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RESEARCH ARTICLE

pH Sensitive graft copolymers for zero order drug release: A mechanistic analysis

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Abstract

Aliphatic polyesters containing pendent unsaturation were synthesized by the polycondensation of a diol, dicarboxylic acid and glycidyl methacrylate. Grafting methacrylic acid (MAA) resulted in graft copolymers containing polyester backbone and MAA grafts. Depending on composition, the polymers swelled extensively and eroded or dissolved at near neutral pH but remained in collapsed state at acidic pH. Three representative drugs differing in solubility, *viz*., Diltiazem hydrochloride (DH), Indomethacin (IM) and Verapamil hydrochloride (VH) were released at constant rate from tablets made by compressing spray-dried microparticles. The release of DH at constant rate has been attributed to increase in diffusion coefficient of the drug from the swollen layer of matrix. The release of IM and VH at constant rate was governed by erosion and was enhanced in matrices which undergo dissolution. The release rate was enhanced with increasing MAA content and the frequency of grafts along the polyester backbone. Once a day dosage forms for drugs differing in solubility have been developed using a single polymer matrix which is easy to manufacture.

Keywords: Graft copolymer, spray drying, microparticles, matrix tablets, sustained release, diffusion, erosion

Introduction

Controlled delivery of drugs reduces the frequency of dose administration, eliminates under and overdosing, reduces toxicity, enhances bioavailability and patient compliance[1]. Physicochemical properties of drugs, *viz*., solubility, ionic nature and stability in gastric fluid, play a critical role in the design of sustained release drug delivery systems.

Kim reported that pH independent hydrophilic polymers do not offer much control over the release of highly soluble drugs especially at higher loadings[2]. Diltiazem hydrochloride (DH) is a highly water soluble drug used to treat hypertension and angina. To reduce the frequency of administration from three or four times in a day, once a day dosage forms have been developed. Cardizem CD™ consists of DH particles coated with ethylcellulose. Dilacor XR™, contains three or four tablets placed in a capsule. The tablets were hydrophilic matrices each loaded with 60 mg of DH. Barrier layers are coated on the matrix to limit the hydration of the core and release the drug in a sustained manner. These tablets have been prepared using multiple polymers and specialized tablet making machines by Geomatrix® technology[3]. Efentakis prepared multilayered tablets containing soluble as well as poorly soluble drugs such as Diclofenac sodium and Furocemide in metolose, polyox and xanthan gum core along with the erodible polymer Gantrez®[4]. However, the release was biphasic. The need to develop matrix devices which can release the drugs differing in their solubility characteristics, over extended time periods has been well understood and efforts continued to develop new matrices for this purpose. For example, Moroni investigated ionotropic gelation of alginate containing mixture for formulating pH dependent sustained release matrix system[5]. Zhilei demonstrated the use of chitosan–polycarbophil interpolyelectrolyte complex as a matrix for sustained release of both highly water soluble as well as poorly soluble drugs[6].

The release of water insoluble drugs by diffusion from hydrophilic gelled polymer matrices is hindered and incomplete. Erodible polymer matrix made from polyethylene oxide has been used for the sustained

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release of poorly soluble drugs such as theophylline, sulfathiazole and salicylic acid at constant rate[7]. The solubility of weakly basic drugs decreases dramatically with increasing pH and poses a challenge for the design of dosage forms to achieve sustained delivery over gastrointestinal tract. The cellulosic polymers are blended with an enteric polymer to suppress the release of weakly basic drugs at acidic pH and to enhance the release at neutral pH[8–11]. Alternately, organic acids are incorporated in the matrix to provide an acidic microenvironment. This enhances the solubility of the drug and release by diffusion[12,13]. However, the loadings required are often very high and limit the dose that can be delivered[11].

The polymers which swell and/or dissolve slowly at near neutral pH and remain in collapsed state at acidic pH would be useful for sustained delivery of drugs in intestinal region. This cannot be achieved by hydrophobic modification of enteric polymers. Methylation of Eudragit® S100 increased the threshold pH at which the polymer dissolved, but the dissolution was rapid. Caffeine was released from a capsule coated with methylated Eudragit® S100 (acid value 90) after a lag time of 2 h and completed within 4 h. Clearly, such polymers would not be useful for delivery of drugs over extended time periods across the gastrointestinal tract[14]. Hence, new architectures are needed.

We developed a series of copolymers comprising an aliphatic polyester backbone and methacrylic acid (MAA) grafts. The polymers swelled and/or dissolved at near neutral pH but collapsed at acidic pH. Matrix tablets were made by compressing spray-dried microparticles. *In vitro* release study showed that DH was released over 18 h and longer by diffusion. The release of Indomethacin (IM) and Verapamil hydrochloride (VH) was controlled by erosion/dissolution of matrix depending on the polymer composition. In all cases release at constant rate could be achieved. The effect of polymer swelling and/or dissolution, drug loading, drug solubility and tablet configuration on the release was investigated to elucidate the release mechanism. The polymers will find applications in the design of once a day dosage form of highly soluble, poorly soluble as well as weakly basic drugs.

Materials and methods

Materials

1,4-Butanediol, succinic acid, adipic acid, sebacic acid, dodecanedioic acid, glycidyl methacrylate, titanium (IV) butoxide and MAA were purchased from Sigma-Aldrich, St Louis, MO. Dimethyl formamide (DMF), chloroform ($CHCl_3$), methanol (CH_3OH), cyclohexane, sodium hydroxide (NaOH), potassium chloride (KCl) and n-dibutyl phthalate (DBP) were purchased from Merck, Mumbai, India. 2,2′-azobisisobutyronitrile (AIBN) was purchased from a local supplier. Span 80 was purchased from s.d.fine-chem Ltd., Mumbai, India. DH and VH were gift samples from Lupin Laboratories Ltd., India. IM was purchased from Fluka chemicals, Mumbai.

Synthesis of polyester-graft-MAA

Unsaturated polyesters were synthesized by melt polycondensation of 1,4-butanediol, dicarboxylic acid and glycidyl methacrylate. The reaction was carried out in a two neck round-bottom flask equipped with a nitrogen containing bladder and a water cooled condenser. The flask was charged with 1,4-butanediol, dicarboxylic acid and glycidyl methacrylate and then 1 wt% of hydroquinone was added as an inhibitor to avoid the free radical polymerization of glycidyl methacrylate. The polymerization was carried out at 165–170°C using 0.1 wt% of titanium (IV) butoxide as a catalyst. The water formed during the reaction was distilled off continuously. After 6 h, vacuum was applied for about 15 min in order to remove the trapped water from reaction mixture and the reaction was continued for further 4 h. The polyester obtained was dissolved in $CHCl_3$ and precipitated into cold CH_3OH. The precipitate was filtered and washed with CH_3OH repeatedly and was finally air dried at room temperature. ^1H NMR spectra for unsaturated polyesters were recorded on Bruker AV 200 spectrometer using $CDCl_3$ as a solvent.

MAA was grafted onto the unsaturated polyesters by free radical copolymerization. Typically, 1.0 g of unsaturated polyester and MAA were dissolved in 40 ml of DMF and purged with nitrogen gas for 15 min. The polymerization was carried out using 1 wt% AIBN as a free radical initiator at 65°C for 20 h. The solvent was partially removed on a rotary evaporator and then the polymer was precipitated into cold water. The polymer obtained was reprecipitated from DMF into cold water to remove the unreacted monomer and MAA homopolymer. The purified polymers were dried under vacuum for 4 days at room temperature. The graft copolymers were synthesized so as to obtain various levels of MAA content by varying the ratio between the unsaturated polyester and MAA in feed. The amount of MAA grafted was determined from acid value. MAA content of the graft copolymer and grafting efficiency were calculated according to following equations.

$$\text{MAA in the graft copolymer (wt\%)} = [(W_1 - W_0)/W_1] \times 100 \quad (1)$$

$$\text{Grafting efficiency (\%)} = [(W_1 - W_0)/W_2] \times 100 \quad (2)$$

Where, W_0, W_1 and W_2 are the weight of unsaturated polyester, weight of graft copolymer and the weight of MAA in the feed, respectively.

The nomenclature of polyester-*graft*-MAA is follows. (a) Poly [(1,4-Butanediol - Succinic acid - Glycidyl methacrylate)-g-MAA]: BSG-g-MAA, (b) Poly [(1,4-Butanediol - Adipic acid - Glycidyl methacrylate)-g-MAA]: BAG-g-MAA, (c) Poly [(1,4-Butanediol - Sebacic acid - Glycidyl methacrylate)-g-MAA]: B(S)G-g-MAA and (d) Poly [(1,4-Butanediol - Dodecanedioic acid - Glycidyl methacrylate)-g-MAA]: BDG-g-MAA.

Preparation of polymer films and determination of DS

The polymer films were prepared by solution casting. The polymer solution was prepared by dissolving 0.200 g of polymer in 2 ml of $CHCl_3$ and CH_3OH mixture (6:4 v/v). The polymer solution obtained was poured in a petri dish and the solvent was evaporated. The resulting films were dried under vacuum for 4 days at room temperature. The thickness and diameter of the films were 0.2 mm and 20 mm, respectively. The degree of swelling (DS) of polymer films was determined by placing them in phosphate buffer, pH 6.8. At regular interval the swollen films were removed and blotted with tissue paper to remove excess water on the surface and weighed. The DS of the films was calculated using equation.

$$DS = [(W_s - W_d)/W_d] \times 100 \quad (3)$$

Where, W_s and W_d are the swollen and dry weight of the polymer films, respectively. The morphology of film on exposure to dissolution medium was examined by Environmental Scanning Electron Microscope (ESEM).

Preparation of microparticles by spray drying

Microparticles were produced in a laboratory mini spray drier (Model: LSD-48 Mini spray drier, Jay Instrumentations and Systems Pvt. Ltd., Mumbai, India). Typically, the graft copolymer and drug were dissolved in $CHCl_3$ and CH_3OH mixture (6:4 v/v) to obtain 10% w/v solution. The solution was spray dried to obtain microparticles. The experimental parameters were as follows. The feed rate was 2 ml/min. The inlet temperature was set at 60°C which gave outlet temperature of 42 ± 0.2°C. The nozzle diameter of 0.7 mm was used throughout all the experiments to introduce droplets. The hot compressed air aspirated by pump caused fast evaporation of solvent from droplets and the formation of solid microparticles. The microparticles were cooled to room temperature and then deposited into a product container by a cyclone. The microparticles were dried under vacuum for 7 days at room temperature.

Particle size and morphology

The mean particle diameter was determined using PSS NICOMP 380 particle sizer. Typically, 5 mg of microparticles were suspended in 5 ml of cyclohexane using Span 80 as a stabilizer. Cyclohexane was used as a medium as both polymer and drug do not dissolve. The suspension obtained was sonicated for 15 s and then particle size was measured at 30°C. The morphology of microparticles was examined by ESEM.

Determination of drug content: assay

Ten milligram of microparticles were accurately weighed and added into 10 ml of phosphate buffer, pH 6.8. The content was sonicated for 2 min and kept for a day. The solution was centrifuged and 0.2 ml of supernatant was removed and diluted appropriately. The drug concentration was determined using UV–Vis spectrophotometer (Shimadzu, UV-1061PC) at 237, 320 and 298 nm for DH, IM and VH, respectively.

Drug-polymer interaction studies

FTIR analysis

DH and VH loaded BSG-g-MAA (MAA content: 53 wt%) microparticles were analyzed by Fourier Transform Infrared Spectrometer (FTIR, Perkin Elmer Spectrum One instrument) in diffuse reflectance mode. Spectra were recorded in the range 4000–400 cm^{-1} by cumulating 10 scans at a resolution of 4 cm^{-1}. The scan speed was set at 0.5 cm/s. Baseline correction was made for all spectra using Perkin Elmer Spectrum software. The same microparticles were treated with phosphate buffer, pH 6.8 and then freeze dried. The freeze dried microparticles were characterized by FTIR.

Turbidity measurement

Turbidity of drug-polymer complex solutions was measured in terms of transmittance using UV spectrophotometer at 27°C. The measurements were carried out at 600 nm where the drug and polymer did not show any characteristic absorption. The graft copolymer solution was prepared by adding 0.500 g of BSG-g-MAA (MAA content: 53 wt%, equivalent to 3.07×10^{-03} moles of carboxyl groups) in 130 ml of phosphate buffer, pH 6.8. The solution was sonicated for 5 min and then filtered. Separately, 1.388 g of DH (equivalent to the moles of carboxylic groups present in the polymer) was dissolved in 130 ml of said buffer solution. The solutions were mixed in different ratios by adding drug solution into the polymer solution. The UV absorbance of solutions was measured and the results were converted into percent transmittance. The measurement was repeated after the addition of 50 mg of KCl.

Preparation of matrix tablets

Monolithic matrix tablets were prepared by compressing 200 mg of drug loaded microparticles and 25 mg of binder hydroxypropyl methylcellulose (5 Cps). Thoroughly, mixed mass was compressed into a tablet by applying the load of 200 kg/cm^2 using a hydraulic press equipped with 8 mm die and flat faced punch. Other ingredients were not incorporated to avoid their influence on the release kinetics of drugs. The matrices of higher thickness were prepared using higher amount of microparticles and binder mixture. The enteric coating was evaluated by applying a coat of graft copolymer on the matrices. The coating solution was prepared in $CHCl_3$ and CH_3OH mixture (6:4 v/v). To this solution, DBP was added as a plasticizer at 5 % level and then tablets were coated.

In vitro release study

In vitro drug release study was carried out in 900 ml phosphate buffer, pH 6.8 by paddle method using Electrolab USP type II apparatus. The paddle rotation speed was 50 rpm and the temperature was maintained at 37 ± 0.5°C. The enteric characteristic of the graft copolymer was studied in 0.1 N HCl for the first 2 h followed by phosphate buffer, pH 6.8. At the predetermined time intervals, a known volume of dissolution medium was

withdrawn and analyzed for drug concentration by UV–Vis spectrophotometer.

Matrix erosion and dissolution

The extent of erosion and dissolution of matrix during drug release was studied in USP dissolution apparatus under identical conditions as maintained for drug release study. At regular intervals of time, the tablets were removed and dried at 60°C until constant weight was reached. By taking into account the drug released, the loss in weight of polymer matrix was calculated.

Results and discussion

The challenges in design of sustained release matrix dosage forms for drugs differing in solubility have already been described in the introduction. pH sensitive hydrogels have been investigated extensively to sustain drug release in intestine[15,16]. However, these necessitate intricate drug loading methods not readily amenable to mass production. Further, the processability of the hydrogels is limited as they are insoluble in solvents[15,17]. To overcome these limitations, we synthesized a series of graft copolymers comprising aliphatic polyester backbone and MAA grafts which swell and/or dissolve at near neutral pH and collapse at acidic pH. We demonstrated that the polymers can be used for the sustained release of highly soluble DH, poorly soluble IM and weakly basic VH. By proper choice of the polymer composition, the drugs could be released at constant rate.

Polymer synthesis

Aliphatic polyesters containing pendent unsaturation were synthesized by polycondensation of a diol, dicarboxylic acid and glycidyl methacrylate. In all cases the amount of glycidyl methacrylate was 6–7 mole %. The dicarboxylic acids varying in chain length were used. The frequency of unsaturation in the polyester decreases on incorporation of dicarboxylic acid in the order succinic acid, adipic acid, sebacic acid and dodecanedioic acid since the number of methylene groups between the carboxyl groups increases from 2 to 10. ^{1}H NMR analysis of the polyester BSG shows a peak at 5.3 ppm which corresponds to the methine proton of ring opened glycidyl methacrylate and confirms the incorporation of glycidyl methacrylate in the polymer chain (Figure 1). The ratio between the peak integral value of vinyl protons (g, g′) and α-methyl protons (h) is 2:3, which confirms that the unsaturation in glycidyl methacrylate did not undergo free radical polymerization during polycondensation. The compositions of unsaturated polyesters and graft copolymers are summarized in Table 1.

Graft copolymerization was carried out in DMF by varying ratios of unsaturated polyesters and MAA in the feed. The reactant concentration in solution was limited to 2 g in 40 ml since at higher concentrations the reticulation takes place. The possibility of some polyester chains linked by MAA grafts even at the low concentrations used by us cannot be completely ruled out. However, it is not possible to confirm the same or otherwise. In any case the graft copolymers synthesized at this concentration were completely soluble in $CHCl_3/CH_3OH$ (6:4 v/v) mixture and could be processed by spray drying to obtain microparticles.

The polyester BDG comprising seven mole % unsaturation was grafted in the presence of three different levels of MAA. The grafting efficiency decreased from 85 to 70% on increasing MAA content in feed from 40 to 60%. This can be attributed to increasing tendency to homopolymerization of MAA as the ratio of unsaturations in the polyester relative to MAA decreases.

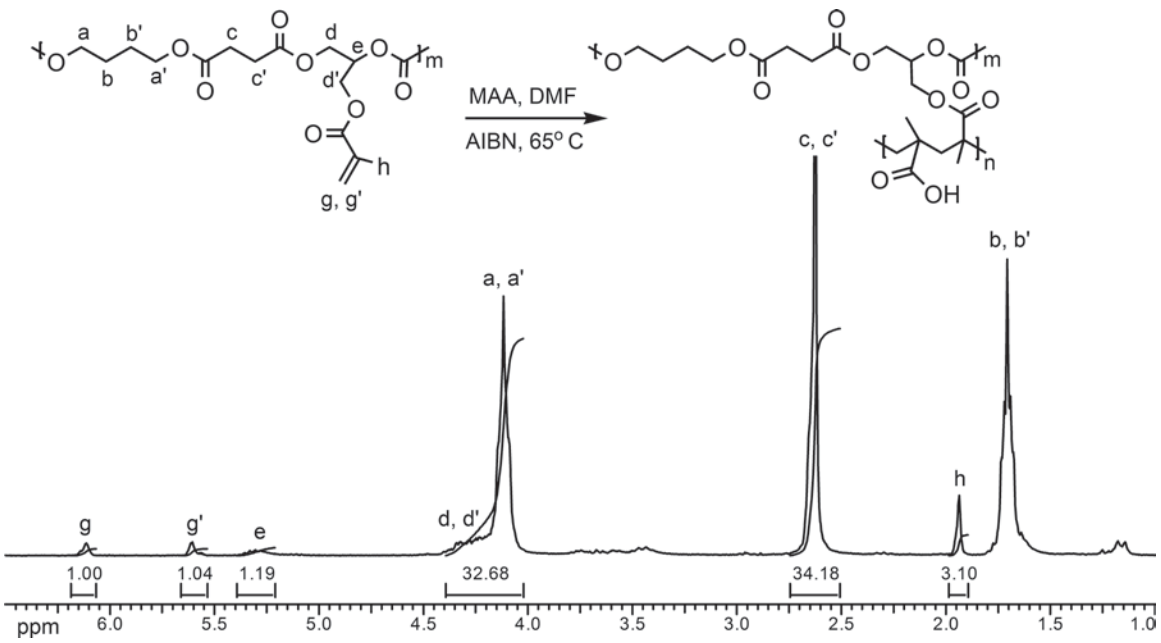

Figure 1. ^{1}H NMR spectrum of unsaturated polyester BSG.

Preparation of drug loaded microparticles

The drug loaded microparticles were prepared by spray drying under optimized conditions to maximize yield and prevent agglomeration. The mean particle diameter and recovery were in the range 3.5–5 μm and 40–50%, respectively. Since spray drying was carried out on a small scale, the recovery was low. The polymer composition, the nature of drug and its loading level did not influence the microparticle size and recovery. The drug content in feed and in microparticles was practically same indicating that the efficiency of drug encapsulation was close to 100%. The morphology observed by ESEM revealed that the microparticles were not agglomerated (Figure 2). The microparticles were then compressed into tablets. The merits of this approach have been elaborated by Palmieri[18].

Drug-polymer interaction

The drug-polymer interactions play a vital role in the performance of delivery systems and range from complex formation, hydrogen bonding to van der waals interactions. Complex formation has been shown to release drug at constant rate[19–22]. The imbibition of DH by MAA based hydrogel was higher when carboxyl groups were ionized because of the interaction between the drug and the polymer[23]. Bettini reported that the rate of metoclopramide release decreased with increasing MAA content of poly (2-hydroxyethyl methacrylate-co-methacrylic acid) as a result of extensive interaction between the drug and the polymer[24]. In the present investigation, the graft copolymer contains carboxyl groups and hence interaction with cationic DH and VH is to be expected.

FTIR analysis

FTIR spectrum of the graft copolymer BSG-g-MAA (MAA content: 53 wt%) microparticles containing 21.89% DH before and after treatment with phosphate buffer, pH 6.8 is shown in Figure 3. No interaction between the drug and the polymer is observed in the microparticles, since the characteristic band positions of DH are retained. In the case of buffer treated microparticles, the ionic interaction between the tertiary amine group of the drug and ionized carboxyl group of the polymer resulted in the appearance of characteristic band of amine salt at 1550 cm^{-1}. In the case of VH, the band appeared at 1555 cm^{-1}. Takka investigated the interaction between the MAA copolymers such as Eudragit® L100, Eudragit® S100 and the cationic drug propranolol hydrochloride[20]. Bands appeared at 1550 and 1556 cm^{-1} for Eudragit® L100 and Eudragit® S100, respectively, because of interaction with propranolol hydrochloride and our findings are similar. The results have been further substantiated by turbidity measurements discussed in the next section.

Turbidity measurements

The graft copolymer BSG-g-MAA (MAA content: 53 wt%) was selected since it was readily soluble in phosphate buffer, pH 6.8. The UV absorbance of drug-polymer complex solutions was measured after 5 min, 4 h and 15 h and the results are shown in Figure 4. The transmittance of solution measured at 5 min was >90% when the molar ratio between the DH and MAA of the graft copolymer was 0.44:0.56. On increasing the molar ratio of DH, the transmittance steadily decreased since the solution became more turbid. When the molar ratio approached 0.52:0.48,

Table 1. Composition of unsaturated polyesters and graft copolymers.

Unsaturated polyesters	Feed composition (mole ratio)[a]	Polymer composition (mole ratio)[b]	Graft copolymers	MAA (feed) wt%	MAA (polymer) wt%
BSG	38:50:12	42:52:06	BSG-g-MAA	40	37
				60	53
BAG	37:50:13	45:49:06	BAG-g-MAA	40	35
B(S)G	35:50:15	40:53:07	B(S)G-g-MAA	40	35
BDG	35:50:15	41:52:07	BDG-g-MAA	40	36
				50	44
				60	51

[a,b]Diol:Dicarboxylic acid:Glycidyl methacrylate.

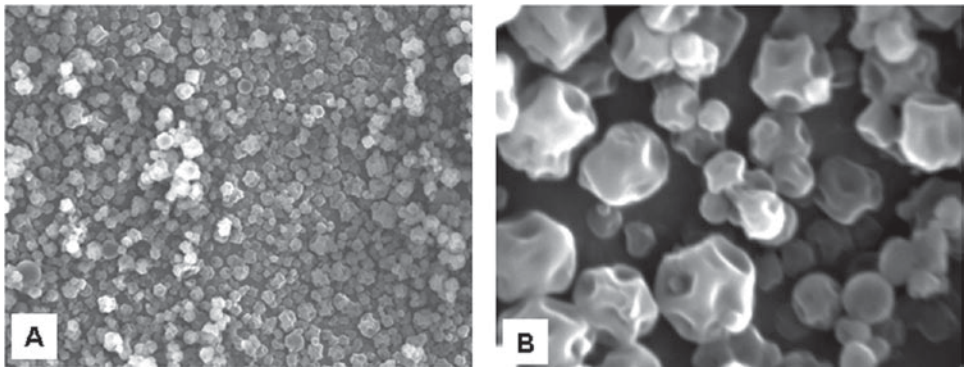

Figure 2. Morphology of DH loaded BDG-g-MAA (MAA content: 36 wt%) microparticles: Magnification, 1000× (A) and 12,000× (B).

the transmittance was ~10%. The solution turned almost opaque because of the extensive complex formation.

The measurement was repeated at 4 h which showed further decrease in transmittance. However, there was no difference in turbidity between samples analyzed at 4 h and 15 h. Thus the complex formation is complete in 4 h. Addition of KCl to these solutions led to the dissociation of the complex since the drug ions associated with the polymer were replaced by potassium ions. The absence of interaction between the drug and the polymer in microparticles is desirable to ensure stability during storage. However, ionic interaction was observed in phosphate buffer, pH 6.8. Blanco-Fuente investigated the interaction between carbopol® and propranolol hydrochloride by FTIR analysis as well as turbidity measurement and noted that the interaction between carboxyl and amino groups resulted in complexation immediately but equilibrium was reached in about 5 h[25].

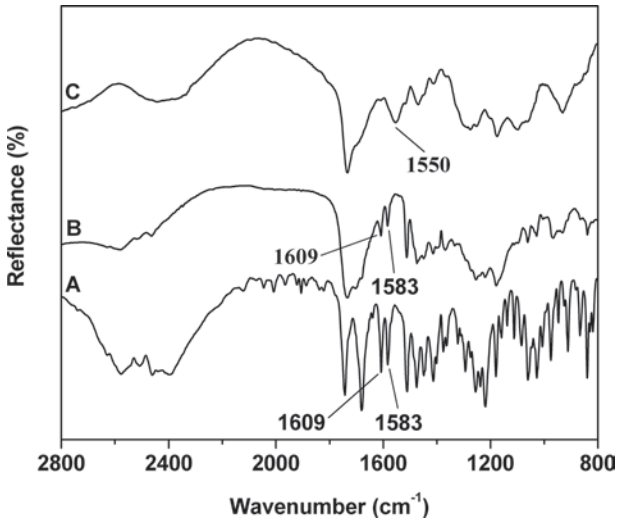

Figure 3. FTIR spectra (A) DH, (B) DH loaded BSG-g-MAA (MAA content: 53 wt%) microparticles and (C) buffer treated microparticles.

DS of graft copolymers

The random copolymers of MAA such as Eudragit® L100 and Eudragit® S100 dissolve rapidly under neutral and basic pH conditions without swelling. The hydrogels comprising MAA are crosslinked, glassy polymer networks. When exposed to the medium of neutral pH, these hydrogels swell as a result of the penetration of the medium and consequent ionization of carboxyl groups. The swelling process is governed by the ionization of the carboxyl groups[24]. The glassy phase turns to swollen rubbery phase through which the solute molecule diffuses out. In the present case, as the medium penetrates, the glassy graft copolymer swells and then erodes or dissolves depending on the polymer composition.

To investigate the swelling behavior, the films of graft copolymers 20 mm in diameter and 0.2 mm in thickness were prepared and exposed to phosphate buffer, pH 6.8. The ionization of carboxyl groups in the graft chains led to swelling followed by erosion or dissolution. The influence of frequency of MAA grafts and MAA content on the swelling of the graft copolymers is shown in Figure 5. The DS decreased with decrease in the frequency of MAA grafts along the polyester backbone as a result of lengthy hydrophobic segment between the grafts. The DS increased with MAA content because of extensive ionization. The change in morphology of representative polymer film BDG-g-MAA (MAA content: 36 wt%) is shown in Figure 6. The film did not swell in 0.1 N HCl solution. On exposure to the phosphate buffer of pH 6.8, swelling of the polymer film is initiated as seen by the formation of uneven surface. The swollen film ruptured and continued swelling with time.

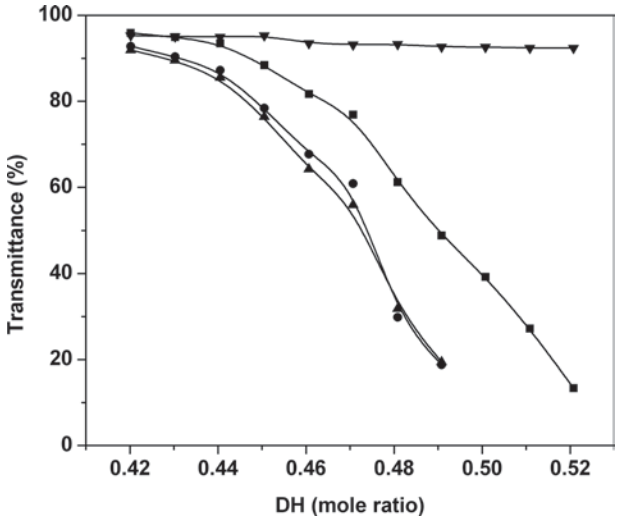

Figure 4. Turbidity measurement: BSG-g-MAA (MAA content: 53 wt%) and DH complex formation in phosphate buffer, pH 6.8. % Transmittance at 5 min (▪), 4 h (•) and 15 h (▴) on mixing the polymer and drug solutions and the dissociation of complex on addition of KCl (▼).

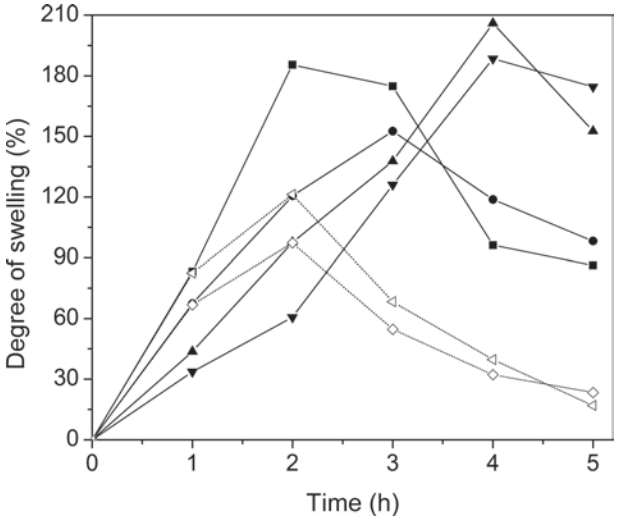

Figure 5. Effect of MAA graft frequency and MAA content in the polymer on degree of swelling in phosphate buffer, pH 6.8. BSG-g-MAA (MAA content: 37 wt%) (■), BAG-g-MAA (MAA content: 35 wt%) (•), B(S)G-g-MAA (MAA content: 35 wt%) (▲), BDG-g-MAA [MAA content: 36 wt% (▼), 44 wt% (◊) and 51 wt% (◁)].

The penetration of medium into polymers bearing lower frequency of MAA grafts, *viz.*, B(S)G-g-MAA and BDG-g-MAA, results in two moving boundaries. As the medium penetrates, the boundary separating the glassy and swollen layer moves inward and leaves behind the swollen layer, which erodes latter. Initially, the rate of penetration of medium is higher than the rate of erosion of polymer. Hence, the DS increases with time. However, as the erosion proceeds, DS as measured by weight gain method decreases with time.

In the case of polymers comprising higher frequency of MAA grafts, *viz.*, BSG-g-MAA and BAG-g-MAA, the penetration velocity of the medium was higher and the polymers attained maximum swelling within 2–3 h (Figure 5). Rapid swelling followed by the dissolution of the swollen layer was observed. As a result, the maximum swelling attained was lower than the value observed for the hydrophobic polymers cited above. Unlike in the case of hydrogels, the maximum swelling was not the equilibrium swelling. This was also true for the graft copolymers comprising higher MAA, *viz.*, BDG-g-MAA (MAA content: 44 and 51 wt%).

In vitro release study

In vitro release of drugs was monitored in phosphate buffer, pH 6.8. The experiments were designed to evaluate the effect of swelling/dissolution behavior of polymer, drug loading, drug solubility and tablet configuration. The enteric behavior of the polymer was also evaluated. The release characteristics were analyzed by fitting the early time dissolution data (up to 60% release) into logarithmic form of Ritger–Peppas equation.

$$\text{Log}\,(M_t/M_\infty) = \text{Log}\,k + n\,\text{Log}\,t \qquad (4)$$

Where, M_t and M_∞ denote the drug released at time t and the total drug present in the matrix, respectively. The constant k indicates the release rate and n is the release exponent. In the case of cylindrical matrix such as a tablet, $0.89 < n < 1.0$ indicates zero order release and $0.45 < n < 0.89$ indicates anomalous release behavior[26].

Effect of MAA graft frequency on DH release

The frequency of MAA grafts decreases as the dicarboxylic acid chain length increases from succinic acid to dodecanedioic acid in the polyester backbone (BSG-g-MAA to BDG-g-MAA). The rate of release of DH decreased with decreasing frequency of MAA grafts as a result of low DS (Figure 7). The composition and release characteristics are summarized in Table 2.

The graft copolymers B(S)G-g-MAA and BDG-g-MAA released DH at constant rate. The penetration of dissolution medium into the matrix led to a boundary separating a swollen and a glassy layer which moved toward the center of the tablet. The increase in diffusion coefficient of drug in the swollen layer results in release at constant rate. Penetration of medium in glassy polymer blends comprising gelatin, hydroxypropyl methylcellulose and pectin and consequent release of DH at constant rate has been reported by Kim[2]. In the present case, the swollen layer eroded after the release of drug as it was mechanically weak. Erosion of the matrix lags far behind the release of DH as will be discussed latter.

In contrast, in the case of polymers BSG-g-MAA and BAG-g-MAA, the swollen layer dissolved rapidly as evident from the fact that the tablet dissolved concomitantly with the release. The release of DH in this case was controlled by complex interplay between swelling and dis-

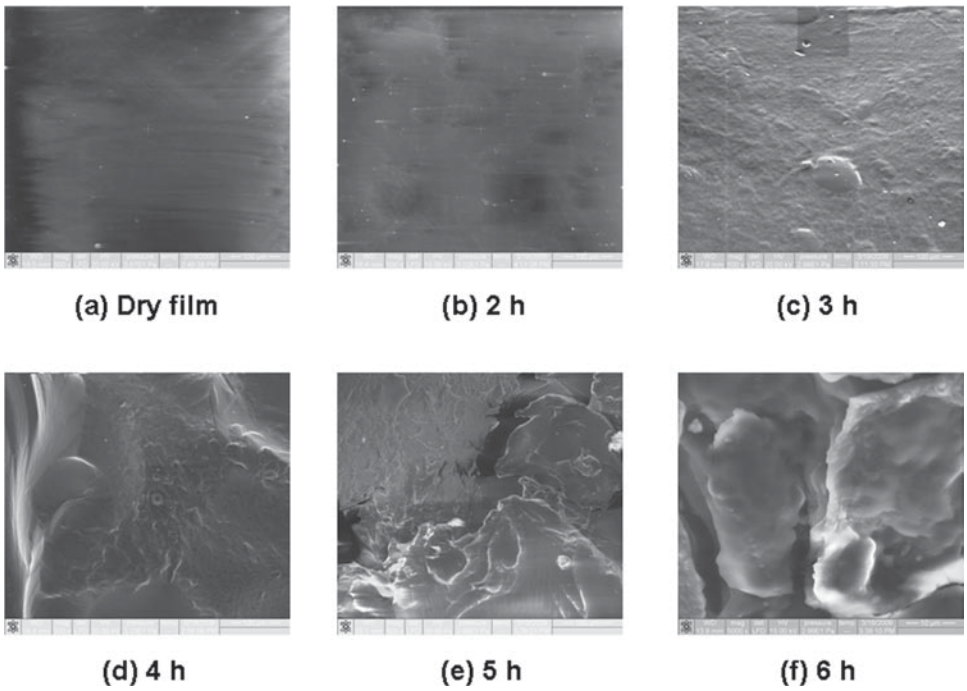

Figure 6. Morphology of the graft copolymer films on exposure to 0.1 N HCl followed by phosphate buffer, pH 6.8.

solution of the polymer and exhibited anomalous release kinetics.

Effect of MAA content of the polymer on DH release

In the previous section it was shown that the DH was released at a constant rate from the polymer BDG-g-MAA (MAA content: 36 wt%) as a result of the enhanced diffusivity from the swollen layer, which subsequently eroded. The rate of release in such cases is known to be controlled by the penetration velocity of the medium which in turn is proportional to equilibrium swelling[27].

Increase in MAA content of the graft copolymer, BDG-g-MAA (MAA content: 44 and 51 wt%) results in swelling followed by dissolution rather than erosion. Increase in the hydrophilicity is reflected in enhanced initial rate of swelling but not in maximum swelling because of the dissolution of swollen layer. This is also reflected in higher rate of DH release because of enhanced penetration velocity of the medium (Figure 7). In this case dissolution front closely followed the boundary separating the core and swollen layer as reflected by the fact that the tablet dissolution was concomitant with the release.

The polymer, BDG-g-MAA contains 51 wt% MAA but has lower frequency of grafts compared to the polymer BSG-g-MAA which contains 37 wt% MAA. Both polymers swelled rapidly and then dissolved slowly. Surprisingly, the release of DH from the polymer BDG-g-MAA which contained 51 wt% MAA was slower than from the polymer BSG-g-MAA which contained 36 wt% MAA. This can be attributed to the extensive complexation between the carboxyl groups and DH. On releasing the drug, the polymer dissolves. This leads to drug release at constant rate from the drug-polymer complex (Table 2). Similar observation has been reported for the complex of anionic polyelectrolytes and cationic drugs[22,28].

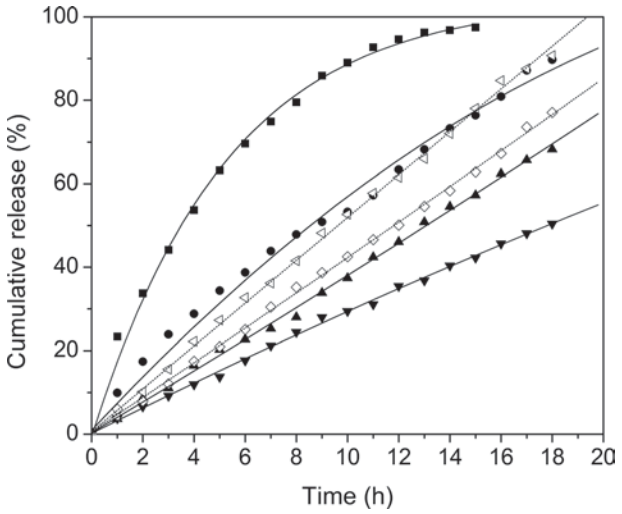

Figure 7. Effect of MAA graft frequency and MAA content in the polymer on DH release in phosphate buffer, pH 6.8. BSG-g-MAA (MAA content: 37 wt%) (▪), BAG-g-MAA (MAA content: 35 wt%) (•), B(S)G-g-MAA (MAA content: 35 wt%) (▲), BDG-g-MAA [MAA content: 36 wt% (▼), 44 wt% (◊) and 51 wt% (◁)].

Table 2. Release characteristics of DH from the matrices of graft copolymers differing in the frequency of MAA grafts and content.

Polymer	MAA Content (wt%)	Drug loading (%)	n	k
BSG-g-MAA	37	22.02	0.59	0.229
BAG-g-MAA	35	21.66	0.72	0.103
B(S)G-g-MAA	35	21.60	0.99	0.038
BDG-g-MAA	36	21.89	0.92	0.035
	44	20.66	0.93	0.048
	51	21.44	1.07	0.079

Effect of loading level of DH on release

The dose of drugs often varies depending on their half-life and the state of disease. For instance, once a day dosage form Dilacor XR® contains 240 mg of DH. Higher drug loading is necessary to limit the size of the tablet. However, this should not compromise the release kinetics. The compositions of matrices containing various levels of DH and their release characteristics are summarized in Table 3.

The polymer, BDG-g-MAA (MAA content: 36 wt%) was selected since it exhibited swelling over longer time period in comparison to other polymers. DH loading was in the range 10–50%. Since the release of DH is a result of enhanced diffusion coefficient from the swollen layer of the matrix, the release rate was expected to be identical irrespective of drug loading. However, the release rate of DH was enhanced (Figure 8). This is because DH is highly water soluble and increasing loading leads to increase in the hydrophilicity of matrix. As a result, the penetration velocity of the medium is enhanced which leads to increase in the rate of DH release. Similar increase in release rate of DH with loading from the blend of gelatin, hydroxypropyl methylcellulose and pectin was reported by Kim[2]. Kim reported that the initial burst release increased with Oxprenolol hydrochloride loading from poly (methyl methacrylate-co-2-hydroxyethyl methacrylate) beads[29]. In the present case, the initial burst (6.7%) was observed when DH loading was 50%.

The release exponent n was ~0.9 upto the loading level of 40% indicating constant release rate. On increasing the loading level to 50%, although n dropped to 0.74, a

Table 3. Release characteristics of DH, IM and VH loaded at various levels from BDG-g-MAA (MAA content: 36 wt%) matrix.

DH loading (%)	n	k	IM loading (%)	n	k	VH loading (%)	n	k
10.42	0.93	0.013	10.18	0.84	0.043	10.57	0.94	0.022
21.89	0.92	0.035	21.19	0.85	0.038	19.64	1.04	0.014
32.36	0.91	0.050	31.69	0.92	0.025	31.03	1.07	0.012
40.63	0.88	0.059	41.36	0.94	0.014	40.95	1.07	0.011
51.95	0.74	0.102	52.24	0.95	0.012	49.09	1.06	0.011

sustained release was observed over 18 h. While this is quite satisfactory, the value of *n* can be further enhanced by modifying the configuration of the tablet as will be seen in subsequent section.

Effect of tablet configuration on release of DH

The dimension of tablet influences the release kinetics of drugs[28]. We designed DH matrices varying in dimensions and monitored the release behavior. Relative surface area of the matrices was calculated using equation 6 and results are summarized in Table 4.

$$\text{Relative surface area} \quad \frac{\text{absolute surface area (SA)}}{\text{absolute volume (V)}} \tag{5}$$

$$SA/V = 2(r+t)/rt \tag{6}$$

Where, *r* and *t* are the radius and thickness of the matrices, respectively.

Increase in thickness of matrix at constant diameter led to sustained and constant release rate of drug (Table 4). This can be attributed to the decrease in relative surface area of the matrix which resulted in suppression of initial burst release of the drug.

Sustained release of IM and VH

In the preceding sections, we demonstrated that the release of highly soluble drug DH (660 mg/ml) from the polymer matrix BDG-g-MAA (MAA content: 36 wt%) was sustained at intestinal pH as a result of swelling of the polymer layer and enhanced diffusivity of the dissolved drug through the swollen layer which eroded at a latter stage. This is evident from the fact that the rate of erosion lags behind the release (Figure 9).

The release of poorly soluble IM (0.23 mg/ml) is controlled by the erosion of polymer[30]. In the present case, only 20% IM was released over 18 h and the rate of release was identical to the rate of matrix erosion (Figure 9). A weakly basic drug like VH is rapidly released in acidic medium because of its high solubility (165 mg/ml at pH 5.0). However with increasing pH along the gastrointestinal tract, the solubility decreases dramatically (10 mg/ml at pH 7.0). It has been reported that the drug precipitated at higher pH and consequently did not diffuse out of the system[8].

The release of VH from the polymer BDG-g-MAA (MAA content: 36 wt%) is shown in Figure 9. The release profile compares reasonably well with that of the erosion profile. This result shows that the release of VH is controlled by erosion of the polymer layer as in the case of IM. The rate of release of VH is comparable to that of IM eventhough the solubility of VH is ~50 times higher than that of IM. This can be attributed to the interaction between VH and polymer which suppressed the drug release.

Unlike in the case of DH, increasing the loading of IM and VH led to suppression of the release rate (Figure 10). When the loading level of the drug was 50%, <25% drug was released at the end of 18 h. This can be attributed to the decrease in the penetration velocity of the medium and the erosion of the matrix which controls the release. Kim showed that the release rate decreased with increasing loading level of poorly soluble drugs and our finding is similar[7]. The rate of release of IM and VH was constant as anticipated (Table 3).

Release behavior of IM and VH from soluble polymers

The release of IM and VH from the graft copolymer BDG-g-MAA (MAA content: 36 wt%) was too slow to be completed within the gastrointestinal tract transit time. Graft

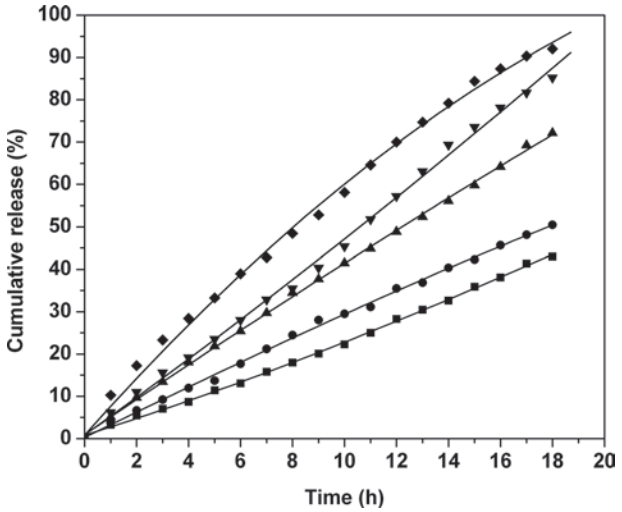

Figure 8. Effect of DH loading on release from BDG-g-MAA (MAA content: 36 wt%) matrix in phosphate buffer, pH 6.8: 10.42% (▪), 21.89% (•), 32.36% (▴), 40.63% (▾) and 51.95% (◆).

Table 4. Release characteristics of DH from BDG-g-MAA (MAA content: 36 wt%) matrices differing in relative surface area.

Micro particles[a] (mg)	Diameter/ thickness (mm)	Relative surface area (mm^2/mm^3)	*n*	*k*
200	8.0/3.80	1.02	0.74	0.102
300	8.0/5.78	0.84	0.92	0.060
400	8.0/7.60	0.76	0.96	0.044

[a]Drug loading: 51.95%.

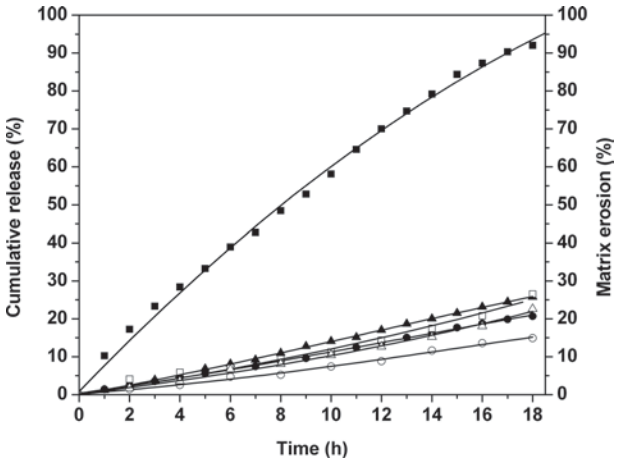

Figure 9. Release behavior of DH (▪), IM (•) and VH (▴) and erosion of DH (□), IM (◇) and VH (△) matrices made from BDG-g-MAA (MAA content: 36 wt%) in phosphate buffer, pH 6.8.

copolymer BSG-g-MAA (MAA content: 37 wt%) which dissolves rapidly after swelling was used as a matrix to accelerate the release of these drugs. The drug loading was 49.21% and 50.66% for IM and VH matrices, respectively. The release of IM was suppressed for the first 2 h as the drug is insoluble in acidic medium (Figure 11). Both drugs were completely released over 18 h when the pH of the medium was switched to 6.8. The release of VH was low at acidic pH since the polymer remained in collapsed state. Sustained as well as complete release occurred at near neutral pH as a result of dissolution of polymer matrix. The release exponent 'n' is 1.18 and 1.01 for IM and VH matrices, respectively. Figure 11 illustrates that the drug release and matrix dissolution are concomitant.

Evaluation as enteric coating

The enteric behavior of a representative graft copolymer BDG-g-MAA (MAA content: 36 wt%) was evaluated by coating the polymer on the matrices containing DH and VH. The same polymer was used for the matrix as well as for enteric coating. The release from coated matrix was followed in 0.1 N HCl for the first 2 h followed by phosphate buffer, pH 6.8. Similarly, the uncoated matrices were studied for their release behavior in identical manner.

The coated matrices did not release the drug in the acidic medium (Figure 12). When the pH of the medium was switched to 6.8, the polymer coating started swelling and then underwent rupture, exposing the matrix within. Thus the graft copolymer can be used for sustained delivery of drugs in intestinal region while suppressing the release in gastric region. In the case of uncoated matrices, the drug released in acidic pH medium eventhough the polymer matrix did not swell/dissolve. This is due the exposure of drug to dissolution medium unlike in the case of coated matrix. Palmieri showed that the release of paracetamol occurred in acidic pH medium from the uncoated matrices of various enteric polymers and our finding is similar[18].

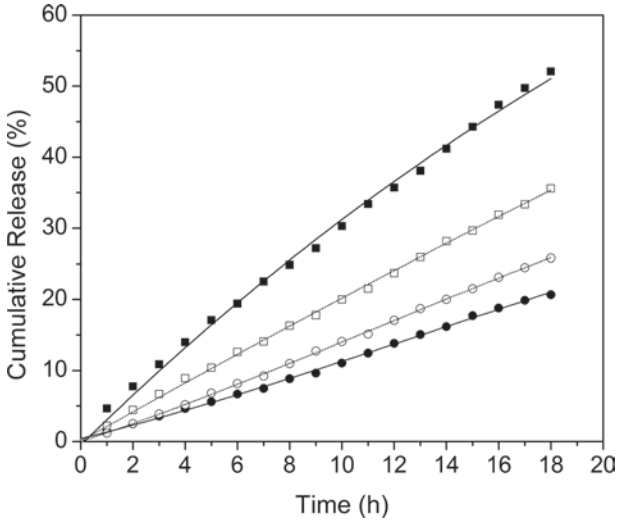

Figure 10. Effect of IM and VH loading on release from BDG-g-MAA (MAA content: 36 wt%) matrix in phosphate buffer, pH 6.8. IM: 10.18% (▪), 52.24% (•) and VH: 10.57% (□), 49.09% (○).

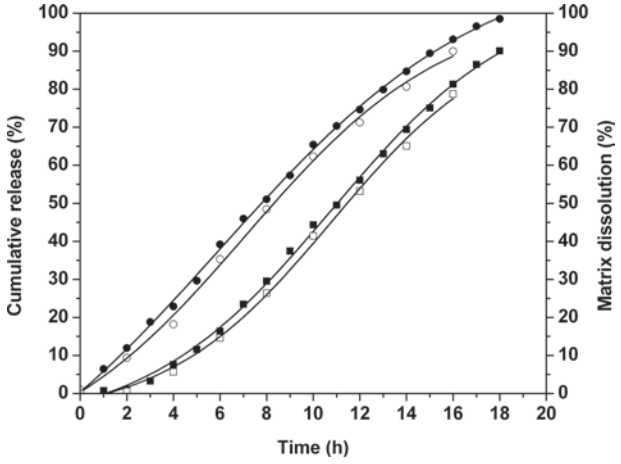

Figure 11. Release behavior of IM (▪) and VH (•) and dissolution of IM (□) and VH (○) matrices made from BSG-g-MAA (MAA content: 37 wt%) in 0.1 N HCl for the first 2 h followed by phosphate buffer, pH 6.8.

Conclusion

In this communication, we have shown that the graft copolymers comprising polyester backbone and MAA grafts can be used for the sustained delivery of highly soluble, poorly soluble and weakly basic drugs. DH was released at a constant rate as a result of increase in diffusion coefficient of drug in the swollen layer. IM and VH released at constant rate from the swellable polymers as a result of erosion of the matrix. The enhanced rate of release could be achieved from the soluble polymers as a result of dissolution of matrix. These graft copolymers will be useful for the development of once a day matrix dosage forms comprising drugs differing in solubility.

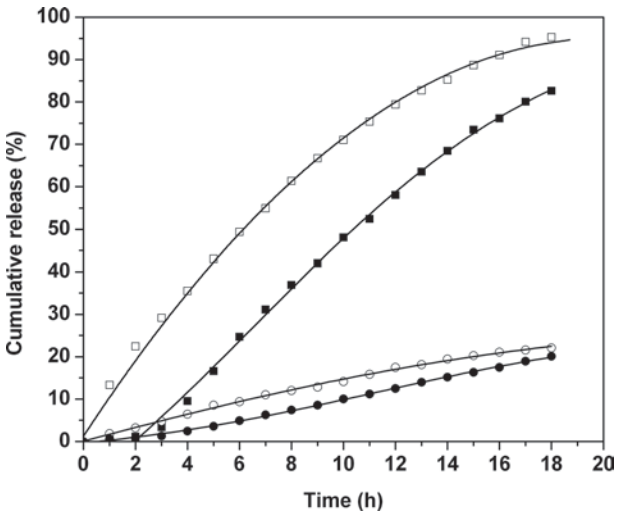

Figure 12. Release of DH (▪) and VH (•) from enteric coated matrices and release of DH (□) and VH (○) from uncoated matrices made from BDG-g-MAA (MAA content: 36 wt%) in 0.1 N HCl for the first 2 h followed by phosphate buffer, pH 6.8.

Declaration of interest

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