixed in the ratio 1:4 in a laboratory mixer. Fifty grams of this mixture was then mixed with different amounts of potassium chloride to obtain powder mixture containing 2.5% to 13.75% wt/wt of potassium chloride. The powder was compressed in the same manner as for plain matrices. Drug-loaded matrices were coded as KD0, KD2.5, and so on depending on the potassium chloride concentration.

Evaluation

Water-Uptake Study

Water-uptake studies were performed by equilibrium weight gain method.[20] The studies were performed using *United States Pharmacopeia (USP)* 24 type I dissolution test apparatus (TDT 08L, Electrolab, Mumbai, India). The matrices were accurately weighed and placed in a dissolution basket. The baskets were immersed in a dissolution vessel containing 900 mL deionized water maintained at 37°C ± 0.5°C; speed of rotation was 100 rpm. At regular intervals, the basket-matrix systems were removed from the dissolution vessels, blotted with tissue paper to remove excess water, and reweighed. The percentage water uptake (ie, the degree of swelling due to absorbed water) was calculated using Equation 1:

$$\% \text{ Water Uptake} = [(W_s - W_i) - W_e]/(W_p - W_{pe}) \times 100, \quad (1)$$

where, W_i and W_s represent initial weight of the matrix and swollen matrix at time t, respectively; W_p and W_{pe} denote initial weight of the polymer added to the matrix and weight of polymer eroded up to time t, respectively; and W_e represents the total weight loss due to dissolution of drug, KCl, and polymer from the matrix up to time t. Drug loss was excluded during calculations for plain matrices. Studies were performed using 5 matrices.

Erosion Study

Erosion studies of plain and drug-loaded matrices were performed as reported by Roy and Rohera.[20] The preweighed matrices were placed in the dissolution basket and subjected to dissolution in 900 mL deionized water maintained at 37°C ± 0.5°C, speed of rotation was 100 rpm. At regular intervals, the basket-matrix systems were removed from the dissolution media and dried to constant weight in hot air oven at 50°C. The percentage matrix erosion (E) at time t was calculated using Equation 2:

$$\% \text{ Matrix Erosion} = [(W_i - W_{dp}) - W_t]/[Wi - (D+P)] \times 100, \quad (2)$$

where, W_{dp} is total weight of drug and polymer lost up to time t, and W_t is weight of dried partially eroded matrix at time t. D and P represent initial weight of drug and polymer added to the matrix; D was excluded from Equation 2 for

plain matrices. The average values of 5 readings were obtained.

In Vitro Release Study

Release of potassium chloride and drug from the matrices was performed using *USP* 24 type II dissolution test apparatus. The matrices were placed at the bottom of a dissolution vessel containing 900 mL of water maintained at 37°C ± 0.5°C; speed of rotation was 100 rpm. Samples were collected periodically and replaced with fresh medium. Solutions were filtered through Whatman filter paper 41 (Springfield Mill, UK) and concentration of metformin HCl was determined spectrophotometrically at 233 nm (Jasco V500, Tokyo, Japan). Amount of potassium chloride released was calculated by estimation of potassium flame photometrically (Flame Photometer 130, Systronics, Ahmedabad, India). Release studies were performed in triplicate.

RESULTS AND DISCUSSION

Water Uptake

Water-uptake profiles of plain and drug-containing matrices having different concentrations of KCl are shown in Figures 1 and 2, respectively. Water uptake by the matrix was calculated using Equation 1. As compared with previous reports,[20] this equation takes into consideration drug release and matrix erosion or dissolution, reflecting only the changes due to water uptake. A plain matrix without KCl (ie, batch K0) did not show any significant water uptake and disintegrated within 4 hours. Batch KD0 showed significant increase in water uptake as compared with K0 and maintained integrity for up to 6 hours. This finding may be because of the coil-helix transition and helix-helix association induced by the cationic drug metformin HCl. Except for batch KD0, water uptake was lower for drug-loaded matrices as compared with corresponding plain matrices.

The effect of concentration of KCl alone and in the presence of drug on water uptake at different time intervals is shown in Figures 3 and 4, respectively. The figures clearly show that water uptake increases linearly with KCl concentration in plain matrices up to 2 hours, after which it deviates from linearity. Where as good correlation was observed in water uptake upto KCl concentration in the range of 2.5 to 10% wt/wt, above which it reduced in drug loaded matrices. Thus, in presence of drug in matrices containing higher KCl concentration, matrix cohesivity is reduced, causing reduced capacity to hold water. The rate of increase in water uptake with KCl concentration was found to be significantly low for drug-loaded batches as compared with plain matrices. After 2 hours, water uptake did not correlate with the concentration of KCl. This finding may be attributed to the changes in gel structure after 2 hours. After 3 hours, matrices showed reduction in cohesivity, especially those containing higher concentration of KCl, and they showed a decline in water uptake.

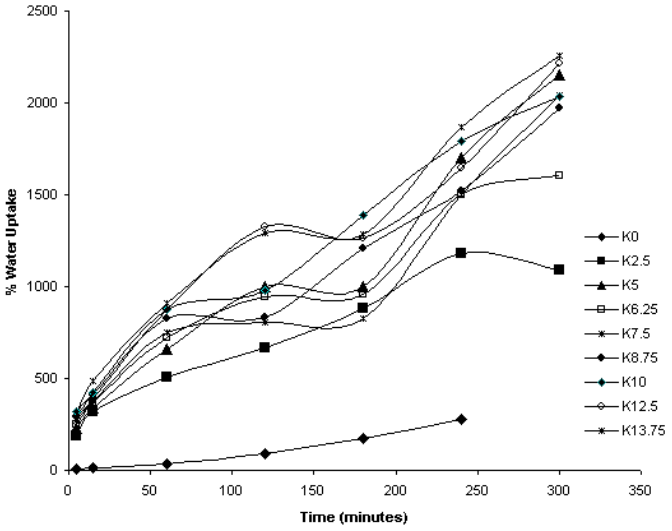

Figure 1. Water-uptake profiles of plain matrices.

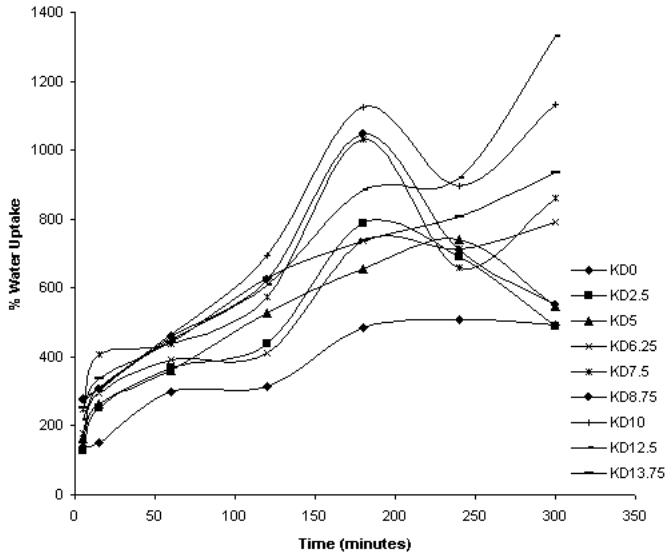

Figure 2. Water-uptake profiles of drug-loaded matrices.

Water uptake data of batches followed the Vergnaud model. The generalized form of the Vergnaud model is as follows:[21]

$$M_t = kt^n, \quad (3)$$

where M_t represents the amount of liquid transferred at time t, and k is the swelling constant, which depends on the

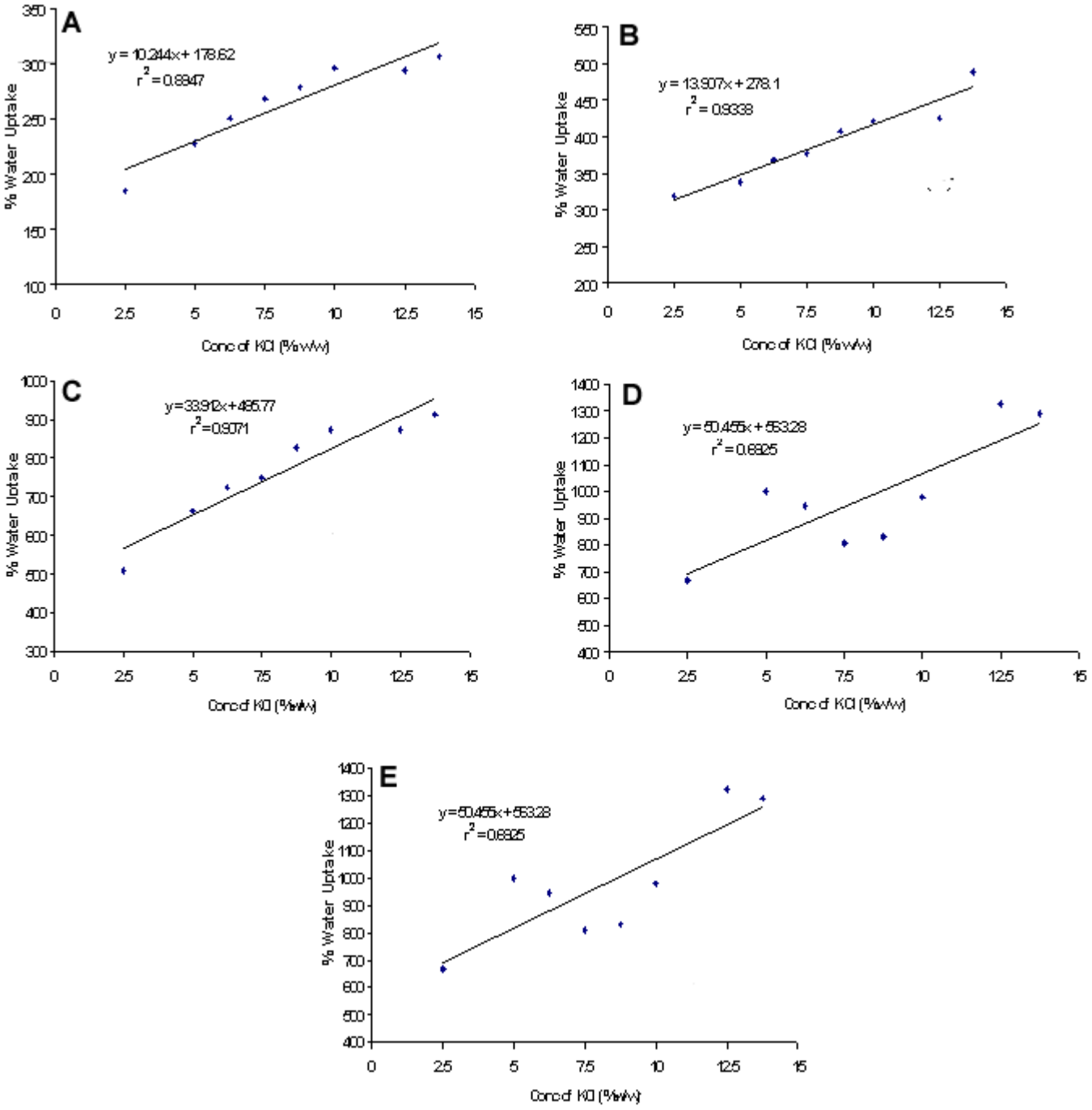

Figure 3. Water uptake by plain matrices at different time intervals: (A) after 5 minutes, (B) after 15 minutes, (C) after 60 minutes, (D) after 120 minutes, and (E) after 180 minutes.

amount of liquid transferred after infinite time, the porosity of the matrix, and diffusivity. The exponent, n, indicates the mechanism of water uptake. The characteristic values of the kinetic model were calculated by fitting the water-uptake data in Equation 3. Various parameters obtained after fitting of Vergnaud model are summarized in Table 1. The model shows that uptake exponent n is <0.5 in both cases. Values of n are lower (0.26-0.4) for drug-loaded batches as compared with plain matrices (0.43-0.51).

Erosion Study

The results of plain matrix erosion are shown in Figure 5. The percentage weight loss of the matrices increased with

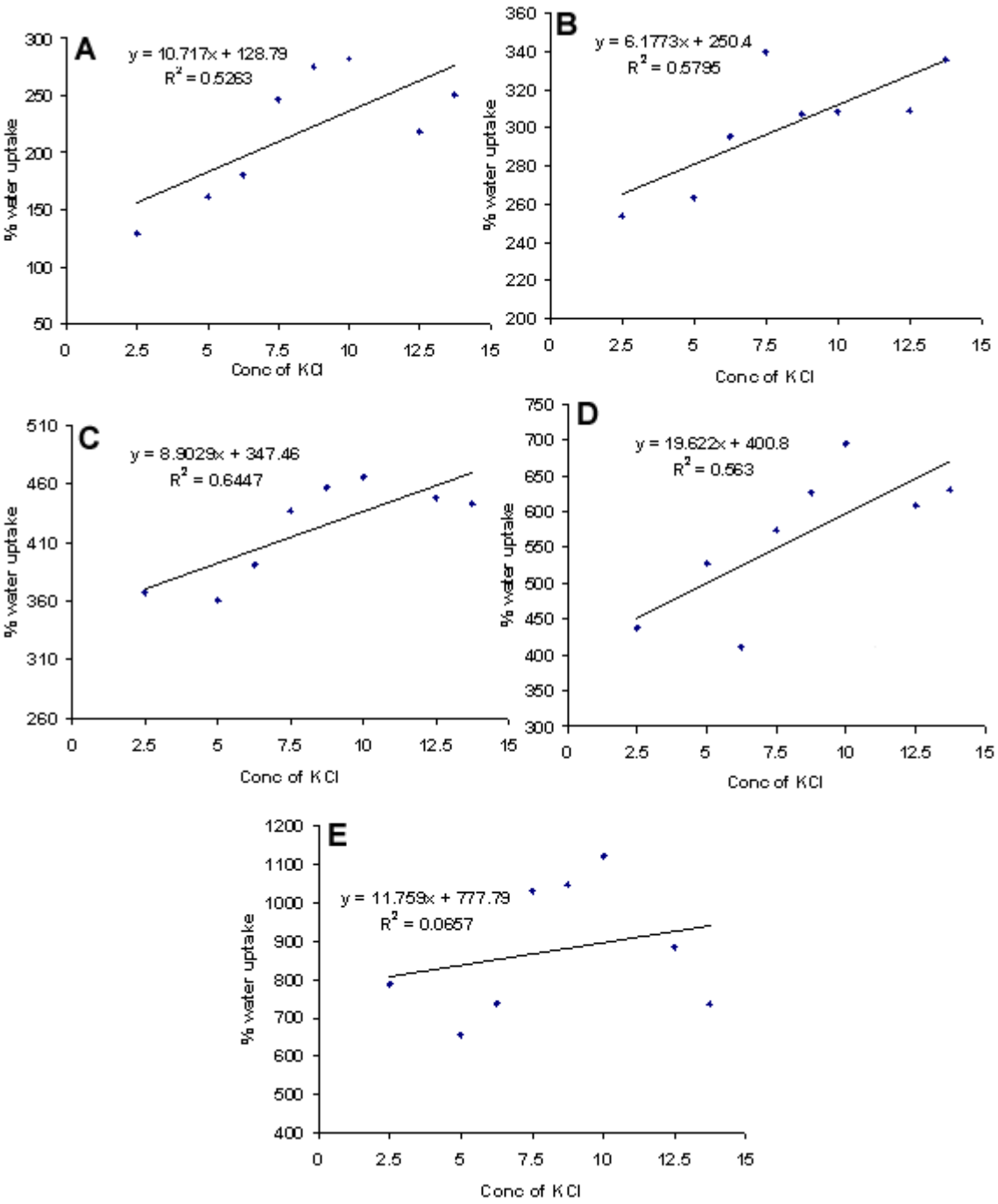

Figure 4. Water uptake by drug-loaded matrices at different time intervals: (A) after 5 minutes, (B) after 15 minutes, (C) after 60 minutes, (D) after 120 minutes, and (E) after 180 minutes.

time. Erosion data were fitted into zero order equation, and regression parameters of various batches are summarized in Table 2. The slope indicates the rate of erosion, and the intercept gives reflection of erosion in the initial stages. The plain matrices prepared without potassium chloride showed less erosion in the initial stage and a faster rate of erosion, as compared with the matrices containing potassium chloride. This finding may be attributed to a lack of swelling in the absence of KCl. Concentration of KCl in the matrix did not significantly affect the rate or amount of erosion in the initial stages of plain matrices.

The erosion profiles of plain matrices show that there is deviation from linearity at a certain time within 2 to 3 hours.

Table 1. Water Uptake Data Analysis by Vergnaud Model*

% KCl	Plain Matrices			Drug-Loaded Matrices		
	(k)*	(n)**	(r^2)***	(K)	(n)	(r^2)
0	0.8100	1.0185	0.9905	69.398	0.3492	0.9740
2.5	91.243	0.4389	0.9917	79.253	0.3774	0.9370
5	87.542	0.5196	0.9783	96.614	0.3454	0.9692
6.25	115.60	0.4457	0.9881	103.89	0.3451	0.9633
7.5	122.56	0.4344	0.9477	161.119	0.2895	0.9159
8.75	130.83	0.4399	0.9780	169.389	0.2640	0.8626
10	137.29	0.4516	0.9854	131.80	0.3633	0.9545
12.25	121.92	0.4817	0.9870	101.630	0.4085	0.9725
13.75	140.52	0.4631	0.9905	142.23	0.3148	0.9878

*k indicates kinetic constant; n, water-uptake exponent; and r^2, correlation coefficient.

Table 2. Zero Order Regression Analysis Data for Matrix Erosion

% KCl	Plain Matrices			Drug-Loaded Matrices		
	Slope	Constant	(r^2)	Slope	Constant	(r^2)
0	0.2893	4.6083	0.9785	0.2030	13.441	0.9348
2.5	0.2120	10.185	0.9724	0.2461	7.7784	0.9798
5	0.2276	9.8880	0.9694	0.2140	11.418	0.9893
6.25	0.2202	9.5820	0.9582	0.2339	10.365	0.9964
7.5	0.2198	7.7461	0.9477	0.2430	8.0823	0.9795
8.75	0.2200	10.488	0.9700	0.2050	9.8405	0.9599
10	0.2170	10.800	0.9832	0.2540	6.9051	0.9876
12.25	0.2200	9.6475	0.9959	0.2590	5.5310	0.9889
13.75	0.2160	10.550	0.9806	0.2550	8.6578	0.9638

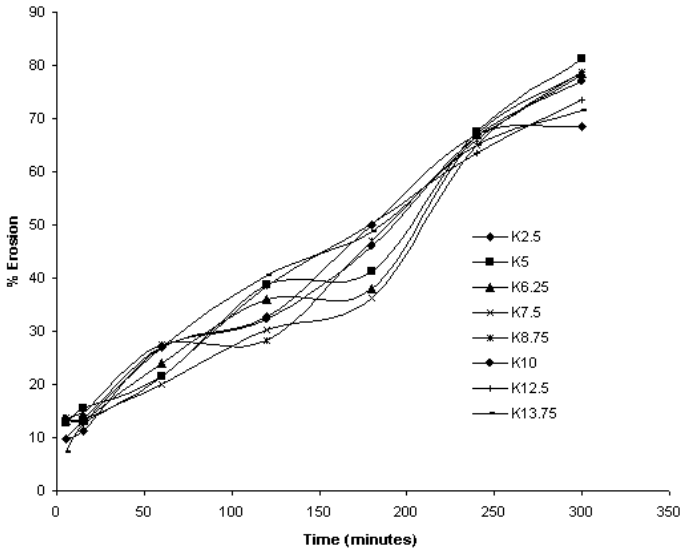

Figure 5. Erosion profiles of plain matrices.

There was a sudden increase in erosion, but matrices containing more than 8.75% wt/wt potassium chloride showed linear increase in erosion. The results of drug-loaded matrix erosion are shown in Figure 6. The drug-loaded matrix without potassium chloride showed significant decrease in erosion rate. This result may be attributed to increased water uptake and, in turn, matrix cohesion due to incorporation of drug. For matrices containing potassium chloride, the erosion profile of those containing 5% wt/wt and 6.25% wt/wt followed complete linearity, whereas other batches showed a sudden rise in erosion. Water-uptake and erosion studies indicated that the concentration of potassium chloride significantly affects water uptake but not erosion. Metformin HCl also showed significant effect on water uptake and erosion. Thus, it is necessary to further elucidate the mutual effects of both the components on drug release. Hence release data were obtained to study the effect of drug and potassium chloride on mutual release.

Release Study

Changes in the amount of KCl remaining in plain and drug-loaded matrices are shown in Figures 7 and 8, respectively. In both cases, the amount of KCl retained in the matrix increased with the concentration of KCl added. Release of KCl increased significantly in the presence of drug for batches containing up to 7.5% wt/wt KCl. At higher concentrations, release rate was independent of KCl concentration. This result may be due to reduction in matrix cohesivity at higher KCl concentrations.

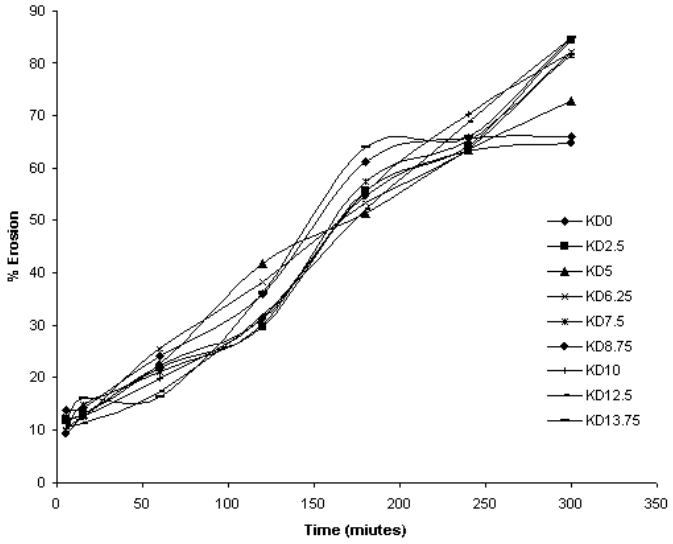

Figure 6. Erosion of drug-loaded matrices.

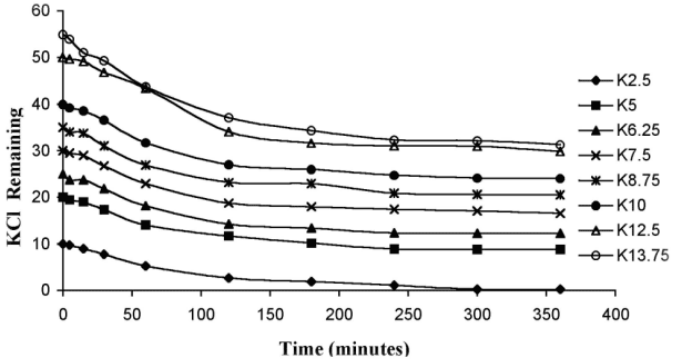

Figure 7. Release profiles of potassium chloride from plain matrices.

Drug release from the matrix system was found to decrease with KCl concentration up to 5% wt/wt, above which the drug release increased again (Figure 9). A previous report on the effect of KCl concentration on theophylline, a neutral drug, showed an increase in drug release due to a decrease in matrix cohesivity after 8% wt/wt[18]. Thus concentration of KCl hampering matrix cohesivity has been decreased to 5% wt/wt in presence of cationic drug metformin HCl. The drug may compete with KCl for carrageenan binding, causing increase in KCl release. Hence, matrix cohesivity was reduced at lower KCl concentration because of a significant amount of other cation present in the system. Thus, optimum KCl concentration was found to be 5% wt/wt. Furthermore, it may be hypothesized that charge and size of cation may also the affect matrix property and, in turn, release of KCl and drug.

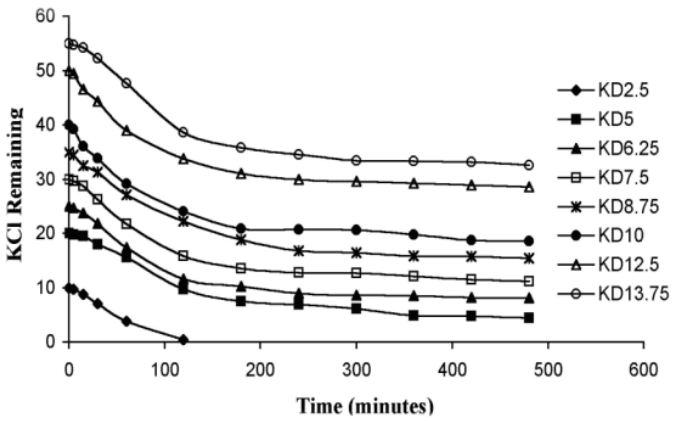

Figure 8. Release profiles of potassium chloride from drug-loaded matrices.

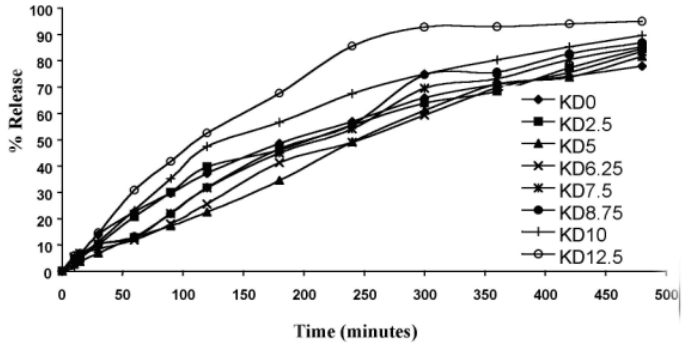

Figure 9. Release profile of drug from carrageenan matrices.

CONCLUSION

It may be concluded from the present study that cationic drug significantly affects water uptake and erosion of carrageenan matrices. In the presence of metformin HCl, the cohesivity of matrices was reduced above 5% wt/wt KCl content. Studies on the effect of size and charge on cationic drug may further elucidate the cause of this effect.

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