Acrylamide-Grafted-Acacia Gum Polymer Matrix Tablets as Erosion-Controlled Drug Delivery Systems

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ABSTRACT: Acrylamide was grafted onto acacia gum in different ratios (1 : 1, 1 : 3, and 1 : 5). The graft copolymers formed were characterized by FTIR, rheological measurements, and differential thermal analysis. Tablets were prepared from these polymers loaded with two antihypertensive drugs, viz., diltiazem hydrochloride and nifedipine. The *in vitro* release experiments were carried out in simulated gastric and intestinal conditions. The graft copolymer prepared in the ratio 1 : 5 of acacia gum : acrylamide matrix was found to be a suitable matrix to investigate the controlled release of diltiazem hydrochloride and nifedipine. The drug release continued up to 6 and 14 h, respectively, for diltiazem hydrochloride and nifedipine. The release mechanism was investigated by using the mathematical equations proposed by Higuchi, Hixson-Crowell, and Kopcha. Based on the release kinetics data, a correlation was attempted between the erosion-controlled release and the dissolution-controlled release. J Appl Polym Sci 93: 2245–2253, 2004

Key words: acacia gum; grafting; controlled release tablets; diltiazem hydrochloride; nifedipine

INTRODUCTION

Among all the routes of drug administration that have been explored for the development of controlled-release (CR) systems, the oral route has by far achieved the most attention and success. The goal of oral CR products is to achieve better therapeutic success than with the conventional dosage forms of the drug. Different types of sustained release formulations have been developed.[1–6] Of these, CR tablets were proved to be the most efficient oral drug delivery systems in view of the simple manufacturing technology[7–11] and due to the possibility of using a variety of new types of polymers. Among the many hydrophilic polymers used as CR devices, natural polymers have gained widespread popularity due to their abundant availability, biocompatibility, and nontoxic nature. Drug release from such matrices depends upon their swelling and erosion characteristics. If the rate of swelling is higher than the rate of erosion, then drug release is mainly controlled by a diffusive transport mechanism. Hydroxypropyl-methylcellulose (HPMC)-based matrices are the best examples of such systems.[12–16] On the other hand, if swelling and erosion can occur simultaneously, then the release becomes erosion controlled. Similarly, sodium carboxymethylcellulose (NaCMC) is another commonly used polymer to develop erosion-controlled systems.[15–18] Since drug release from the swelling-controlled matrix is governed by factors such as hydration, gelation, diffusion, and partial erosion, achieving zero-order release may be difficult. However, in erosion-controlled systems, one can easily achieve zero-order release. Other matrices used in these applications are natural gums such as xanthane gum and luwcost bean.[19,20]

In the present study, we have developed the graft copolymers of acrylamide (AAm) with acacia gum (AG). The latter is a natural polymer comprising of (−)-arabinose, (+)-galactose, (−)-rhamnose, and (+)-glycuoronic acid. It is conventionally used as a tablet binder. The AG is grafted onto polyacrylamide (pAAm) in different ratios to investigate the effect of grafting on the drug-release characteristics. To test the effectiveness of these matrices as oral drug delivery vehicles, we have chosen two model antihypertensive drugs, viz., diltiazem hydrochloride (DIL) and nifedipine (NFD). Of these, DIL is water-soluble while NFD is water insoluble. DIL has a very short plasma life[21] of 4 h, hence, it requires multiple daily dosing if used as a conventional dosage form. NFD has a plasma half-life[22] of 3–4 h. Thus, there is a need to develop CR formulations for these drugs to increase the patient compliance, leading to an improved therapy. Tablets were punched from these matrices after incorporating

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TABLE I
Synthetic Details of Polyacrylamide-*grafted*-Acacia Gum

Polymer type	Mass of polymer (g)	Mass of AAm (g)	Mass of initiator (g)	% Grafting	Grafting efficiency	% Conversion of AAm
AG (1:0)	0	0	0	0	0	0
AG-1 (1:1)	2	2	0.15	94.5	47.2	94.5 ± 2
AG-2 (1:3)	2	6	0.15	278	73.6	92.8 ± 2
AG-3 (1:5)	2	10	0.15	459	73.5	91.8 ± 2

DIL and NFD. The *in vitro* release experiments were performed to seek a correlation between release kinetics and matrix erosion of the polymers. Furthermore, the release data were fitted to different mathematical equations proposed earlier by Kopcha et al.,[23] Hixson-Crowell,[24–26] and Higuchi[27] to understand the mechanistic aspects of the drug release from the tabletted polymeric matrices. To the best of our knowledge, the drug-loaded polymeric systems of this study have not been previously investigated.

EXPERIMENTAL

Materials

Analytical grade samples of acrylamide, potassium dihydrogen phosphate, sodium hydroxide, ceric ammonium nitrate, and hydrochloric acid were purchased from S. D. Fine Chem. Ltd., Mumbai, India. The acacia gum used was of laboratory grade sample, purchased from S. D. Fine Chem. Ltd.. Diltiazem hydrochloride and nifedipine were of USP grade and were obtained as gift samples from Torrent Pharmaceuticals, Ahmedabad, India. Double-distilled water was used throughout.

Synthesis of polyacrylamide-*grafted*-acacia gum (pAAm-*g*-AG)

Acacia gum (2 g) was dissolved in 50 mL of water, stirred for 24 h, and deaerated by passing nitrogen gas for about 2 h. The required amount of AAm (see details in Table I) was added and stirred for another 2 h at 70°C. To this, 25 mL of solution containing 0.15 g of ammonium persulfate (initiator) was added and stirred for another 3 h. While preparing the graft copolymers, we observed that the solution viscosity increased considerably when higher concentrations of acrylamide were used, i.e., AG-2 (1 : 3 ratio of acacia gum to acrylamide) and AG-3 (1 : 5 acacia gum to acrylamide). This resulted in some difficulty in achieving uniform mixing. To decrease the viscosity, we added 50 mL of distilled water in aliquots of 10 mL each time over the period of 3 h. The reaction mixture was cooled and a pinch of quinhydrone was added to arrest the reaction. Acetone then was added as a nonsolvent to precipitate the polymer, which was washed with 30% of aqueous methanol to remove the unreacted monomers and the homopolymer of acrylamide. The solid polymer obtained was dried at 40°C in a vacuum oven. The % grafting, % grafting efficiency, and % conversion of acrylamide were calculated, respectively, using the following equations.

$$\%\ \text{Grafting} = \frac{\text{Mass of acrylamide in the polymer}}{\text{Mass of graft polymer}} \times 100 \quad (1)$$

$$\%\ \text{Grafting efficiency} = \frac{\text{Mass of graft polymer}}{\text{Mass of (polymer + acrylamide)}} \times 100 \quad (2)$$

$$\%\ \text{Conversion} = \frac{\text{Mass of acrylamide in the polymer}}{\text{Mass of acrylamide taken}} \times 100 \quad (3)$$

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of the pure acacia gum and graft copolymers were taken using a Nicolet, Model Impact 410 Madison, WI. Polymers were crushed in a mortar with KBr to make pellets under a hydraulic pressure of 300 kgf/cm^2. FTIR spectra were taken in the wavelength range of 400 to 4,000 cm^{-1}.

Rheological measurements

The 20, 10, 10, and 5% aqueous solutions of AG, AG-1, AG-2, and AG-3 polymers were prepared and rheological measurements of these solutions were performed using the Brookfield Rheometer (Model DV-III) with a UL-Adapter between 10 and 75 rpm. The bath temperature was maintained constant at 30°C by circulating water into the rheometer jacket using a constant temperature circulating bath (Grants, Model Y14, UK).

Differential thermal analysis (DTA)

DTA analyses of pure acacia gum and graft copolymers were performed using SICKO, Model TG/DTA-320, Japan. About 4 mg of the sample was taken and heated at the rate of 10°C/min under a constant flow

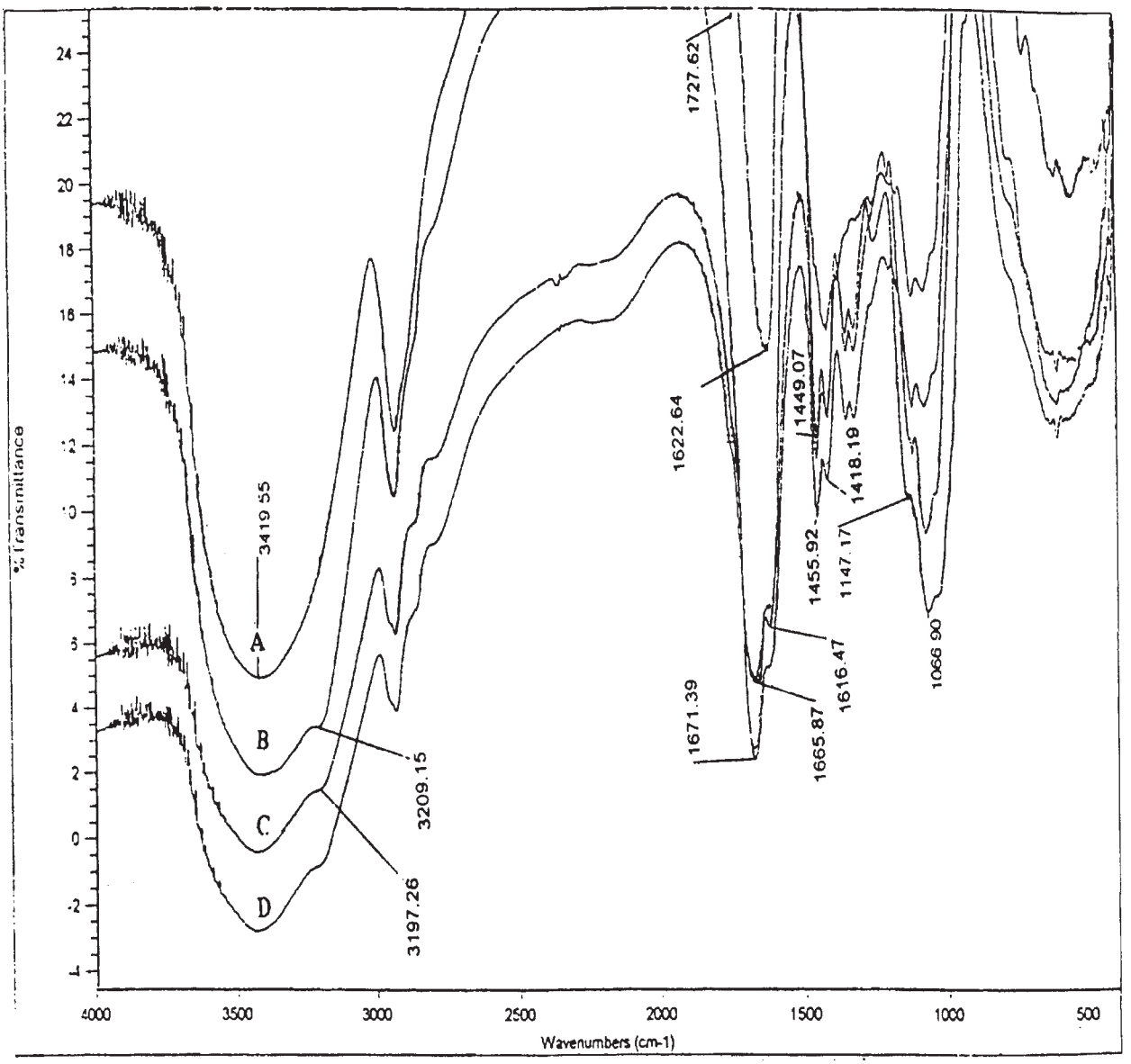

Figure 1 FTIR spectra of (A) pure AG, (B) AG-1, (C) AG-2, and (**D**) AG-3 copolymers.

of nitrogen. Spectra were recorded as a function of temperature with the change in heat flow.

Preparation of drug-loaded tablets

The required amount of the polymer was dissolved in distilled water. To maintain uniform distribution of the drug in the polymer, 90 mg of DIL or 10 mg of NFD was added independently to the respective polymer solutions and stirred for 2 h. The amount of drug to be added was selected to match the dosages that are comparable with the commercial products. To avoid the loss of drug during precipitation, the solution was freeze dried (Freeze Drier, Model, 3DL, Jouan, France) at −45°C. A fine powder was obtained in the case of pure AG and AG-1 formulations, but with formulations AG-2 and AG-3, the freeze-dried product was in the form of flakes. For the compaction of freeze-dried products, we kept the flakes in a 80% RH chamber for about 12 h and samples were dried at 50°C. Upon further crushing, we obtained flakes of smaller size, which were used for punching tablets.

Tablets were formed using an IR hydraulic pellet maker (Riken Seiki Co. Ltd., Japan) under a pressure of 300 kgf/cm^2 applied uniaxially for 15 s of dwell time. Initially, a die of 1.28 cm was filled with the powder by applying a small pressure; then 300 kgf/cm^2 of hydraulic pressure was applied manually at a controlled rate until maximum pressure was attained. The compression behavior of tablets was studied by calculating the apparent density of the tablet using mass and volume measurements of the tablets. Tablets were evaluated for hardness by using a Pfizer-type hardness tester.

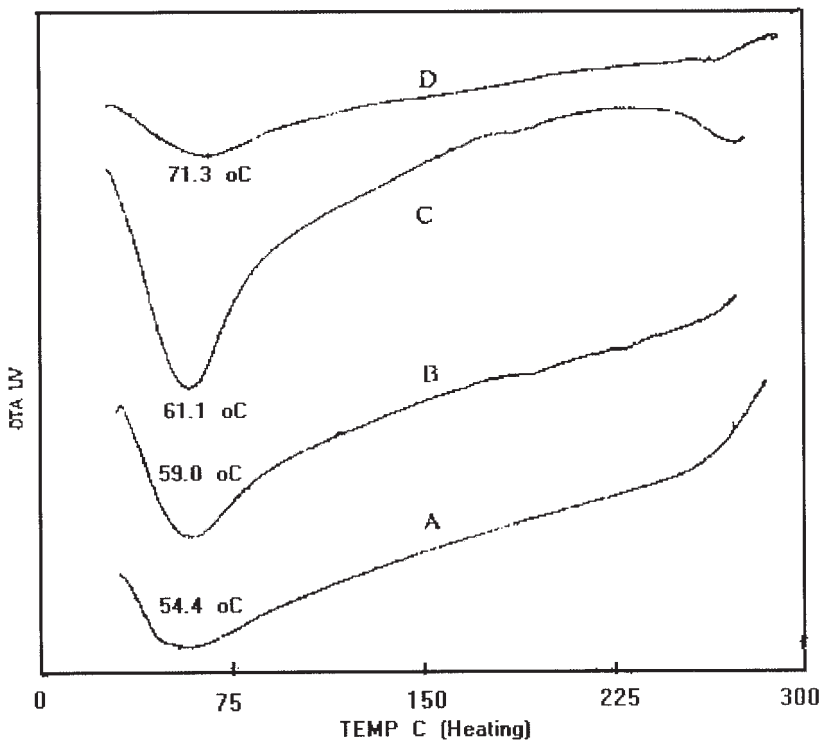

Figure 2 TGA thermograms of (A) pure AG, (B): AG-1, (C): AG-2, and (D) AG-3 copolymers.

In vitro release

To study the release kinetics of tablets, *in vitro* release experiments were carried out in triplicate for each batch of tablets using a Tablet Dissolution Tester (Desotest, LabIndia, India) at 37 ± 0.2°C. Three tablets of each formulation were subjected to dissolution in the simulated gastric condition and intestinal conditions using the USP paddle method at 100 rpm. For DIL-containing formulations, the simulated gastric media was 0.1*N* HCl, while the simulated intestinal media was phosphate buffer, pH 7.4. For NFD-containing formulations, the simulated gastric media was 0.1*N* HCl with 0.1% sodium lauryl sulfate, while the simulated intestinal media was phosphate buffer, pH 7.4, with 0.1% Tween-80 as a surfactant. The surfactants used to study the dissolution of NFD were helpful in increasing the solubility of the released drug. To avoid having the tablet stick to the bottom of the jar and to allow it to suspend freely in the dissolution media, the tablet was placed in a nylon mesh of 200-μm pore size and tied to the paddle using the nylon thread. A 10-mL aliquot of the sample was withdrawn at regular intervals of time and 10 mL of the same solution maintained at 37 ± 0.2°C was replaced back to the dissolution vessel to maintain sink conditions. The withdrawn sample was analyzed for the amount of drug released using a UV-VIS spectrophotometer (Secomam, Model Anthelie, France) at λ_{max} value of 238 nm. For DIL, λ_{max} was set at 237.3 nm and, for NFD, it was set at 238. However, while using the UV instrument, the absorbance was measured at 238 nm for both the drugs since the differences were negligible.

Polymer matrix erosion

Polymer matrix erosion was studied by using the dissolution apparatus for all formulations in the same way as was done for release studies of the drugs mentioned before. Here, a 50-mL aliquot was withdrawn from the dissolution vessel at regular time intervals (same amount of fresh solution was replaced), dried in a previously weighed crucible at 60°C, and weighed on a top-loading single-pan digital microbalance (model AE 240, Switzerland) sensitive to ± 0.01 mg. Drying and weighing steps were repeated until constant mass was attained.

RESULTS AND DISCUSSION

Synthesis of pAAm-*g*-AG

Grafting of AG was done by using polyacrylamide in the presence of ammonium persulfate as an initiator. Concentration of the initiator, 7.5 mM, was found to be optimum for the persulfate-induced grafting reaction.[28] The generation of the free radical site by abstracting the hydrogen from the –OH group of the polymer facilitated the grafting reaction. The monomer conversion was up to 94%. Formulation details are given in Table I.

Polymer characterization

FTIR spectra of the pure AG and pAAm-*g*-AG graft copolymers in three different ratios of AG and AAm

TABLE II
Physical Properties of Tablets

Formulation code	Drug incorporated (mg)	Tablet density (g/cm^3)	Tablet hardness ± 0.5 (kg)
AG-DIL	90 ± 1	1.354 ± 0.02	10
AG-1DIL	90 ± 1	1.291 ± 0.01	13
AG-2DIL	90 ± 1	1.242 ± 0.01	12
AG-3DIL	90 ± 1	1.205 ± 0.01	11
AG-NFD	10 ± 0.25	1.405 ± 0.02	10.5
AG-1NFD	10 ± 0.25	1.295 ± 0.02	12.5
AG-2NFD	10 ± 0.25	1.254 ± 0.02	13.0
AG-3NFD	10 ± 0.25	1.259 ± 0.01	13.0

are presented in Figure 1. In the FTIR spectra, (A) refers to pure AG while (B), (C), and (D), respectively, represent the spectra of copolymers, AG-1, AG-2, and AG-3. In case of pure AG, a broad band appearing at ~ 3,420 cm^{-1} corresponds to –OH stretching vibrations of AG. A sharp peak at 1,622 cm^{-1} is due to C=O stretching of the carboxylic group of AG. In the spectra of graft copolymers, a new shoulder peak appeared at ~ 3,200 cm^{-1} and a sharp peak at ~ 1,670 cm^{-1}, respectively, correspond to –NH and C=O stretching vibrations, thus confirming the grafting reaction. The new peak observed at ~ 1,450 cm^{-1} corresponds to the –CN bending vibrations, which further supports the grafting reaction.

From the rheological measurements, it was found that viscosity of 20 mass % of pure AG solution at a shear rate of 61 is 18.8 mPa.s, while viscosities of 10 mass % of AG-1 and AG-2 and 5 mass % of AG-3 solutions were found to be 73.2, 103, and 71.1 mPa.s, respectively. This increase in viscosity is attributed to an increase in molecular mass of the polymer leading to a complex entanglement of the graft copolymeric chains acting as temporary crosslinkers. This might have hindered the hydrodynamic flow of the solution, thus confirming the grafting reaction.

The TG/DTA thermograms of pure AG and graft copolymers are displayed in Figure 2. For pure AG (Fig. 2A), an endothermic peak corresponding to a T_g of AG was observed at 54.4°C. In the case of graft copolymers, this peak is shifted at higher temperatures, i.e., 59, 61.1, and 71.3°C, respectively, for (B) AG-1, (C) AG-2, and (D) AG-3, which also confirms the grafting reaction.

Preparation of drug-loaded tablets

The CR tablets were prepared by punching 385 ± 5 mg drug-loaded polymers in the case of DIL and 400 ± 5 mg drug-loaded polymers in the case of NFD using a hydraulic pressure of 300 kgf/cm^2. This pressure was enough to produce the slow release rates of the drug from the matrix tablets because of the more compact nature of the void-free tablets.[29] Tablets prepared in this study contain 90 ± 1 mg of DIL or 10 ± 0.25 mg of NFD. Dimensional details and apparent density of the tablets are given in Table II for each formulation. A decrease in apparent density from AG to AG-3 tablets suggests the decreased compressibility of the formulated tablets.

In vitro release

Both of the drugs chosen in this study have a plasma half-life between 3 and 4 h and hence are supposedly the best candidates to enhance their release rates by using the graft polymeric matrices developed in this study. Of the two drugs, DIL is water soluble, but NFD is water insoluble. Absorption of poorly soluble drugs is often dissolution rate-controlled and such drugs must be typically stable in the pH range of 1 to 8. In the present study, the drug-release profiles from tablets were investigated by carrying out dissolution experiments in simulated gastric (0.1*N* HCl) and intestinal (pH 7.4) conditions for DIL-containing formu-

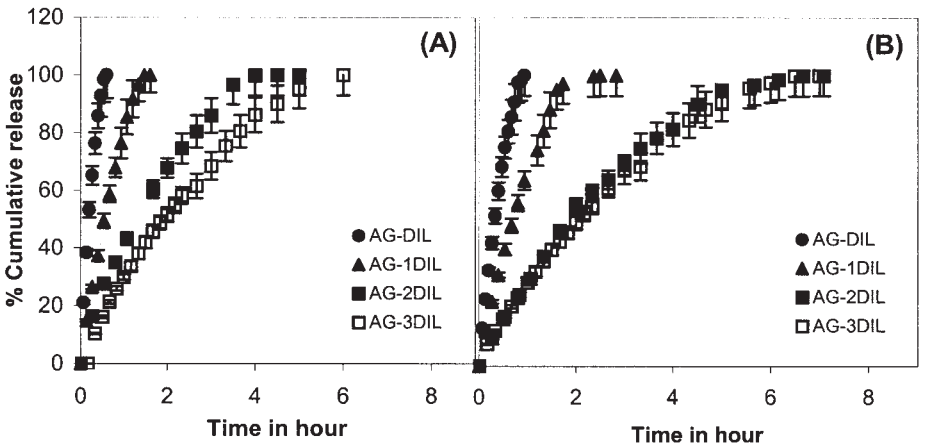

Figure 3 Plot of % cumulative release versus time in (A) 0.1*N* HCl and (B) pH 7.4 buffer for (●) AG-DIL, (▲) AG-1DIL, (■) AG-2DIL, and (□) AG-3DIL (n = 3).

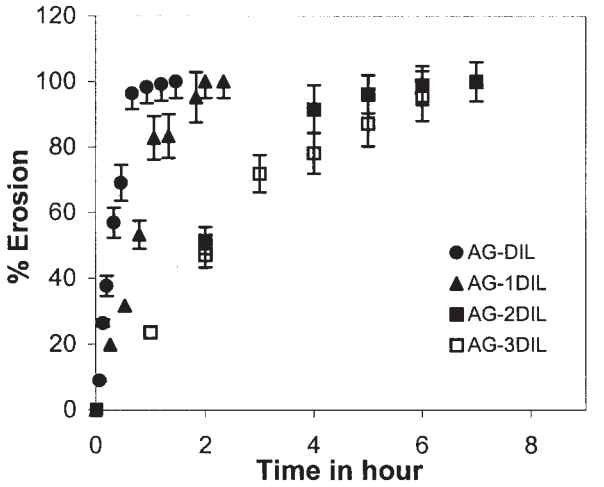

Figure 4 Plot of % erosion versus time for (●) AG-DIL, (▲) AG-1DIL, (■) AG-2DIL, and (□) AG-3DIL (n = 3).

lations. In the case of NFD, which is less soluble in water, its dissolution was performed in 0.1*N* HCl containing 0.1% sodium lauryl sulfate taken in phosphate buffer, pH 7.4, with 0.1% Tween-80 so as to enhance its solubility toward water. The process of tablet disintegration and dissolution was possible for the water-insoluble NFD under these conditions.

The % cumulative release of DIL from different formulations is compared in Figure 3 in 0.1*N* HCl and pH 7.4 buffer solutions. The drug release was fast in AG- DIL and AG-1DIL formulations in comparison to a much slower release rate observed for AG-2DIL and AG-3DIL formulations. The release data clearly suggest that pure AG is not an effective matrix in controlling the release of DIL, which is rather highly water soluble. However, grafting of acrylamide onto acacia gum helped in increasing the release rate of the polymer to some extent as shown by the AG-DIL matrix. On the other hand, a considerably slower release rate is observed in AG-2DIL and AG-3DIL formulations. This suggests that, with increasing grafting, the matrix becomes more rigid and, hence, the free volume space within the polymeric matrix also reduces, thereby resulting in lower drug-release rates. A considerable decrease in the release of DIL has occurred in pH 7.4 buffer solutions compared to 0.1*N* HCl solutions. This may be due to the fact that, at higher pH, the polymer matrix might have acquired higher rigidity, thereby influencing the polymer chain conformation. It may be noted here that Boniferoni et al.[18] made similar observations in case of NaCMC gels wherein they studied the influence of the medium on dissolution–erosion behavior of NaCMC and on the viscoelastic properties of the gels. Their results are in fair agreement with the present data.

Erodible polymers as vehicles for drug delivery are attractive because surgery to remove the implanted device is unnecessary. Drugs may be dissolved or dispersed uniformly throughout the matrix or incorporated within an erodible system. In the latter case, the drug may be released by degradation or erosion of the polymer matrix. In such a system, the polymer matrix must physically erode and, therefore, lose its mass as a consequence of dissolution in the presence of aqueous media, in which AG is soluble. To understand the drug-release mechanism, the polymer matrix erosion was studied in distilled water for DIL-containing formulations. The % erosion results of the DIL-containing tablets are displayed in Figure 4. It is observed that the erosion rate decreased with increased grafting of the polymer. This is logical because pure AG is more soluble in water than its grafted matrices with acrylamide. Other studies in the literature have described polymer matrix erosion mechanisms for many drug–polymer systems.[30,31] However, in the present systems, erosion could be based on the degradation of water-soluble AG. Such a release could occur by either surface or bulk erosion mechanisms, which are directly related to the solubility and dissolution rates of the polymer matrix in the medium of interest. In our further attempt to establish a correlation between drug-release and erosion rate, we have plotted (see Fig. 5) the results of % cumulative release versus % erosion rate for AG-3DIL matrix formulations. For all formulations, a correlation coefficient, r^2 of 0.96 to 0.99 was observed, suggesting that drug release from the present systems is predominantly erosion controlled.

The release profiles of water-insoluble NFD drug-loaded formulations in 0.1*N* HCl and pH 7.4 phosphate buffer solutions are displayed in Figure 6. In AG and AG-1NFD formulations, a similar trend as observed for DIL was also observed for NFD-based formulations. In AG-2NFD and AG-3 NFD formulations, the release was controlled about twofold times greater than that of DIL-containing formulations. Since NFD

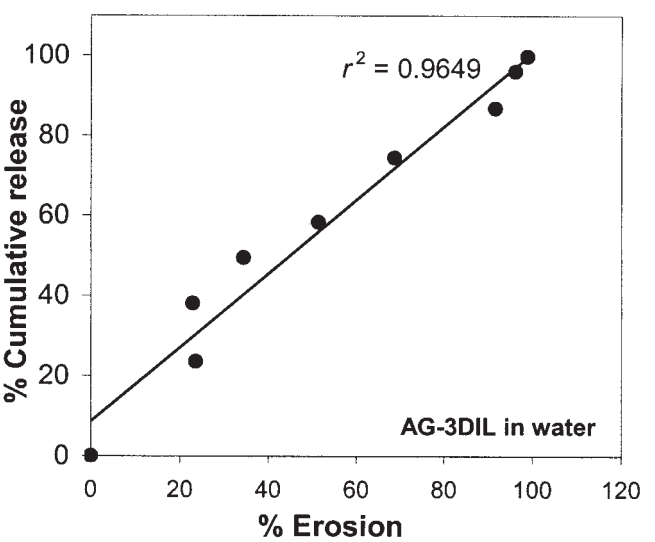

Figure 5 Plot of cumulative release versus % erosion (for AG-3DIL) (n = 3).

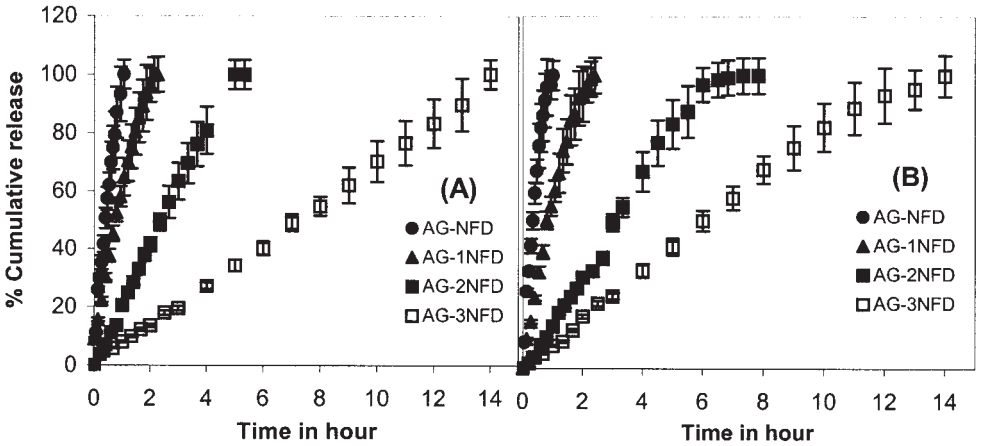

Figure 6 Plot of % cumulative release versus time in (A) 0.1*N* HCl and (B) 7.4 pH buffer for (●) AG-NFD, (▲) AG-1NFD, (■) AG-2NFD, and (□) AG-3NFD (n = 3).

is a hydrophobic drug, it acts as an inert filler in the polymer matrix, thus resulting in a slow polymer chain relaxation. Erosion study carried out for these formulations (see data displayed in Fig. 7) and correlated with the cumulative release data (see Fig. 8) reveals the predominance of the erosion mechanism for the release of the drug.

We could also advance alternative explanations. For instance, the matrix dissolution controlled delivery is generally used to achieve a dissolution control. Hence, the rate of drug availability can be controlled by the rate of penetration of the dissolution media into the polymer matrix. This rate of penetration of the dissolution media is further controlled by the porosity of the tablet matrix and the presence of hydrophobic additives including drug particles and wettability of the tablet. However, porosity of the tablet depends upon the applied compression force while punching the tablets. Size and shape of particles can also affect porosity of the dosage form as well as viscosity (rheological properties) of the dissolution media.

In addition to the study of experimental parameters in characterizing the oral CR formulations, it is equally important to use appropriate theoretical equations to assess the *in vitro* pharmacokinetic parameters. Most important in this regard is the measurement of *in vitro* release rate and its correlation with the *in vivo* dissolution profiles. Despite a large variety of CR dosage forms and variations in drug-release rates, kinetic models that describe drug-release rates are generally of two types, i.e., first order and zero order. Both of these models may have an initial period of rapid drug release conforming to first-order release kinetics. In addition, the diffusion phenomenon also plays an important role in the matrix erosion. However, in the present study, to understand the nature of drug release and to seek its relationship with the drug-diffu-

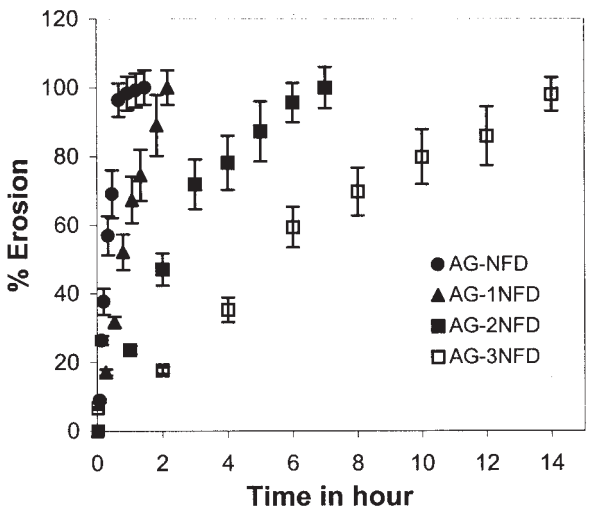

Figure 7 Plot of % erosion versus time in 0.1*N* HCl for (●) AG-NFD, (▲) AG-1NFD, (■) AG-2NFD, and (□) AG-3NFD (n = 3).

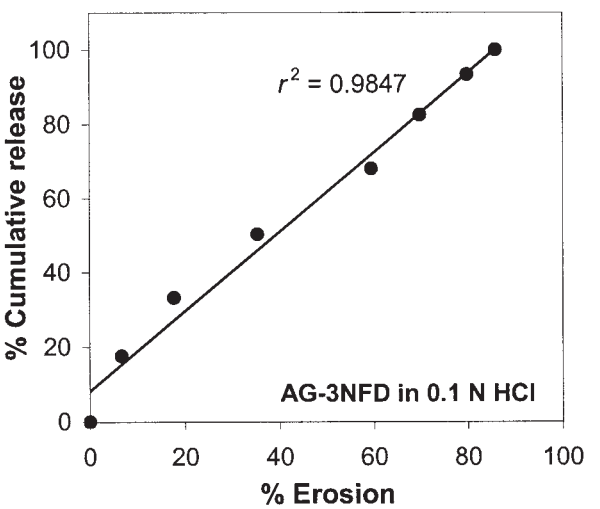

Figure 8 Plot of cumulative release versus % erosion (for AG-3NFD) (n = 3).

TABLE III
Comparison of Parameters of Different Mathematical Equations for AG-DIL and AG-NFD Formulations

Equation	Parameters	Acacia gum : Acryl amide 1 : 0 (Neat AG)	1 : 1 (AG-1)	1 : 2 (AG-2)	1 : 3 (AG-3)
DIL-containing formulations in 0.1*N* HCl					
Kopcha eq. (4)	*A*	43.285	17.242	24.134	21.42
	B	163.67	66.546	17.102	12.48
	A/B	0.2644	0.2591	1.4111	1.7163
	r^2	0.9987	0.9993	0.9994	0.9996
Hixson-Crowell eq. (5)	*c*	70.493	26.29	9.135	7.375
	d	2.078	1.394	3.277	3.176
	r^2	0.9810	0.9933	0.9726	0.9835
Higuchi eq. (6)	*a*	139.45	85.92	52.53	47.148
	b	−7.186	−10.513	−7.471	−10.05
	r^2	0.9687	0.9513	0.9833	0.9770
DIL-containing formulations in pH 7.4					
Kopcha eq. (4)	*A*	20.713	16.00	12.83	15.57
	B	117.38	52.27	16.59	13.16
	A/B	0.1765	0.3061	0.7734	1.1831
	r^2	0.9998	0.9997	0.9965	0.9965
Hixson-Crowell eq. (5)	*c*	41.21	19.37	6.543	6.183
	d	2.207	2.045	2.776	2.915
	r^2	0.9834	0.9869	0.9731	0.9767
Higuchi eq. (6)	*a*	116.12	76.97	46.44	44.19
	b	−12.47	−11.66	−12.14	−12.19
	r^2	0.9642	0.9621	0.9743	0.9752
NFD-containing formulations in 0.1*N* HCl					
Kopcha eq. (4)	*A*	34.18	6.71	−2.71	0.5206
	B	71.07	47.88	22.65	6.719
	A/B	0.4798	0.1401	−0.1196	0.0775
	r^2	0.9935	0.9989	0.9989	0.9979
Hixson-Crowell eq. (5)	*C*	34.27	16.12	6.994	2.287
	D	2.305	1.313	−0.2405	0.189
	r^2	0.9864	0.9923	0.9984	0.9991
Higuchi eq. (6)	*a*	101.35	73.04	45.47	26.69
	b	−10.84	−16.00	−19.01	−17.99
	r^2	0.9633	0.9531	0.9236	0.9344
NFD-containing formulations in pH 7.4 buffer					
Kopcha eq. (4)	*A*	19.89	8.20	−5.311	−0.6723
	B	117.16	49.63	19.09	8.663
	A/B	0.1698	0.1652	−0.2782	−0.0772
	r^2	0.9928	0.9952	0.9922	0.9985
Hixson-Crowell eq. (5)	*C*	43.69	17.04	5.637	2.762
	D	1.541	1.399	−0.825	0.004
	r^2	0.9862	0.9891	0.9943	0.9987
Higuchi eq. (6)	*a*	115.7	74.09	29.69	42.43
	b	−12.71	−15.00	−19.15	−22.56
	r^2	0.9543	0.9525	0.9375	0.9066

sion rates, we have fitted the release data to mathematical equations proposed by Kopcha[23] [eq. (4)], Hixson-Crowell[24] used recently by others[25,26] [eq. (5)], and Higuchi[27] [eq. (6)] as given below.

$$M = At^{1/2} + Bt \quad (4)$$

$$100^{1/3} - (100 - Q)^{1/3} = ct + d \quad (5)$$

$$Q = at^{1/2} + b \quad (6)$$

Here, M ($\leq$ 70%) and Q ($\leq$ 90%) are the % of drug released at time, a, b, c, and d are constants; and A and B are, respectively, diffusion and erosion terms.[23] Results of the estimated parameters are compiled in Table III.

The release data were fitted to the Kopcha equation with a statistical fitting correlation coefficient, r^2 value of greater than 0.992, which monitored the diffusion and erosion ratio, A/B. If $A/B = 1$, the release mechanism is controlled by both diffusion and erosion phenomena equally. If $A/B > 1$, then diffusion prevails, while for $A/B < 1$, erosion is predominant.[32] In all cases, except the AG-3DIL formulation studied in 0.1*N* HCl, the ratio A/B is < 1, indicating the predominance of erosion on drug-release rates rather the diffusion aspects. Even though the diffusion term, A, is greater

than erosion term, *B*, in AG-3DIL formulations, no swelling of the matrix occurred during the entire dissolution experiment. Instead, dimensions of the tablets decreased with time. However, the process of polymer dissolution appears to be much slower compared to other formulations because of the longer chain length of the graft copolymers used. Hence, even though matrix erosion is observed, a considerable amount of DIL might have diffused from the hydrated layer of the matrix tablet. Further, the remaining amount of the drug might have been released along with the dissolving hydrated layer of the matrix. Supporting the above hypothesis, the value of $A/B < 1$ (predominance of erosion for drug release) is observed when a water-insoluble drug is loaded in the same polymer matrix. These data can very well be fitted to the Hixson-Crowell model rather than the Higuchi model with the r^2 values ranging between 0.973 and 0.999, thereby supporting the predominance of erosion drug release from the matrix tablets employed.

CONCLUSION

The present study is an effort to develop a bench-scale methodology to prepare the drug-loaded polymeric tablets by combining the properties of a natural polymer such as acacia gum with a synthetic polymer such as polyacrylamide. Grafting of acrylamide onto acacia gum was important to the development of this concept. Grafting was achieved by using different ratios of the monomers, which produced polymers with different release characteristics. These polymers were further processed to form tablets loaded with both water-soluble (diltiazem hydrochloride) and water-insoluble (nifedipine) drugs. Release of both the drugs was well controlled for more than 6–14 h, i.e., much longer than their intrinsic plasma half-life The *in vitro* release data were analyzed using the equations of Kopcha, Hixson-Crowell, and Higuchi to acquire a deeper understanding of the erosion-controlled release of the drugs from the tablets. Theoretical analysis suggests that erosion is the governing factor in controlling the drug-release kinetics. At higher grafting ratios of acrylamide, tablet erosion can be controlled as well as the release kinetics. Results of this study are helpful in undertaking the scale up operations if one could establish a close interrelationship between laboratory *in vitro* studies and the *in vivo* studies on animal models. These efforts are currently being investigated in our laboratories.

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