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Evaluation of acrylamide-grafted-xanthan gum copolymer matrix tablets for oral controlled delivery of antihypertensive drugs ☆

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Abstract

The present study was conducted to investigate the utilization of xanthan-grafted copolymer of acrylamide (AAm) as a controlled release (CR) matrix for antihypertensive drugs such as atenolol (ATL) and carvedilol (CDL). Graft copolymerization of AAm onto xanthan gum (XG) was carried out by taking two different ratios of XG to AAm (1:5, 1:10) by free radical initiation polymerization using ceric ammonium nitrate (CAN). Tablets were prepared from plain XG, its grafted copolymer with AAm, and other excipients by incorporating ATL and CDL, which have different physicochemical properties. *In vitro* release studies were performed in simulated gastric fluid (SGF) followed by simulated intestinal fluid (SIF) without enzymes at 37 °C. Effect of grafting ratio, drug loading, and other excipients on the release kinetics were evaluated for both the class of drugs. The release time increased with increasing grafting ratio and swelling was carried out in SIF at 37 °C, which indicated that XG exhibited maximum swelling compared to graft copolymers. The surface morphology of plain XG, modified XG, and tablet surfaces was studied by scanning electron microscopy (SEM), which revealed that grafting introduced major changes on surface morphology as well as size of the particles. The nature of drug transport through matrix tablets followed the non-Fickian (anomalous) trend. Statistical analyses of release data were performed using analysis of variance (ANOVA) method, which indicated a significant difference in the release rate of ATL from the tablets prepared from XG and the grafted copolymer. The *in vitro* release studies were also carried out on commercial tablet formulations of ATL and CDL. The release rate of CDL containing tablets with XG and grafted copolymer did not show significant difference, whereas CDL containing tablets with XG, grafted copolymer, and commercial formulations have shown significant differences. Matrix tablet formulations along with the excipients were characterized by Fourier transform infrared spectrophotometer (FT-IR), which indicated no interaction between drugs and the polymers.

Keywords: Xanthan; Graft copolymer; Atenolol; Carvedilol; Controlled delivery

1. Introduction

The use of biopolymeric matrix devices to control the release of therapeutic agents has become important in the development of modified release dosage forms (Bhardwaj, Kanwar, Lal, & Gupta, 2000; Billa & Yuen, 2000; Munday & Cox, 2000; Talukdar et al., 1998). The development of improved drug release systems is dependent on the selection of an appropriate carrier capable of controlling the delivery. Responsive polymers, in particular hydrophilic natural carbohydrate polymers, are the promising new versatile carriers for the preparation of oral controlled release (CR) systems (Colombo, Bettini, Santi, & Peppas, 2000; Siepmann & Peppas, 2000). The matrix systems are swellable and can be developed by compression of a hydrophilic polymer with the drug. Their success is linked to carbohydrate polymers, which respond to the presence of water or biological fluids, which can change their structure to form a

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gel layer enabling the drug to be released from the matrix throughout the gastrointestinal tract (GIT) at the desired rate and time (Colombo et al., 2000). Gums from natural sources hydrate and swell when in contact with water and these have been used for the preparation of single unit dosage forms (Toti & Aminabhavi, 2004). The powdered drug is embedded uniformly in a matrix of hydrogel and compressed to form a tablet, a production method that is relatively simple and cheap. Upon contact with biological fluids, water penetrates the tablet, gradually dissolving the drug, which then diffuses out through the tablet. Therefore, in contrast to purely diffusion-controlled drug delivery systems, swelling and polymer dissolution must also be considered (Siepmann & Peppas, 2000).

Xanthan is a commercial hydrophilic polymer, secreted from *Xanthomonas campestris*. The xanthan (see Fig. 1(a)) consists of β-(1 → 4)-D-glucopyranose glucan backbone with side chains of (3 → 1)-α-linked D-mannopyranose-(2 → 1)-β-D-glucuronic acid-(4 → 1)-β-D-mannopyranose on alternating residues. The anionic character of xanthan is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain (Cottrell, Kang, & Kovaca, 1980). Xanthan gum therefore offers a potential utility as a drug carrier because of its inertness and biocompatibility. It is compatible virtually with all salts and solution pH; temperature has very little effect on the viscosity of its gel. It has been reported by many researchers (Munday & Cox, 2000; Talukdar et al., 1998) that XG can be used as an effective excipient for developing CR formulations. Combinations of XG, hydroxypropyl methylcellulose, hydroxypropyl cellulose, and ethylcellulose in enteric-coated tablets have been evaluated for CR applications (Guley, Deneale, & Milosovich, 1982). The rate of drug release was slowed down by decreasing particle size of the gum or by increasing the gum concentration. The release of soluble drugs was mainly via diffusion, whereas sparingly soluble or insoluble drugs were released primarily via erosion. Drug release from XG matrix was slightly faster in acidic media due to more rapid initial surface erosion. After hydration of the gum, drug release was essentially pH-independent. Xanthan gum not only retards *in vitro* drug release and provides time-independent release kinetics, but also it works effectively *in vivo* and establishes the constant drug plasma levels (Baichwal & Staniforth, 1991; Talukdar et al., 1998).

Graft copolymerization of synthetic polymers onto polysaccharide backbone offers one of the best ways to use polysaccharides for a variety of purposes (Goni, Gurruchaga, Valero, & Guzman, 1983). Among the synthetic polymers, acrylics occupy a significant position (Bhabhe, Galvankar, Desai, & Athawale, 1995). Thus, in the past few decades, the wide range of vinyl and other monomers available suggests that grafting is a powerful method of producing substantial modification of polysaccharide properties, thereby enlarging its range of utilization. Native polysaccharides may not be suitable in controlled drug

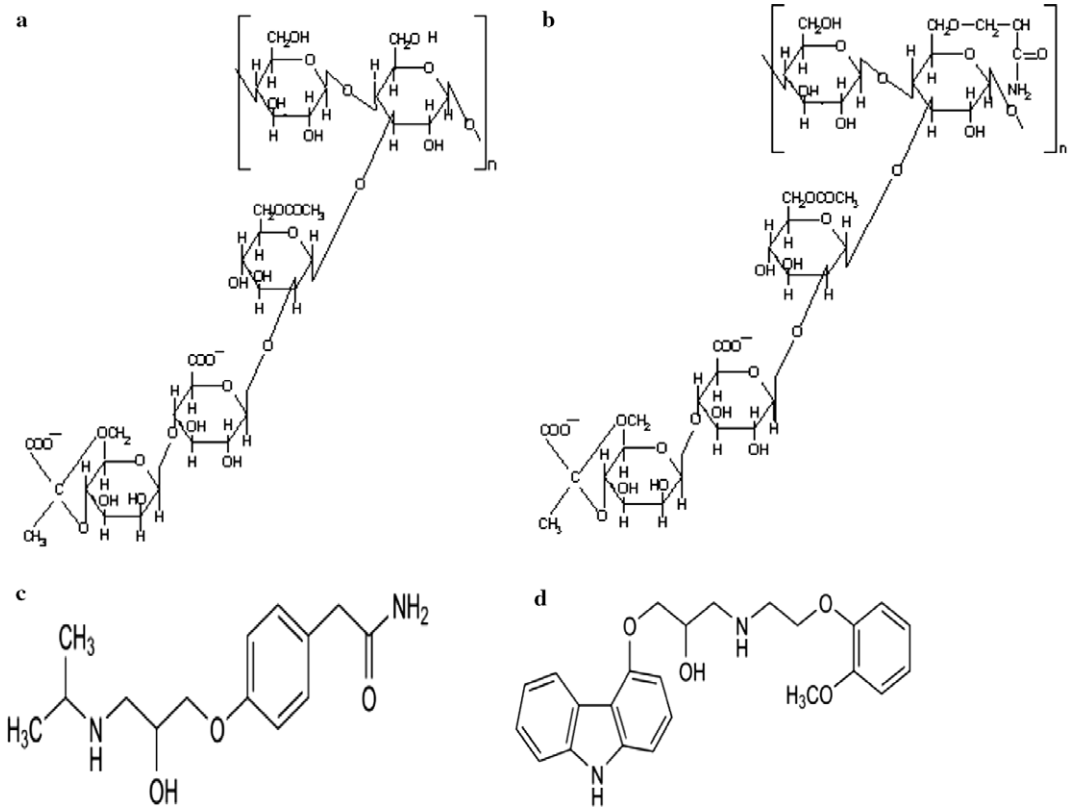

Fig. 1. Structures of (a) XG, (b) grafted copolymer, (c) ATL, and (d) CDL.

delivery systems due to their substantial swelling and rapid enzymatic degradation in biological fluids (Tuovinen, Peltonen, & Jarniven, 2003). Graft copolymerization introduces hydrophobicity and steric bulkiness, which considerably protects the matrix and carbohydrate backbone to retard the drug release. In earlier work (Toti & Aminabhavi, 2004), it was reported that acrylic polymers grafted onto guar gum allowed the CR of drugs. There is still a wide range of acrylic monomers and polysaccharide derivatives that can be tested for such purpose.

Atenolol (ATL) [see Fig. 1(c)], a β-1-selective adrenergic blocking agent, which is prescribed widely in diverse cardiovascular diseases, e.g., hypertension, angina pectoris, arrhythmias, and myocardial infarction (Hoffman, 2001). The drug is frequently indicated in the prophylactic treatment of migraine. However, ATL was reported to be subjected to extensive hepatic first-pass metabolism following the oral administration and has a short biological half-life of 4 h. It is hydrophilic in nature. Administration of conventional tablets of ATL has been reported to exhibit fluctuations in the plasma drug levels, resulting either in the manifestation of side effects or reduction in drug concentration at the receptor site (Sastry, Reddy, & Khan, 1997). Accordingly, studies have been reported on the regulation of drug release by formulating CR systems using hydrophilic matrices (Vázques, Casalderrey, & Duro, 1996), osmotic pumps (Sastry et al., 1997), and transdermal drug delivery systems (Kim & Shin, 2004). Carvedilol, (CDL) (Fig. 1(d)) is an arylethanolamine, which is a racemic mixture of two enantiomers; it has β-adrenoceptor blocking activity and α_1-receptor blocking activity. Carvedilol has been used extensively in patients with hypertension and has been reported to be of benefit in patients with angina or congestive cardiac failure. The drug is well tolerated and has relatively few adverse effects. The drug is highly lipophilic and highly protein-bound. It has a low solubility in gastrointestinal fluids and undergoes extensive first-pass metabolism in the liver, which leads to the low absolute oral bioavailability, which is about 20% in humans (Morgan, 1994). In order to avoid the above-mentioned disadvantages, several formulations have been developed of CDL tablets (Oh, 1999), buccal sprays and capsules (Dugger, 2003), CR dosage forms (Agnihotri & Aminabhavi, 2005), CR solid dispersions dosage forms (Fischer & Bar-Shalom, 2003), a CDL–cyclodextrin complex (Oh, 2003a), and oral suspensions (Oh, 2003b).

The objective of this study is to evaluate the performance of these newly developed pAAm-*g*-XG copolymers as the main components of CR tablets containing drugs of different physicochemical properties. The formulations were prepared using plain XG, grafted copolymers, and other excipients. *In vitro* release studies were performed on matrix tablet formulations in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) at 37 °C to investigate their applications as successful oral dosage formulations. Scanning electron microscopy was employed to investigate the morphology of XG, graft copolymer, and the tablet. The release data have been fitted to an empirical equation proposed by Ritger and Peppas (1987) to understand the mode of drug release; further, results were subjected to analysis of variance (ANOVA). XG, graft copolymer, and tablet formulations were characterized by FT-IR to predict the possible drug–polymer interactions. To the best of our knowledge, systems studied in the present work are not reported earlier.

2. Experimental

2.1. Materials

Atenolol, XG, microcrystalline cellulose (MCC), magnesium stearate, poly(vinylpyrrolidone), and carvedilol were received as gift samples from Medreich Sterilab Ltd., Himalaya Drug Co., Bangalore, and SPARC, Baroda, India. The conventional ATL and CDL tablets of 25 mg dosage were procured from drug house. AAM, CAN, acetone, and methanol were all purchased from s.d. Fine Chemicals, Mumbai, India. Throughout the experiment, double-distilled water was used.

2.2. Graft copolymerization

The graft copolymer derived from AAm and XG was prepared by free radical polymerization. Briefly, 1.0 g of XG was dispersed in 120 mL of water and dissolved overnight under constant stirring in a 250 mL round-bottomed flask. Then, 5 or 10.0 g of AAm was mixed with 30 mL of water, added to XG solution, and stirred for 1 h. A quantity of initiator equivalent to 0.05 mmol was dissolved in 30 mL of water and added to the above solution. Polymerization was carried out at 60 °C under continuous purging of nitrogen gas for 4 h in a thermostatic water bath under constant stirring. After complete polymerization, the reaction mixture was cooled by running under tap water and poured into excess acetone to induce the precipitation. The graft solid polymer formed was washed several times with methanol–water (80:20, v/v) mixture, distilled water to remove the unreacted monomer and reagents. It was then vacuum dried at 40 °C to a constant weight. The % grafting (% G), grafting efficiency (% GE), and % conversion (% C) were calculated by using:

$$\%\ \text{Grafting}\ (\%\ \text{G}) = \left(\frac{W_1 - W_0}{W_0}\right)100, \tag{1}$$

$$\%\ \text{Grafting efficiency}\ (\%\ \text{GE}) = \left(\frac{W_1 - W_0}{W_2}\right)100, \tag{2}$$

$$\%\ \text{Conversion}\ (\%\ \text{C}) = \left(\frac{W_1}{W_2}\right)100, \tag{3}$$

where W_0, W_1, and W_2 denote the weight of XG, graft copolymer, and AAm, respectively.

2.3. Preparation of matrix tablets

The required amount of polymer was mixed with ATL/CDL (25/50 mg/tablet) to get uniform distribution of drug in the polymer. The composition of different formulations along with formulation codes is given in Table 2. Tablets were prepared by using an IR hydraulic pellet maker (Riken Seiki Co. Ltd., Japan) under a pressure of 300 kgf cm^{-2} for 15 s of dwell time uniaxially. Exactly weighed quantity of the powder mixture was filled into a die of 12.8 mm diameter using little pressure and then, hydraulic pressure was applied to form a uniformly compressed tablet. Tablets were evaluated for hardness by using a Pharma test tablet hardness tester (model: ptb 411, Hyderabad, India). Thickness of the tablets was measured by using a vernier caliper.

2.4. Determination of drug content

Five tablets were finely powdered; quantity equivalent to 50 mg of ATL/CDL was accurately weighed and transferred to 100 mL volumetric flask containing 50 mL of methanol. This was allowed to stand for 6 h with an intermittent sonication to ensure complete solubility of the drug. Solutions were made up to volume, filtered, suitably diluted, and estimated for ATL and CDL contents at λ_{max} values of 226 and 240 nm, respectively, using a UV–visible spectrophotometer (Model Anthelie, Secomam, France).

2.5. Swelling studies

The uncoated tablets in a wire basket were put into a 250-mL beaker containing 200 mL of pH 7.4 phosphate buffer and were allowed to swell at 37 °C. Tablets were periodically removed and changes in weight were measured before and during swelling. The swelling ratio was then calculated using:

$$\text{Swelling ratio} = \left(\frac{W_t - W_0}{W_{tab}}\right), \quad (4)$$

where W_{tab} is the weight of the dry tablet (mg), W_t and W_0 are the weights of the tablet and basket at time t (h) and at the beginning, respectively.

2.6. In vitro drug release studies

Dissolution experiments were performed using a fully automated dissolution tester coupled with UV system (Logan Instruments Corp., Model D800, NJ, USA) equipped with six baskets at the stirring speed of 100 rpm maintained at the constant temperature of 37 °C. Drug release studies for ATL tablets were conducted in 500 mL of 0.1 N HCl initially for 2 h, followed by 500 mL of pH 7.4 phosphate buffer. For CDL tablets, the release was conducted only in SIF. The instrument automatically measures the concentration of drug released at particular time intervals by a online UV spectrophotometer coupled with the flow-through cells attached to the instrument and it then puts the solution back into the dissolution bowl. The ATL and CDL concentrations were determined spectrophotometrically at the λ_{max} values of 226 and 240 nm, respectively. These studies were performed in triplicate for each sample and the average values were used in data analysis.

2.7. FT-IR analysis

XG, pAAm-*g*-XG, ATL, CDL and formulations were analyzed by FT-IR to predict the possible interactions between drug and the polymer by using KBr pellet technique. Spectra were scanned on a Nicolet, Model Impact 410, Milwaukee, WI, USA, in the range of 500–4000 cm^{-1}.

2.8. Scanning electron microscopic (SEM) studies

SEM studies were performed using a SEM (JEOL Model JSM-840A, Japan) on the samples of XG, grafted XG particles, and the tablet. The samples were coated with gold and mounted on a sample holder. Photographs were taken at an accelerating voltage of 15 kV, depending upon the sample at different magnifications.

2.9. Statistical analyses

Statistical analyses were done by SPSS statistical package. Analysis of variance followed by the least significant difference (LSD) procedure was used for comparison of drug release rates from different formulations and $p < 0.05$ was considered significant.

3. Results and discussion

3.1. Synthesis of poly(acrylamide)-grafted-xanthan gum

In the present study, we have attempted to synthesize the graft copolymer by using ceric ion. The reaction conditions were standardized to minimize the homopolymerization as well as to give a better yield. The reactive vicinal group where the grafting is initiated on XG backbone is CH_2OH. The overall reaction mechanism is that ceric ion attacks the XG macrochains and generates the formation of a XG–ceric complex. The ceric(IV) ions in the complex are then reduced to ceric(III) ions by oxidizing hydrogen atom and thereby, creating a free radical onto XG backbone. The grafting of poly(acrylamide) (pAAm) onto XG was then initiated by the free radical reacting with the monomer. In the presence of pAAm, the XG free radical is chemically coupled to the monomer unit, thereby resulting in a covalent bond between pAAm and XG to create the chain reaction for propagation. Finally, termination was achieved through a combination of two radicals.

The structure of graft copolymer is shown in Fig. 1(b). The earlier methods (Adhikary & Singh, 2004; Behari, Pandey, Kumar, & Taunk, 2001) reported the synthesis

of graft copolymerization of AAm onto XG initiated by Fe^{2+}/BrO_3^- redox system and CAN as the catalyst in aqueous medium. Details of the reaction scheme were reported before (Mundargi, Agnihotri, Patil, & Aminabhavi, 2006). Formulation details used in the synthetic procedure are summarized in Table 1. The % grafting varied from 369 to 842 and the monomer conversion was increased with increasing the ratio of AAm to XG. In the present study, the reaction mixture was precipitated in acetone and washed several times with methanol–water (80:20, v/v) mixture and finally, with distilled water to remove the unreacted monomer as well as the unwanted reagents. Hence, the presence of ceric ions and homopolymers is excluded. As far as toxicology is concerned, as per the investigation made by Jakupec, Unfried, and Keppler (2004) it was observed that Ce(IV) salts are not biologically stable in aqueous media. Several drug-loaded pAAm hydrogels have also been used for *in vitro* studies (Makarand & Bhonde, 2000). In addition, *in vivo* systems have been explored for AAm-based matrices in developing superporous hydrogels (Karadag, Saraydin, Cetinkaya, & Guven, 1996; Makarand & Bhonde, 2000).

3.2. Preparation and physical characteristics of tablets

Controlled release tablets have been prepared by using pAAm-*g*-XG copolymers as the main components by incorporating drugs of different physicochemical properties. Tablets were prepared by punching a required amount of the polymer and 25/50 mg of the drug ATL/CDL. Results of thickness, hardness, and drug content of the formulations are presented in Table 3. Hardness was found to be in the range from 20.26 to 78.26 N. Thickness and drug content of the tablets were well within the acceptable limits. Drug content was analyzed on five tablets of each formulation individually, but only the mean values are presented in Table 3. Drug content was found to vary between 98.25% and 99.38%, indicating a uniform mixing of the polymer, drug, and other formulation excipients. All the formulations were found to be swollen, yet retained their physical integrity till the end of the 24-h dissolution study except that the edges of the swollen formulations were rounded off due to slight erosion of the swollen gum.

3.3. FT-IR analysis

FT-IR spectra of (a) XG, (b) grafted copolymer, (c) ATL and powdered sample of matrix tablets (d) F1 and (e) F3 are shown in Fig. 2. In case of pure XG, a broad absorption peak at 3450 cm^{-1} indicates the hydrogen-bonded OH groups. Two peaks, one at 1615 cm^{-1} and the other at 1476 cm^{-1}, are attributed to COO^- groups. Additional characteristic absorption bands of XG appear at 1417 cm^{-1} and 1023 cm^{-1} due to C–H bending and O–H bending vibrations, respectively. In case of grafted copolymer of pAAm-*g*-XG, the bands at 1675 and 1635 cm^{-1} are attributed to amide-I (C–O stretching) and amide-II (N–H bending) of the amide group of AAm. The peak at 3421 cm^{-1} in pAAm-*g*-XG is attributed to the overlap of N–H stretching band of amide group and O–H stretching band. However, the C–N stretching band appears at 1450 cm^{-1}. FT-IR spectra of the pristine ATL showed characteristic bands due to different functional groups. However, the band appearing at 3356 cm^{-1} is due to O–H/N–H stretching vibrations, while those at 2924 and 2963 cm^{-1} are due to aliphatic C–H stretching

Table 1
Synthetic details of polyacrylamide-*grafted*-xanthan gum

Code	Wt. of XG (g)	Wt. of AAm (g)	Wt. of initiator (mmol)	Yield (%)	Grafting (%)	Grafting efficiency (%)	Conversion (%)
XG1	1	5	0.05	78.16	369	73.8	93.8
XG2	1	10	0.05	85.63	842	84.2	94.2

Table 2
Formulations of tablets (quantity in mg)

Formulation code	Graft copolymer	ATL	CDL	XG	MCC[a]	Magnesium stearate	PVP-K30[b]
F1	–	50	–	250	–	–	–
F2	250 (1:5)	50	–	–	–	–	–
F3	250 (1:10)	50	–	–	–	–	–
F4	250 (1:10)	25	–	–	–	–	–
F5	250 (1:10)	50	–	–	129.75	2.25	18
F6	–	–	50	250	–	–	–
F7	250 (1:5)	–	50	–	–	–	–
F8	250 (1:10)	–	50	–	–	–	–
F9	250 (1:10)	–	25	–	–	–	–
F10	250 (1:10)	–	50	–	129.75	2.25	18

[a] Microcrystalline cellulose.
[b] Poly(vinylpyrrolidone).

Table 3
Physical characteristics of the tablets

Formulation code	Thickness (average, mm)	Strength (N)	Drug content (%)
F1	1.78	69.68	98.25
F2	1.87	35.26	99.01
F3	1.88	51.26	98.97
F4	1.58	20.26	99.19
F5	2.62	75.55	98.26
F6	1.76	72.68	98.78
F7	1.86	34.19	98.69
F8	1.82	50.69	99.26
F9	1.57	21.65	98.36
F10	2.56	78.26	99.38

vibrations. The band at 3175 cm^{-1} is due to the aromatic C–H stretching vibrations, whereas those appearing at 1637 and 1583 cm^{-1} are due to primary amide bond stretching and aromatic C=C stretching vibrations, respectively. The N–H bending vibrations are seen at 1516 cm^{-1}. Bands at 1180 and 1092 cm^{-1} are due to C–O–C stretching vibrations of the ether linkages. The C–N stretching vibrations are seen at 1037 cm^{-1}, while the one that appeared at 1243 cm^{-1} is due to aromatic C–O stretching vibrations. The peaks appearing at 3349, 2971, 2924, 1639, 1519, 1249, and 1041 cm^{-1} for ATL have also appeared in ATL-matrix tablets, indicating the chemical stability of ATL in the polymeric matrix.

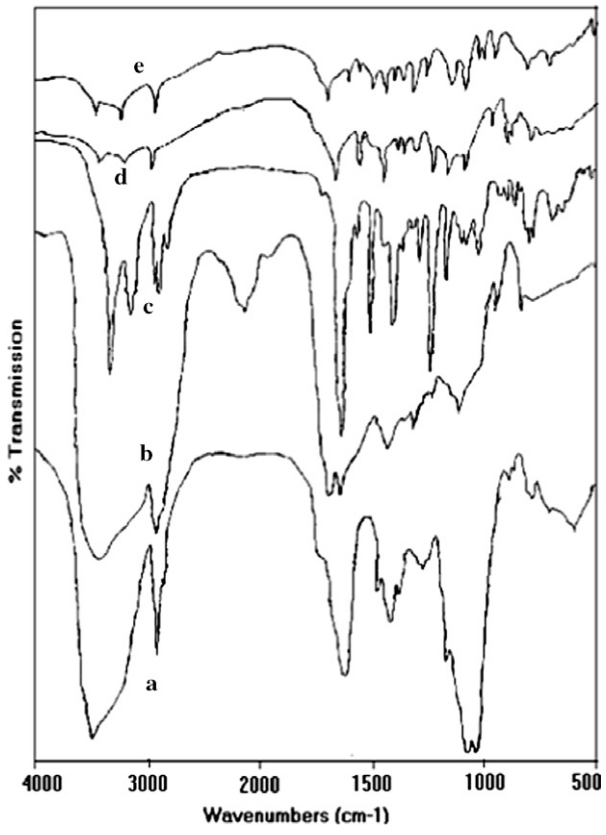

Fig. 2. FT-IR spectra of (a) XG, (b) grafted copolymer, (c) ATL and powder sample of matrix tablets (d) F1 and (e) F3.

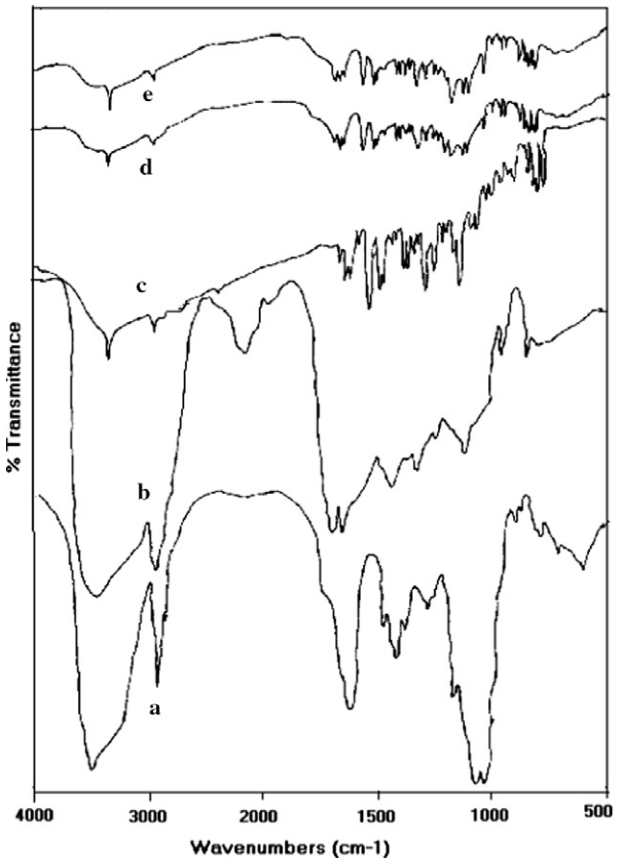

Fig. 3. FT-IR spectra of (a) XG, (b) grafted copolymer, (c) CDL and powdered sample of matrix tablets (d) F6 and (e) F8.

FT-IR spectra of (a) XG, (b) grafted copolymer, (c) CDL and powdered sample of matrix tablets (d) F6 and (e) F8 are shown in Fig. 3. Pristine CDL showed characteristic bands due to different functional groups. However, the band appearing at 3351 cm^{-1} is due to O–H/N–H stretching vibrations. The bands at 3061 and 2999 cm^{-1} are due to the aromatic C–H stretching vibrations, whereas those appearing at 1606, 1591, and 1503 cm^{-1} are due to aromatic C=C stretching vibrations. The N–H bending vibrations are seen at 1503 cm^{-1}. Bands at 1210 and 1190 cm^{-1} are due to C–N stretching vibrations, while the one appeared at 1253 cm^{-1} is due to aromatic C–O stretching vibrations. The peaks appearing at 3336, 3067, 3000, 2919, 1606, 1600, 1505, 1252, 1216, and 1174 cm^{-1} for CDL are also appearing in the CDL-matrix tablets, indicating the chemical stability of CDL in the polymeric matrix. Based on the FT-IR spectral data, there appears to be no possibility of interaction between ATL, CDL, XG, and the grafted copolymer used in matrix tablet formulations.

3.4. Scanning electron microscopy

Scanning electron microscopy allows much high magnification of the grafted copolymer particles in which we can see the shape and the surface. SEM images of the XG indicated a fibrous nature as seen in Fig. 8(a). In

Fig. 8(b) and (c), the surface photographs of the grafted polymers are displayed. It is noticed that pAAm-*g*-XG particles are of larger dimensions than plain XG. The grafting introduces changes on the surface and size of the carbohydrate particles. The particles, after copolymerization, show irregular morphology, as a lobule aggregate with higher heterogeneity in case of pAAm-*g*-XG. The wrinkled or porous topography could enhance the water absorption capacity, attributable to their chemical structure. Another factor to be considered is the use of tablets to perform the test of the copolymer. This makes compaction one more factor to be taken into account. Fig. 8(d) shows the morphology of compressed matrix tablets obtained from the graft copolymer studied in this work. The dry tablet surface showed a porous surface formed by compressed particles and also a degree of mechanical interlocking of the tablet excipient particles without brittle fracture when compressed. The surface image of the tablet compacts also indicated that there was some degree of elastic deformation of the tablet excipients.

SEM photographs of the crushed surfaces were depicted in Fig. 8(e). There are lobules of particles that could compact, giving rise to a very good particle–particle interaction. Again, the more irregular forms of pAAm-*g*-XG particles often give rise to the formation of bigger number of voids or channels to allow water to permeate. Thus, the particle surface morphology is more important in compaction than particle size distribution. Nevertheless, copolymers formed are hydrophilic in nature.

SEM studies of the hydrated tablets were reported earlier (Nerurkar, Jun, Price, & Park, 2005), wherein three-dimensional changes and the texture of the tablet surface on hydration were discussed. A common observation of wet tablet is the gelation of swollen hydrated polymers. Upon hydration, the surface of tablets will form a porous film that due to gel layer formed by polymer relaxation upon absorption of water molecules. However, the cross-sectional SEM images indicated a highly porous honeycomb structure of the polymer network, which allows the drug to diffuse out from the core of the surface. Further, the possible formation of smaller pores on the outer surface will explain the routes for drugs to come out of the gel layer. Since the gel layer undergoes surface erosion, it is possible that inner porous network is exposed after the dissolution of outer film of the tablet. A similar sponge-like pore network structure was also reported for tablets prepared from polymer blends of carrageenans or cellulose ethers, which also swell upon hydration and were used in CR applications (Nerurkar et al., 2005).

3.5. Swelling studies

Swelling of polymeric matrices was analyzed to compare their water uptake capacities. Fig. 4 shows the rate of swelling of matrix tablets containing ATL. Swelling of the matrix, as indicated by a transition of the polymer from glassy to rubbery state, is an important parameter in the determination of release characteristics of the matrix system. A correlation of polymer swelling to drug release would help to predict drug release mechanisms for different types of polymer matrices. Fig. 4 shows that matrices containing XG exhibited the maximum swelling ratio, indicating a high degree of swelling due to water uptake and a small degree of erosion due to polymer relaxation. On the other hand, formulation F5 exhibited the least swelling ratio, due to the fact that excipient microcrystalline cellulose used in formulating the tablet formulations might have hydrated to a lesser extent, when combined with the graft copolymer. Such matrices were hydrated up to 24 h after which no increase in tablet weight was observed due to water uptake. For formulations F2 and F3 containing graft copolymers, much lesser swelling ratio was observed. This is due to varying grafting ratios, the amount of XG in the copolymer will change and length of the side chain in the copolymer will increase, resulting in a lesser swelling ratio. We could not observe much difference in the swelling behavior of the graft copolymers studied. When the amount of drug was reduced to 25 mg in case of formulation F4, there was no appreciable change in the swelling ratio.

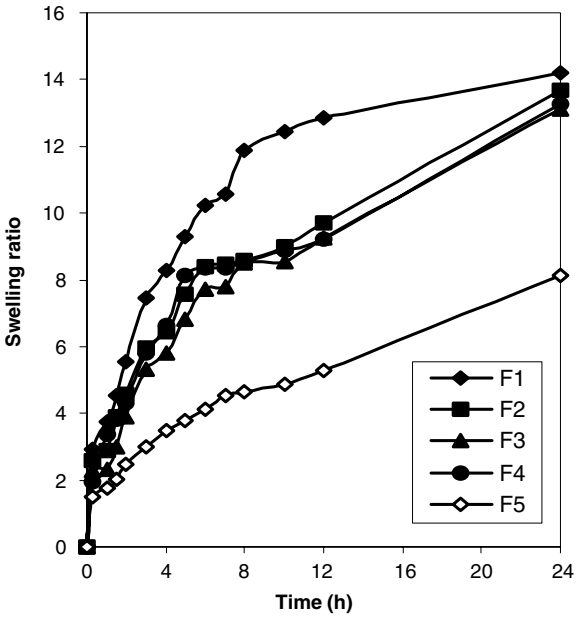

Fig. 4. Swelling ratio vs time graph of ATL tablets at 7.4 pH (37 °C).

3.6. In vitro release studies

In order to understand the release profiles of the drugs from the tablet formulations, dissolution experiments were performed in SGF media initially for 2 h and later, in SIF media without enzymes. The *in vitro* release profiles of various formulations containing XG and graft copolymers at various grafting ratios are displayed in Fig. 5. Notice that formulation F1 released 99% of drug within 12 h. In case of other formulations containing ATL, F2 releases higher

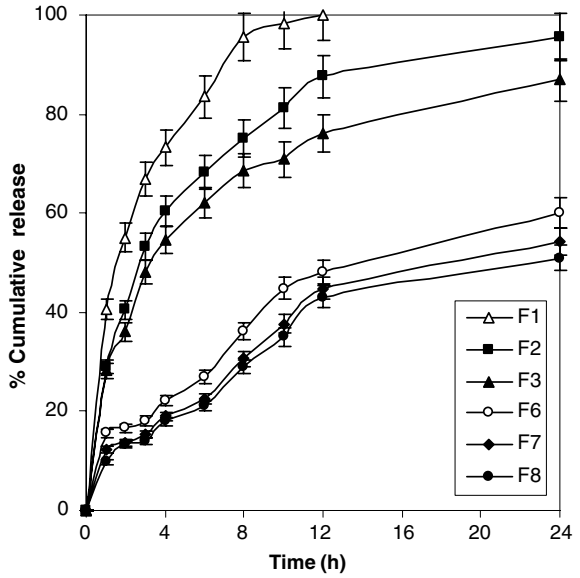

Fig. 5. Release profiles of ATL and CDL from the tablet formulations F1, F2, F3, F6, F7, and F8.

amount of drug as compared to formulations F3 and F5, i.e., it released about 95% of drug in 24 h, whereas formulation F3 released only 80% under similar conditions. It is interesting to note that with increasing grafting ratio of the copolymer, a decrease in release rate of the drug occurred, suggesting that release depends upon the chain length of pAAm part of the copolymer. Thus, by varying the grafting ratio, the amount of XG in the copolymer will change and length of the side chain of the copolymer will also increase. This has greatly affected the release patterns in all the grafted copolymers. The observed initial rapid release rate may be accounted for the direct exposure of the matrix to the diffusion media with a quick release of the drug present at the surface (Brazel & Huang, 2001). Such an initial rapid release is attributed to the fact that polymeric matrix may form loose channels within the network due to its hydrophilic nature and the dissolution of hydrophilic polymers during the diffusion process. The formation of such loose channels leads to a decrease in the mean diffusional path length of the drug molecule to leach out into the diffusion medium, thereby resulting in higher rates of drug release from the polymeric matrix. The observed initial release may thus be helpful to achieve the therapeutic plasma concentration of drug in a short time along with a constant release rate at longer time period facilitating CR of drug. This type of initial effect is related to the initial migration of drug particles toward the surface of the polymeric matrix.

Comparison of drug release from ATL and CDL tablets formulated with XG and graft copolymer containing ATL and CDL were statistically evaluated by ANOVA. In case of formulations F1 and F3, the F value was found to be 4.64 ($df = 17$, $p < 0.05$), indicating the significant difference in the release rates of ATL containing tablets. On the other hand, for formulations containing graft copolymers and both ATL and CDL, the F value was found to be 11.95 ($df = 35$, $p < 0.05$), which indicates a significant difference in the drug release rates from various formulations that is attributed to drug solubility. Formulations containing ATL and CDL with different grafting ratios exhibited ($p > 0.05$), indicating there was no significant difference in the release rates between tablets formulated with different graft copolymers.

Carvedilol is a less soluble drug and all the tablets containing CDL showed similar release patterns. CDL tablets containing plain XG released about 60% of the drug within 24 h, whereas formulations containing graft copolymers, viz., F7 and F8 exhibited not much difference in the release rates. By varying the grafting ratios at 24 h, about 50% of release was observed as a result of varying grafting chain length. This increase in release time for CDL tablets is attributed to its hydrophobicity, which might be responsible for such a delayed release. In addition, the slower polymer chain relaxation will also contribute to this type of slow release. However, such an effect was not observed for formulations containing ATL, possibly due to its hydrophilic nature.

In contrast, when the commercial CDL tablets were added to the release media, it dissolved quickly (see Fig. 6). Therefore, the matrix plays the main role in controlling the drug release. All the tablets containing CDL showed a lower degree of swelling and did not erode significantly during the 24 h of the experiment in any of the release media. However, the presence of CDL appears to alter the interaction of the copolymers with the aqueous medium, modifying the water uptake by the tablets (they seemed less hydrated) and the consistency of the gel layer formed at the tablet surface. Tous, Samy, and Saad (1995) observed that nitrofurantoin forms hydrophobic complexes with various acidic non-steroidal anti-inflammatory drugs (NSAIDs) because of the formation of ion pairs

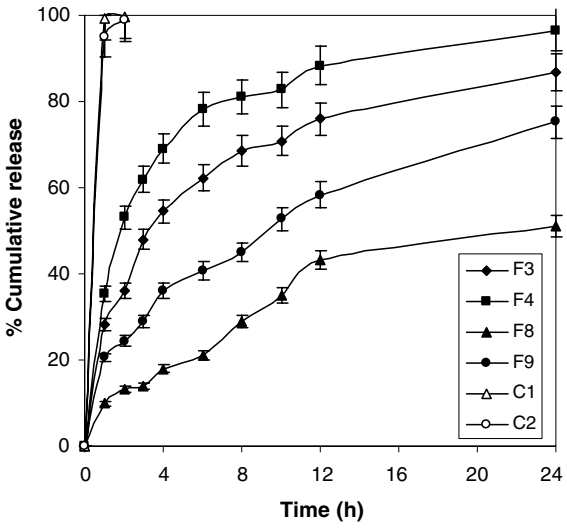

Fig. 6. Release profiles of ATL and CDL from the tableted formulations F3, F4, F8, F9, and commercial formulations C1 and C2.

between the protonated species of nitrofurantoin and the carboxylic acid groups of NSAIDs as well as the establishment of hydrogen bonds, which mask the hydrophilic groups. It is foreseeable that these interactions can also occur in the gel layer enhancing the hydrophobicity of CDL as well as the polymer chains that carry carboxylic groups. Therefore, CDL lowers the release rate, which can be attributed to its relatively high dose that increases the tablet hydrophobicity and hinders its swelling in water.

The effect of drug loading on the release rate from graft copolymer matrix was studied with different drug loadings of 25/50 mg/tablet. The *in vitro* release profiles at various drug loadings of ATL and CDL along with the commercial formulations are depicted in Fig. 6. Total amount of drug released from formulations F3 and F4 is about 80% and 98%, respectively, at the end of 24 h, whereas formulations F8 and F9 released 50% and 70%, respectively. Atenolol is a hydrophilic drug, which will exert an interaction with water-soluble polymers, resulting in an increase of drug release. Also, the hydrophilic XG will readily absorb water molecules and will swell, resulting in the formation of large pores. It was observed (Munday & Cox, 2000) that increasing the amount of drug led to a decrease in drug release in tablet formulations. A comparison of drug release from tablets with different drug loadings was statistically evaluated by ANOVA. The F value for ATL tablets was 1.99 ($df = 17$, $p > 0.05$) and for CDL tablets ($p < 0.05$), which indicated insignificant difference in drug release for ATL, but significant difference in the release of CDL tablets. All formulations containing XG and graft copolymers showed more prolonged release profiles than the commercial products of ATL (C1) and CDL (C2), which released the entire drug within 2 h. The differences of release profiles observed between the present systems and the commercial C1 and C2 systems can be attributed to the use of XG, a polysaccharide and its modified form of XG. The ANOVA results for the commercial formulations (C1 and C2) and CR formulations (F4 and F9) are found to be $p < 0.05$, indicating a significant difference between the marketed products and the newly developed formulations.

For a specific dose of the drug, varying the polymer concentration is probably the most efficient way to adapt the release characteristics to a specific criterion. Moreover, adjuvants are often necessary for the tableting operation. On the other hand, the role of diluents is very much pronounced, and actually an increase in the dissolution rate is noticed with both insoluble and soluble drugs. The dissolution profiles of formulations containing with or without the excipients are displayed in Fig. 7. It is observed that formulations containing microcrystalline cellulose (MCC) as filler exhibit a faster release in case of ATL, but for CDL tablets, there was no appreciable difference in the release rate with the filler, which could be due to hydrophobicity of the drug. A general observation that occurred during the dissolution testing of the matrix tablets was the rapid surface hydration of the matrix, which resulted in its swelling and consequent formation of the gel layer. In

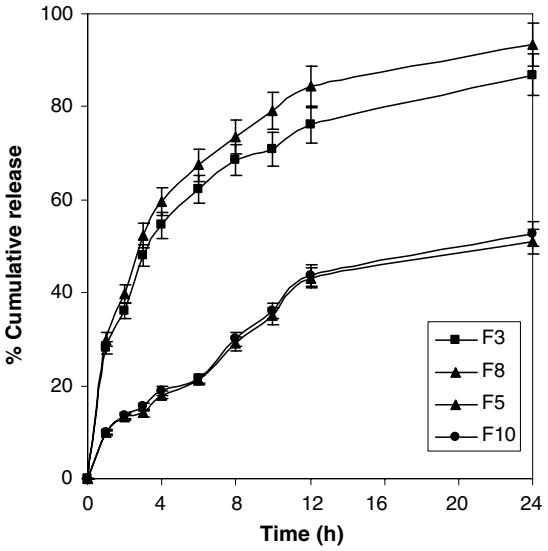

Fig. 7. Release profiles of ATL and CDL from the tableted formulations F3, F8, F5, and F10.

any case, hydration progressed from surface to the core of the tablet. Upon sufficient hydration, the gel layer was slowly dissolved and eroded away exposing the new gel layer as is commonly observed with the swellable CR tablets (Wan, Heng, & Wong, 1993). The use of water-insoluble MCC as the tablet excipient also partly contributed to the prevention of tablet matrix from disintegrating. Microcrystalline cellulose has crystalline and amorphous regions. Upon contact with water, the amorphous regions swell, while the denser crystalline domains prevent the dissolution of the matrix due to its limited interaction with water. A comparison of drug release from the tablets formulated using graft copolymer and co-excipients was statistically evaluated by ANOVA. The F value was found to be 0.31 ($df = 17$, $p > 0.05$), which indicates a insignificant difference in drug release rate from (F3, F8) and (F5, F10) formulations.

3.7. Release kinetics

The drug release mechanism was determined by fitting the initial release data (i.e., $M_t/M_\infty \leqslant 60\%$) vs time to the empirical equation (Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = Kt^n. \tag{5}$$

Here, M_t/M_∞ is the fraction of drug released at time t, K is the kinetic constant, and n is the diffusional exponent characterizing the release mechanism. For cylindrical systems, if $n = 0.45$, Fickian diffusion occurs; if $0.46 < n < 0.89$, it suggests anomalous (non-Fickian) transport and for $n = 0.89$ zero-order release is possible and if $n > 0.89$, super-Case-II transport is operative. To predict the release trends of the drugs from the matrices of this study, we have fitted the release data to Eq. (5) to estimate n values. The n

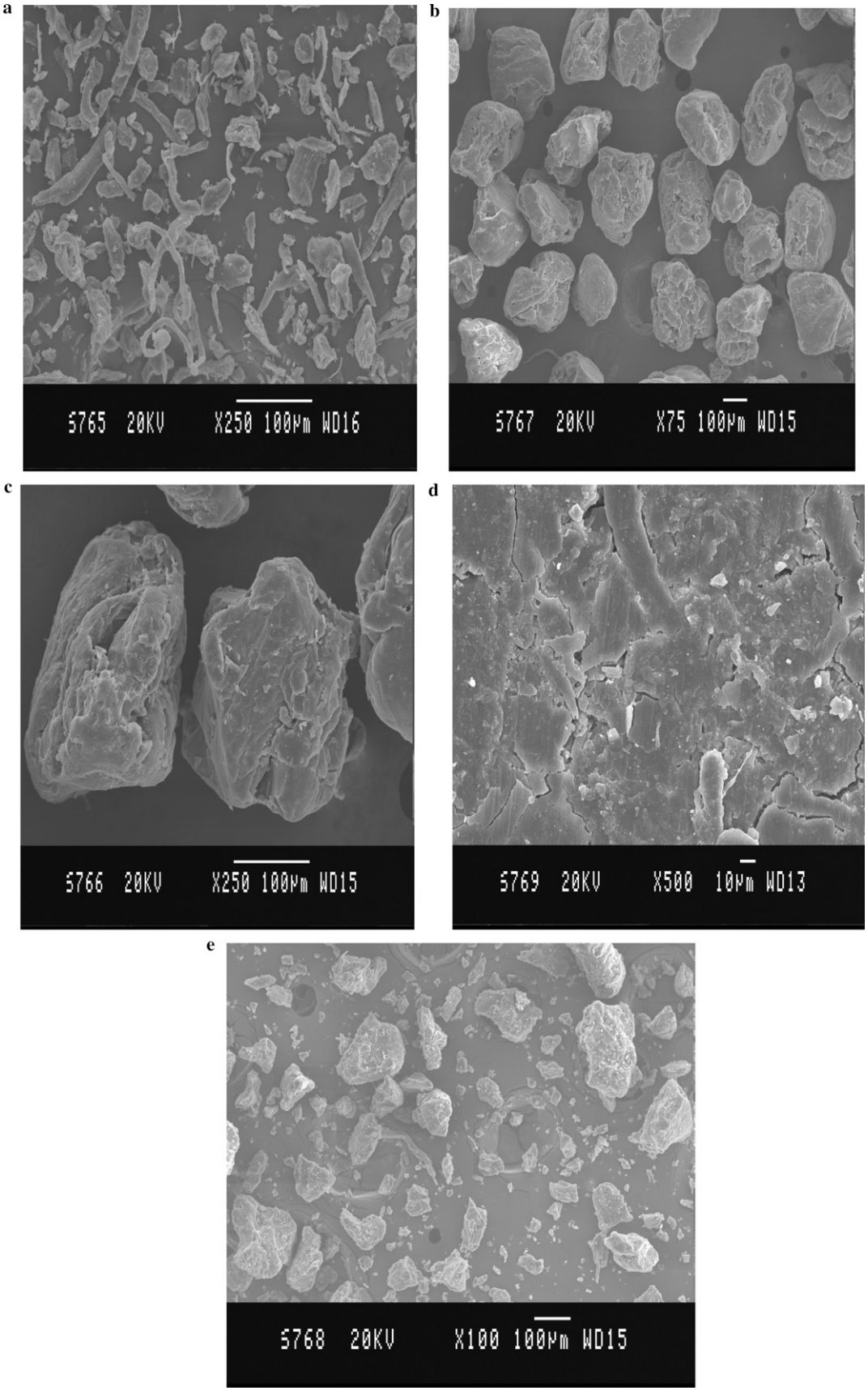

Fig. 8. SEM images of particles: (a) XG, (b) graft copolymer, (c) single grafted copolymer particle, (d) tableted formulation F3, and (e) crushed tablet of formulation F3.

values calculated for all formulations are depicted in Table 4; these found to vary between 0.42 and 0.58, indicating a non-Fickian/anomalous to Fickian transport. Under these conditions, the release trends are influenced by: (i) non-homogeneous gel microstructure as well as the existence of polymeric domains within the swollen gel, (ii) the rate of fluid ingress into the matrix, (iii) dissociation/erosion and total disentanglement at the dissolution front, and (iv) rate of matrix swelling, relaxation, as well as molecular diffusion of drug through the swollen gel (Kim & Fassihi, 1997). When pAAm-*g*-XG was used as the retarding hydrophilic polymer, drug release profiles suggest three mechanisms, viz., swelling, erosion, and diffusion fronts, which synchronize and contribute for a slow drug release. XG, an anionic natural derivative of cellulose, showed that drug release from this microbial exocellular polysaccharide follows almost a time-independent release kinetics. Notice that XG is compatible with virtually all the salts and solution pH. Temperature has very little effect on the viscosity of its gel. XG matrix swells in the presence of a solvent due to polymer relaxation, which is characterized by the formation of a gel-like network structure surrounding the system. For formulations containing only XG, the *n* value is found to be 0.43 and 0.49, indicating a Fickian trend.

The formulation F4 has a *n* value of 0.52, which is slightly greater than observed for F5, i.e., plain grafted copolymer. This is attributed to the physical changes induced in the polymer by the excipient. For formulation F10, which is a mixture of graft copolymer with the excipients, the *n* value was 0.58. Thus, formulation F10 also contributes in the drug release by coupling of drug diffusion and polymer relaxation processes. In general, the solubility of drug itself crucially governs the rate and extent of diffusional release. For diffusion to occur, the first step is wetting of the drug by water, followed by its dissolution such that drug molecule is available in its molecular form to diffuse out of the matrix. Hence, the net release rate observed is a cumulative effect of drug's solubility (influenced by its structure, molecular weight, and pK_a value), polymer property (hydrophilicity/lipophilicity, molecular weight, and tortuosity), as well as the relative ratio of drug and polymer in the tablet. In high concentrations of hydrophilic drug as in case of formulations F3 and F9, considering the high level of erodability of graft copolymer, it may be concluded that drug is released by the Fickian diffusion mechanism. In this case, the rate of polymer chain relaxation is much slower than the rate of diffusion of drug through the polymer matrix.

Table 4
Diffusional parameters estimated by Eq. (5) for the release of ATL and CDL from hydrophilic matrices at 37 °C

Formulation code	*n*	*r*[a]	Transport mechanism
F1	0.43	0.99	Fickian
F2	0.54	0.99	Anomalous
F3	0.48	0.98	Fickian
F4	0.52	0.98	Anomalous
F5	0.50	0.98	Anomalous
F6	0.49	0.90	Fickian
F7	0.54	0.91	Anomalous
F8	0.58	0.94	Anomalous
F9	0.42	0.98	Fickian
F10	0.58	0.96	Anomalous

[a] *r* is correlation coefficient calculated at 95% confidence limit.

Transport often occurs in rubbery polymers that possess a sufficient chain mobility to allow for water penetration. It is an ideal case in which there is no interference of effects such as polymer chain rearrangements. However, the overall rate of release of drug from XG matrix is higher than that from the pAAm-*g*-XG matrices; these results are a clear indication of the fact that pAAm-*g*-XG has higher drug-retarding ability than XG alone.

4. Conclusions

The present study is aimed at developing oral controlled delivery systems for antihypertensive drugs using pAAm-*g*-XG as a carrier. Matrix tablets containing various graft copolymers of xanthan were prepared and subjected to *in vitro* drug release studies. For pAAm-*g*-XG matrix tablets containing ATL, the release continued up to 24 h by releasing 85% of the drug in SGF and SIF media. However, in case of plain XG matrix, the release reached 99% in 12 h only. In case pAAm-*g*-XG, the release time increased with increasing grafting ratio of the grafted copolymer. On the other hand, for tablet formulations composed of graft copolymer (pAAm-*g*-XG) and CDL, there was no significant difference in the release rate compared to the plain XG, which is attributed to its hydrophobicity along with a slower polymer chain relaxation. Swelling studies indicated that formulations containing plain XG exhibited maximum swelling ratio, whereas formulations with graft copolymer and excipients showed the least swelling. The surface morphology of the plain and grafted XG matrices was studied by SEM, which showed that pAAm-*g*-XG matrices have the larger dimensions than the plain XG. The grafting introduced big changes on the surface morphology as well as the size of the particles. The surface image of the tablet compacts indicated that there was some degree of elastic deformation of the tablet excipients. FT-IR studies indicated no interaction between ATL, CDL, XG, and the graft copolymer/other excipients used in the tablets. The nature of drug transport through grafted copolymers followed the non-Fickian (anomalous) trend, since diffusion through the matrix was dependent upon polymer chain relaxation processes. The results of this study clearly indicate that pAAM-*g*-XG in the form of matrix tablet is a potential hydrophilic carrier in the design of oral controlled drug delivery systems for antihypertensive drugs.

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