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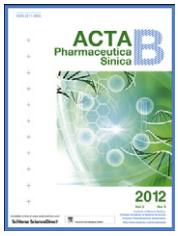

ORIGINAL ARTICLE

Design of a gastroretentive mucoadhesive dosage form of furosemide for controlled release

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KEY WORDS

Gastroretentive dosage form;
Controlled release;
Furosemide;
Bioadhesion;
Bilayer film;
Hydroxypropyl β-cyclodextrin;
Carbopol

Abstract The aim of the present study was to develop and characterize a gastroretentive dosage form suitable for controlled drug release. It consists of a drug loaded polymeric film made up of a bilayer of immediate (IR) and controlled release (CR) layers folded into a hard gelatin capsule. Gastroretention results from unfolding and swelling of the film and its bioadhesion to the gastric mucosa. Furosemide, a drug with a narrow absorption window, was selected as the model drug. Inclusion of hydroxypropyl β-cyclodextrin in both layers and Carbopol® 971P NF in the CR layer of the bilayer film resulted in optimum drug release, bioadhesion and mechanical properties. The film with zig-zag folding in the capsule was shown to unfold and swell under acidic conditions and provide IR of drug over 1 h and CR for up to 12 h in acidic medium. X-ray diffraction, differential scanning calorimetry and scanning electron microscopy revealed uniform dispersion of furosemide in the polymeric matrices. The results indicate the dosage form is gastroretentive and can provide controlled release of drugs with narrow therapeutic windows.

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1. Introduction

The development of controlled release formulations has had a tremendous impact on the drug delivery field particularly for drugs with a narrow absorption window. However, typical controlled release formulations are limited by insufficient retention in the stomach. To extend the residence time of dosage forms in the stomach, a number of strategies have been developed[1–4], including (a) reducing the density to promote floating in the gastric contents, (b) increasing the density to promote retention in the lower part of the stomach, (c) introducing mucoadhesive properties and (d) producing a formulation that swells or unfolds in the stomach to hinder its escape through the pyloric sphincter. Each of these approaches has its advantages and disadvantages.

An alternative strategy is to combine bioadhesion with the ability to expand by unfolding and swelling. This paper describes the design of a formulation incorporating a drug loaded polymeric film folded in a hard gelatin capsule. After ingestion, the capsule dissolves and releases the film which then unfolds in the stomach and swells to a larger dimension resulting in its increased retention. The concept of a gastroretentive drug loaded polymeric films has been previously reported and the effects of shape, folding pattern and polymer characteristics on performance of gastroretention has been studied[1].

Although this type of dosage form has various advantages such as the convenience of a hard gelatin capsule and the ability to modify drug release through using a multilayer design, there remain a number of issues. These include the difficulty in formulating a drug loaded polymeric film and the selection of a polymer with the desired ability to unfold and expand in the stomach. This paper focuses on practical aspects of designing such a dosage form and the difficulties encountered in its development.

Furosemide (4-chloro-2-furfurylamino-5-sulphamoyl benzoic acid) is a loop diuretic widely used in the treatment of congestive heart failure and edema. It works by inhibiting the $Na^+/K^+/2Cl^-$ transporter in the ascending limb of the loop of Henle[5]. Furosemide is a Biopharmaceutical Classification System (BCS) class IV drug with poor aqueous solubility and permeability. It is mainly absorbed in the upper gastrointestinal tract and has a short half life of less than 2 h. The conventional dosage form shows erratic absorption which results in poor bioavailability (30–60%) and the requirement for dosing 3–4 times/day[6]. In addition, the peak diuretic effect results in significant adverse effects in some geriatric patients. On this basis, a controlled release formulation of furosemide is very desirable.

Generally, a controlled release formulation is designed to provide immediate release (IR) to achieve the therapeutic drug concentration in a short period of time and controlled release (CR) to maintain the concentration for the desired period of time. The dose of furosemide to be incorporated in the developed formulation was decided on the basis of the *in vitro* release pattern of the marketed formulation, Lasix Retard® 60 mg. It was found that the marketed formulation showed the desired controlled release in pH 6.8 buffer but slower release at lower pH (Supplementary Fig. 1). At pH 6.8, about 30% of the drug was released in the first hour followed by release of the remaining drug over the subsequent 12 h. By considering biopharmaceutical parameters including oral bioavailability, half life and plasma steady state concentration[7], it was decided to design a formulation incorporating 30% of the total furosemide dose in a polymeric film for IR and the remainder in a mucoadhesive film folded and inserted in a capsule for CR. The aim was to design a dosage form providing optimal drug release for maximum absorption.

2. Materials and methods

2.1. Materials

Furosemide was obtained from Ipca Labs (Mumbai, India). Polyvinyl alcohol (Gohnesol®), hydroxypropyl methylcellulose (Methocel® E4M, HPMC E4M), poly(ethyl acrylate-*co*-methyl methacrylate-*co*-trimethylammonioethyl methacrylate chloride) (Eudragit® RLPO) and acrylic acid polymer (Carbopol® 971P NF) for preparation of polymer films were provided by Nippon Gohsei (Japan), Colorcon (India), Degussa-Evonik (Germany) and Noveon (India) respectively. Polyethylene glycol 400 (PEG 400, Lutrol® E400) from Merck (India) was used as a plasticizer. PEG-40 hydrogenated castor oil (Cremophore® RH 40), 2-pyrrolidinone (Soluphor® P) and hydroxypropyl β-cyclodextrin (HPBCD, Kleptose® HP) for use as solubilizers were supplied by BASF Ltd. (Germany), Colorcon (India) and Signet Chemical Corporation (India) respectively. All other reagents and chemicals were of analytical reagent grade and used as received.

2.2. Preparation of films

Films with single and double layers were prepared by the solvent casting method on a Mathis lab dryer and lab coater (Mathis AG, Switzerland) using a knife over the roll assembly. Preparation of the solutions used to make single films and the method of making the bilayer film are as follows.

2.2.1. Solution A (controlled release (CR) layer)

A polymeric dispersion was prepared by dissolving HPMC E4M, Eudragit® RLPO, Carbopol® 971P NF (5:0.95:0.05) in isopropanol:water (3:1). A furosemide solution was prepared containing furosemide:Soluphor® P:Cremophore® RH 40 in the ratio 1:1.75:1.75. The furosemide solution was mixed with the polymeric dispersion (1:1) followed by addition of HPBCD (1.5 M) with vigorous stirring to give solution A.

2.2.2. Solution B (immediate release (IR) layer)

Polyvinyl alcohol (15% *w*/*w*) was dissolved in distilled water to which PEG 400 (5%, *w*/*w*) was added as plasticizer. Furosemide was dissolved in 0.05 M NaOH solution and the solution mixed with the polymer solution (1:1) followed by addition of HPBCD (1.5 M) with vigorous stirring to give solution B.

2.2.3. Bilayer film

First solution A was cast on the release liner and allowed to dry at 40 °C for at least 90 min. Then solution B was cast over the formed controlled release layer and allowed to dry for 60 min at 40 °C followed by 30 min at 60 °C. On removal for the release liner, the films were checked for possible imperfections before being cut into 4 cm × 2 cm rectangles and used to fill hard gelatin size 00 capsules by zigzag folding.

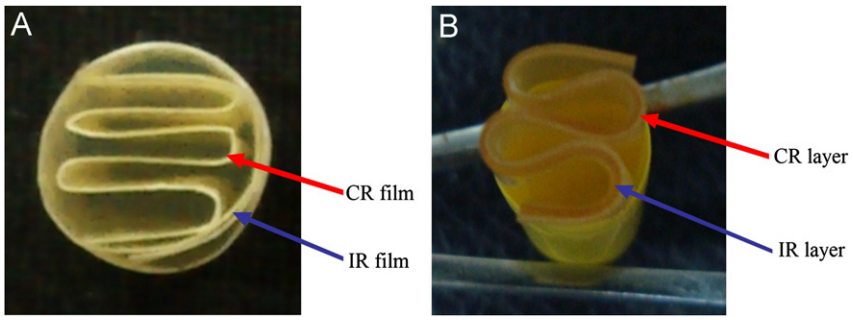

Figure 1 Folding patterns of film in hard gelatine capsule for (A) Case I and (B) Case II.

Table 1 Composition of formulations containing different HPMC E4M concentrations in the CR layer.

Ingredient	Formulation		
	F1	F2	F3
IR layer			
Drug	1	1	1
Soluphor® P	1.75	1.75	1.75
Cremophore® RH 40	1.75	1.75	1.75
PEG 400	0.75	0.75	0.75
Polyvinyl alcohol	15	15	15
Water	100	100	100
CR layer			
Drug	1	1	1
Soluphor® P	1.75	1.75	1.75
Cremophore® RH 40	1.75	1.75	1.75
Eudragit® RLPO	5	5	5
HPMC E4M	0.5	1	1.5
Isopropanol:water (3:1)	100	100	100

All values are % *w*/*w*.

Table 2 Composition of formulations containing different HPBCD concentrations in both IR and CR layers.

Ingredient	Formulation			
	F2	F4	F5	F6
IR layer				
Drug	1	1	1	1
HPBCD	0	0.5	1	1.5
PEG 400	0.75	0.75	0.75	0.75
Ploy vinyl alcohol	15	15	15	15
Water	100	100	100	100
CR layer				
Drug	1	1	1	1
HPBCD	0	0.5	1	1.5
Soluphor® P	1.75	1.75	1.75	1.75
Cremophor® RH 40	1.75	1.75	1.75	1.75
Eudragit® RLPO	5	5	5	5
HPMC E4M	1	1	1	1
Isopropanol:water (3:1)	100	100	100	100

All values are % *w*/*w* except that HPBCD is in molar proportion to drug.

2.3. *Optimization of formulation*

The drug loaded polymeric film was optimized for folding behavior, drug release, mucoadhesion and integrity as described below.

2.3.1. *In vitro unfolding study*

Two methods of film folding were compared for their ability to unfold. In case I, the two layers remained separated; the CR layer was folded in a zig-zag manner and the IR layer rolled over the CR layer (Fig. 1A) before insertion into the capsule. In case II, the bilayer film was prepared and folded in a zig-zag manner (Fig. 1B) before insertion into the capsule. Eight capsules of each type were prepared and subjected to an *in vitro* dissolution study in 900 mL aqueous hydrochloric acid pH 1.2 at 37.5±0.5 °C using the USP XXIII Apparatus 1 (basket) at 50 rpm. Baskets were removed after 5, 15, 30, 60, 120, 240, 480 and 720 min and the films examined for their unfolding behavior.

2.3.2. *Effect of HPMC E4M concentration in the CR layer*

Different formulations of the CR layer were prepared by varying the concentration of HPMC E4M whilst maintaining the composition of the IR layer as shown in Table 1. *In vitro* drug release of the prepared formulations in 900 mL pH 6.8 phosphate buffer, aqueous hydrochloric acid pH 1.2 and pH 4.5 acetate buffer was determined as described in Section 2.3.1. Samples were removed at 0, 1, 2, 4, 8 and 12 h and furosemide content analyzed by UV spectrophotometry at 274 nm. Standard curves in media at pH 1.2, 4.5 and 6.8 were $y=0.0586x+0.0039$ ($R^2=0.9999$), $y=0.0641x+0.0101$ ($R^2=0.9996$), $y=0.634x+0.0032$ ($R^2=0.9996$) and $y=0.0625x+0.0178$ ($R^2=0.9989$), respectively. The UV spectra of placebo and drug containing formulations were compared to show the assay was free from interference from constituents in the formulations (Supplementary Fig. 2).

2.3.3. *Effect of HPBCD concentration in both layers*

To reduce the effect of pH on the formulation, HPBCD was incorporated. Batch F2 from the study described in Section 2.3.2 was prepared by incorporating HPBCD in both layers (IR and CR) with different drug:HPBCD molar ratios (Table 2). *In vitro* drug release in aqueous hydrochloric acid pH 1.2 was tested at 37.5±0.5 °C and 50 rpm as described above.

Table 3 Composition of formulations containing different Carbopol® 971P NF: HPMC E4M ratios in the CR layer.

Ingredient	Formulation			
	F6	F7	F8	F9
IR layer				
Drug	1	1	1	1
HPBCD	1.5	1.5	1.5	1.5
PEG 400	0.75	0.75	0.75	0.75
Ploy vinyl alcohol	15	15	15	15
Water	100	100	100	100
CR layer				
Drug	1	1	1	1
HPBCD	1.5	1.5	1.5	1.5
Soluphor® P	1.75	1.75	1.75	1.75
Cremophor® RH 40	1.75	1.75	1.75	1.75
Eudragit® RLPO	5	5	5	5
HPMC E4M	1	0.75	0.9	0.95
Carbopol 971P NF	0	0.25	0.1	0.05
Isopropanol:water (3:1)	100	100	100	100

All values are % *w/w* except that HPBCD is in molar proportion to drug.

2.3.4. *Effect of Carbopol® 971P NF: HPMC E4M ratio in the CR layer*

To improve the integrity of the film during *in vitro* dissolution, Carbopol® 971P NF was incorporated in the CR layer of the formulation. The composition of the IR layer was the same for each formulation whilst that of the CR layer contained different proportions of Carbopol® 971P NF and HPMC E4M (Table 3). The prepared formulations were tested for *in vitro* drug release, bioadhesion, swelling and mechanical performance.

2.3.4.1. In vitro bioadhesion. Bioadhesion of the CR layer of the film to stomach mucosa was evaluated in triplicate using a double beam physical balance as described previously[8]. Briefly, the stomach mucosa of Wistar rats was excised, washed with Tyrode's solution and tied tightly (mucosal side upwards) using a thread to the end of a cylindrical Teflon block. The cylinder was placed into a glass container which was then filled with either aqueous hydrochloric acid pH 1.2 or pH 4.5 acetate buffer at 37 ± 1 °C until the fluid just reached the surface of the mucosal membrane. This was placed below the left arm of the balance. The moist film was then brought into contact with a film (CR layer downwards) attached to the lower surface of another Teflon cylinder suspended from the left arm of the balance by removing a 5 g weight from the right pan of the balance. The balance was kept in this position for 3 min after which weights were added slowly to the right pan until the film separated from the mucosal surface. The excess weight on the pan (total weight minus 5 g) is the bioadhesive strength required to separate the film from the mucosa. The force of adhesion was calculated using the formula:

$$\text{Force of adhesion (N)} = (\text{Bioadhesive strength}/1000) \times 9.81 \quad (1)$$

2.3.4.2. In vitro residence time. The *in vitro* residence time was determined in triplicate as described previously[9]. The CR side of a film was applied to freshly prepared rat stomach mucosa fixed to a glass slide with cyanoacrylate glue and suspended from a reciprocating motor. The slide was suspended in a beaker filled with 800 mL aqueous hydrochloric acid pH 1.2 or pH 4.5 acetate buffer and moved vertically in and out of the medium by switching on the motor. The experiment was continued until the film detached or eroded from the mucosa.

2.3.4.3. Swelling behavior. Swelling of films was examined in triplicate in simulated gastric fluid (pH 1.2) and pH 4.5 acetate buffer according to the following procedure[10]. After recording the initial weight of a film (W_1), it was immersed in medium maintained at 37 ± 1 °C for 360 min and then weighed again (W_2). The swelling ratio was determined as $(W_2 - W_1)/W_1$.

2.3.4.4. Mechanical performance. Mechanical properties of films free of physical defects were determined in triplicate using a universal testing machine (UTM, LLOYD) as previously described[11,12]. Rectangular samples of film (30 mm × 5 mm) were subjected to analysis based on ASTM D-882. The films were carefully placed between the two vertical grips of the tester and the movable grip then driven upward at 5 mm/min until the film ruptured. From the recorded load-extension profile, the tensile strength, percent elongation at break and Young's modulus were calculated.

2.4. *Characterization of optimized formulation*

2.4.1. *In vitro drug release*

In vitro dissolution of optimized formulation F9 was studied in media of different pH using the procedure described in Section 2.3.2. Dissolution of the marketed formulation, Lasix Retard® 60 mg, was also determined in aqueous hydrochloric acid pH 1.2 for comparison. *In vitro* release profiles were fitted to different kinetic models including zero order, first order, Korsmeyer–Peppas model, Higuchi model and Hixson–Crowell model and the correlation coefficients of the fits compared.

2.4.2. *Scanning electron microscopy (SEM)*

Morphological characteristics (deformities, drug crystals and cracks) of the IR layer, CR layer and bilayer film of formulation F9 were studied using a Jeol Scanning Electron Microscope (JSM-6380 LA) at an acceleration voltage of 10 kV.

2.4.3. *Differential scanning calorimetry (DSC)*

The thermal behavior of furosemide, HPBCD, the IR layer, CR layer and bilayer film of formulation F9 was estimated in terms of their melting endotherms using a Pyris 6 instrument (Perkin Elmer) with 3 mg film samples in standard aluminium pans. The samples were heated from 30 °C to 250 °C at a constant rate of 5 °C/min under nitrogen.

2.4.4. *X-ray diffraction (XRD)*

XRD analysis was carried out to characterize the physical structure (crystallinity, amorphousness, etc.) of furosemide, HPBCD, the IR layer, CR layer and bilayer film of formulation F9 using a Rigaku Miniflex instrument (Japan) with "Ni-filtered" CuK radiation of wavelength $\lambda = 1.54060$ Å. The scan was taken in the 2θ range of 5–40° with a scanning speed and step size of 1°/mm and 0.01°, respectively.

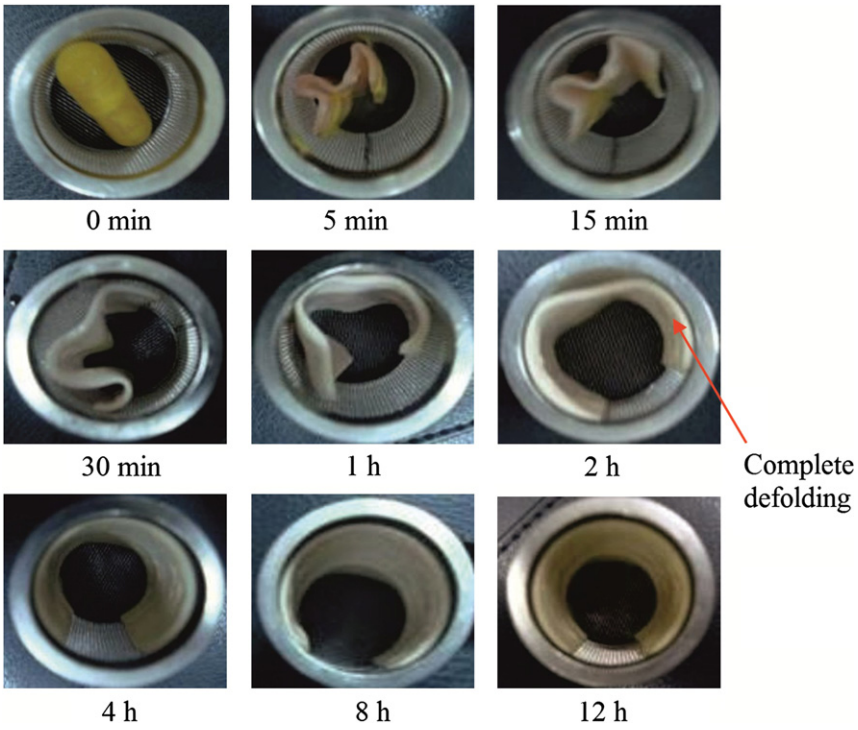

Figure 2 Unfolding behavior of Case II film.

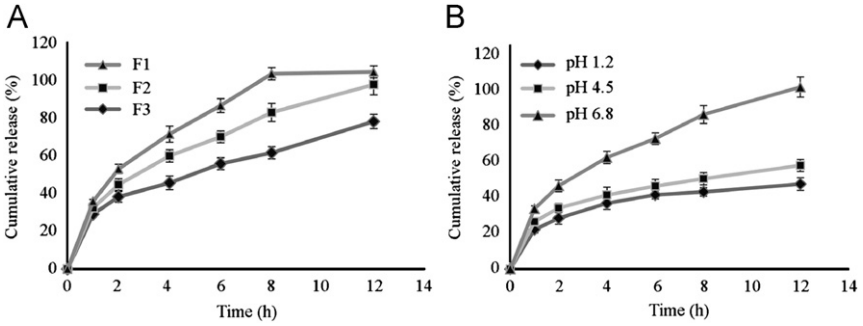

Figure 3 *In vitro* release of furosemide in pH 6.8 buffer as a function of (A) HPMC E4M concentration (% *w*/*w*) in the CR layer in batches: F1, 1.5%; F2, 1%; F3, 0.5%. (B) *In vitro* release of furosemide from batch F2 in aqueous hydrochloric acid pH 1.2 and pH 4.5 and 6.8 buffers.

3. Results and discussion

3.1. Unfolding behavior

The unfolding behavior of the IR and CR films placed separately in case I capsules was not acceptable in that, although the IR layer dissolved within 10 min and the CR layer swelled with time, the CR layer failed to unfold (Supplementary Fig. 3). In contrast, the behaviour of the bilayer film in case II capsules was satisfactory in that the CR layer swelled and the film unfolded in an acceptable manner (Fig. 2).

The problem of unfolding of a film arises due to a reduction in its resiliency to restore its original shape (its so-called mechanical shape memory) after prolonged stress applied during its storage[1]. Films made of polymeric material with prolonged shape memory are therefore useful since they undergo less plastic deformation and maintain their elasticity whilst folded. Such polymers have glass transition temperatures close to ambient temperature. In the present formulation, the CR layer was prepared from polymeric materials (Eudragit® RLPO, HPMC E4M and Carbopol® 971P NF) with very high glass transition temperatures. In contrast, the IR layer was prepared from polyvinyl alcohol which has a glass transition temperature closer to ambient temperature. In using a bilayer as in case II, the IR layer helps to maintain the mechanical shape memory of the CR layer resulting in a film with the desired unfolding characteristics. The CR layer failed to unfold after release from case I capsules due to its low mechanical shape memory.

3.2. Optimization of formulation

3.2.1. Effect of HPMC E4M concentration in the CR layer

An increase in the HPMC E4M concentration in the CR layer was found to retard drug release from the bilayer in pH 6.8 phosphate buffer (Fig. 3A). Batch F2 showed a better controlled release profile than batches F1 and F3 which

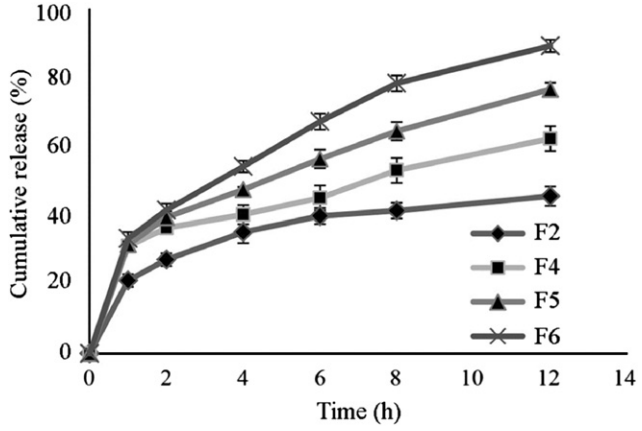

Figure 4 *In vitro* release of furosemide in aqueous hydrochloric acid pH 1.2 as a function of HPBCD concentration (in molar proportion to drug) in batches: F2, 0; F4, 0.5; F5, 1; F6, 1.5.

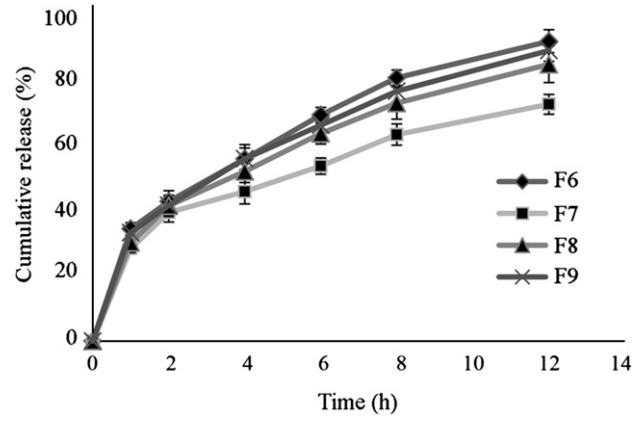

Figure 5 *In vitro* release of furosemide in aqueous hydrochloric acid pH 1.2 as a function of Carbopol® 971P NF: HPMC E4N ratio (total concentration 1% *w*/*w*) in the CR layer in batches: F6, 0:1; F9, 0.05:0.95; F8, 0.1:0.9; F7, 0.25:0.75.

showed early and slow release respectively. After its dissolution, HPMC swells and creates a viscous gel around the film which is resistant to water penetration. Dissolved drug is released by diffusion through the viscous gel but, with an increase in HPMC concentration, the thickness of the gel layer increases and release of drug is retarded[13].

Comparison of the release profiles of batch F2 in aqueous hydrochloric acid pH 1.2 and pH 4.5 acetate buffer with that in pH 6.8 phosphate buffer is shown in Fig. 3B. Given that furosemide is practically insoluble at acidic pH, the slower drug release with decreasing pH is to be expected.

3.2.2. *Effect of HPBCD concentration in both layers*

An increase in the HPBCD concentration in both layers resulted in a proportional increase in drug release (Fig. 4). This is consistent with the reported increase in solubility of furosemide in the presence of HPBCD[14]. HPBCD has high water solubility and is extensively applied to increase permeability and aqueous solubility of poorly soluble drugs[15].

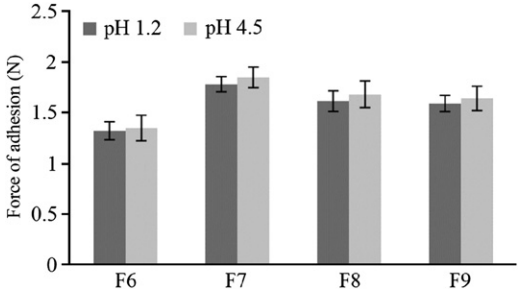

Figure 6 Effect of Carbopol® 971P NF: HPMC E4N ratio (total concentration 1% *w*/*w*) in the CR layer on *in vitro* bioadhesion of the CR layer for batches: F6, 0:1; F9, 0.05:0.95; F8, 0.1:0.9; F7, 0.25:0.75.

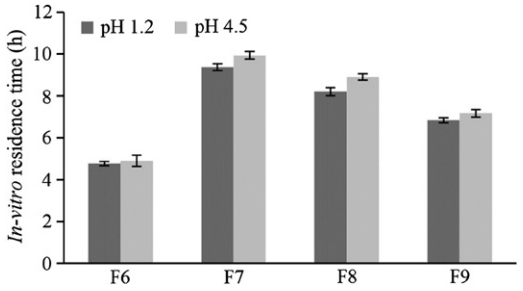

Figure 7 Effect of Carbopol® 971P NF: HPMC E4N ratio (total concentration 1% *w*/*w*) in the CR layer on *in vitro* residence time of the CR layer for batches: F6, 0:1; F9, 0.05:0.95; F8, 0.1:0.9; F7, 0.25:0.75.

3.2.3. *Effect of Carbopol® 971P NF: HPMC E4M ratio in the CR layer*

3.2.3.1. Drug release. The increase in Carbopol® 971P NF: HPMC E4M ratio in the CR layer (F6 < F9 < F8 < F7) (Table 3) led to a small but proportional decrease in drug release (Fig. 5). In order to optimize the controlled release profile of furosemide, the integrity of the bilayer film needs to be maintained throughout the dissolution period. As stated in Section 3.2.1, HPMC forms a viscous, swollen and non-continuous gel on dissolution due to its high hydration index[16] whereas Carbopol undergoes less swelling because less than 10% of the acrylic acid groups are ionized at lower pH resulting in little stiffening by electrostatic charge repulsion. This helps to maintain the integrity of the film.

3.2.3.2. In vitro bioadhesion. The formulations containing both Carbopol 971P NF and HPMC E4M (Batches F7, F8 and F9) showed greater *in vitro* mucoadhesion than the formulation with no Carbopol (Batch F6) (Fig. 6). The reason for the weaker mucoadhesion of batch F6 is because the proton donating carboxylic groups in the acrylic acid polymer, Carbopol® 971P NF, form hydrogen bonds with the negatively charged mucus gel leading to greater physical entanglements[17] and improved mucoadhesion. In addition, HPMC E4M has more neutral cellulose groups and thus forms fewer hydrogen bonds with glycoprotein mucin leading to weaker adhesive forces[18]. Thus the high molecular weight, presence of strong hydrogen bond forming groups (carboxylic acid), anionic nature and sufficient chain flexibility all contribute to the benefit of including Carbopol 971P NF[19].

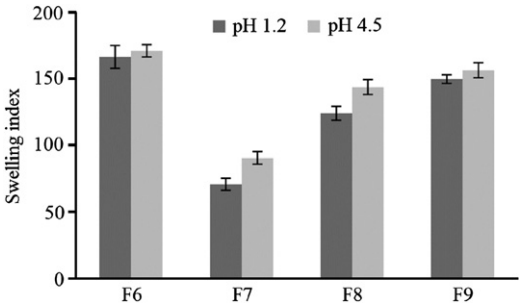

Figure 8 Effect of Carbopol® 971P NF: HPMC E4N ratio (total concentration 1% *w*/*w*) in the CR layer on swelling behavior of the CR layer for batches: F6, 0:1; F9, 0.05:0.95; F8, 0.1:0.9; F7, 0.25:0.75.

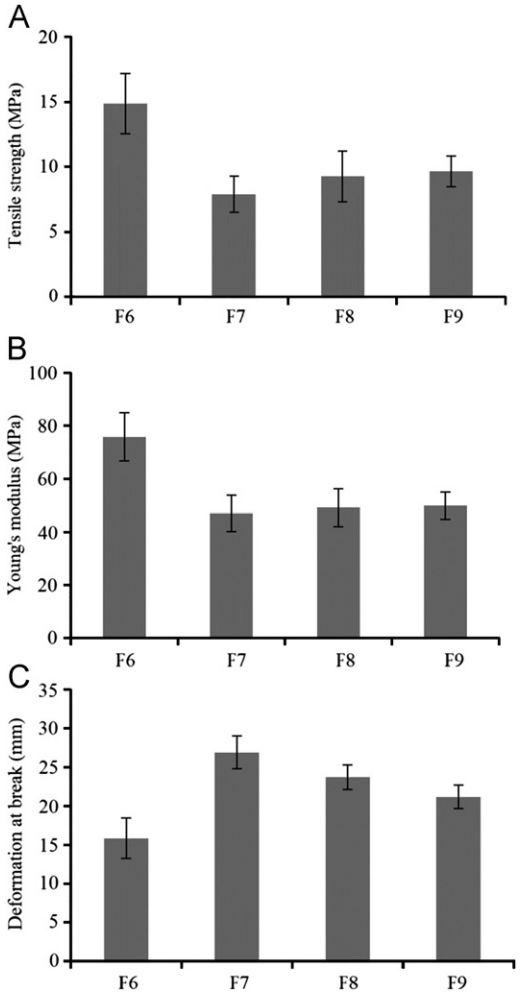

Figure 9 Effect of Carbopol® 971P NF: HPMC E4N ratio (total concentration 1% *w*/*w*) in the CR layer on mechanical performance of the CR layer. (A) tensile strength; (B) Young's modulus; (C) deformation at break for batches F6, 0:1; F9, 0.05:0.95; F8, 0.1:0.9; F7, 0.25:0.75.

3.2.3.3. In vitro residence time. As *in vitro* residence time follows the same principle as *in vitro* bioadhesion, it is not surprising that residence time for the four formulations increased to a small but proportional extent as the Carbopol® 971P NF: HPMC E4M ratio increased (Fig. 7).

3.2.3.4. Swelling behavior. Generally, the swelling of polymers results in enhancement of their mucoadhesion. Here it was found that the swelling of films decreased as the Carbopol® 971P NF: HPMC E4M ratio in the CR layer increased (Fig. 8). However, the results contradict those of the mucoadhesion study in that Carbopol® 971P NF in the film leads to a reduction in swelling but enhanced mucoadhesion.

3.2.3.5. Mechanical performance. Films with increasing Carbopol® 971P NF: HPMC E4M ratio showed poorer mechanical performance with batch F6 showing the highest tensile strength (Fig. 9A), and Young's modulus (Fig. 9B) and the lowest deformation at break (Fig. 9C). The decrease in tensile strength results from the lower glass transition temperature of Carbopol® 971P NF as compared to HPMC E4M.

As the optimum formulation should combine the best combination of *in vitro* drug release, mucoadhesion and mechanical performance, formulation F9 was selected as the optimized formulation. The results of the study of mechanical performance confirm that formulation F9 has sufficient strength, flexibility and elasticity.

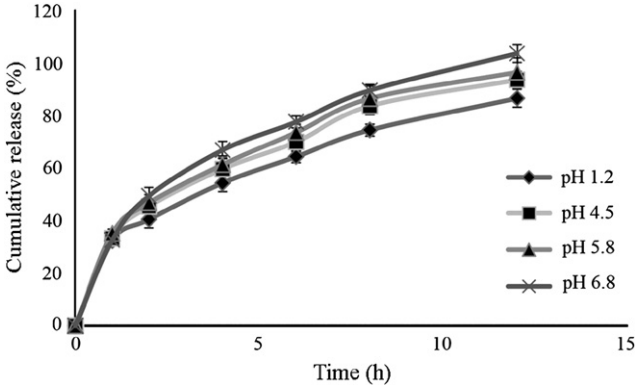

Figure 10 *In vitro* release of furosemide from batch F9 in buffers of different pH.

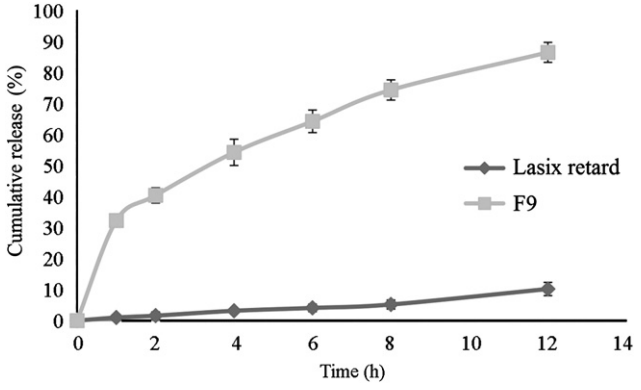

Figure 11 Comparison of *in vitro* release of furosemide in aqueous hydrochloric acid pH 1.2 from the marketed formulation, Lasix Retard® 60 mg, and batch F9.

Table 4 Correlation coefficient (R^2) and constant (K) of different kinetic models of drug release for formulation F9 in aqueous hydrochloric acid pH 1.2.

Kinetic model	Parameter	Value
Zero order	R^2	0.6151
	K_0	8.852
First order	R^2	0.9335
	K_1	0.197
Krosmeyer–Peppas	R^2	0.999
	K_P	30.93
	n^*	0.414
Higuchi	R^2	0.9862
	K_H	26.2
Hixon–Crowell	R^2	0.885
	K_{Hc}	0.053

*Release exponent.

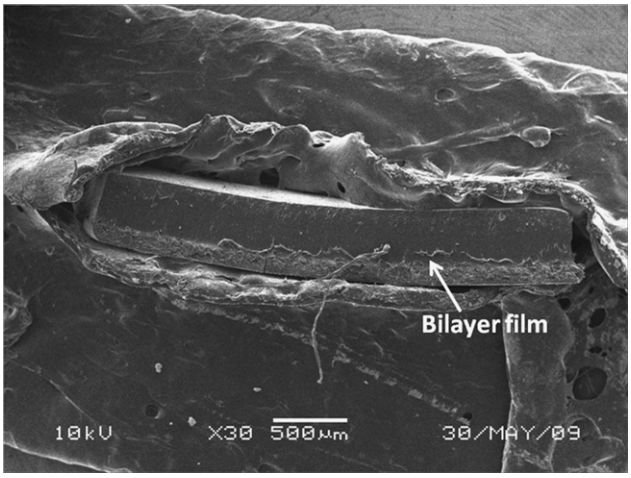

Figure 12 Scanning electron microscopy of the bilayer film.

3.3. *Characterization of optimized formulation*

3.3.1. *In vitro drug release*

In vitro drug release from formulation F9 in media of different pH follows a similar pattern (Fig. 10) with a small increase in amount released with increasing pH from 1.2 to 6.8. Comparison of the drug release pattern of formulation F9 with that from the marketed formulation, Lasix Retard® 60 mg (Fig. 11), shows release was significantly greater from F9 (89% *versus* 10% after 12 h). This is partly because of the rapid release during the first hour (about 30% drug release) resulting from dissolution of the IR layer. As described earlier, the mechanical properties of the IR layer facilitate unfolding of the film that then provides controlled drug release over the subsequent period of 12 h.

Table 4 shows the correlation coefficients of different kinetic models for drug release from formulation F9 in aqueous hydrochloric acid pH 1.2. The best fit was to the Korsmeyer–Peppas model ($r^2 = 0.999$) closely followed by the

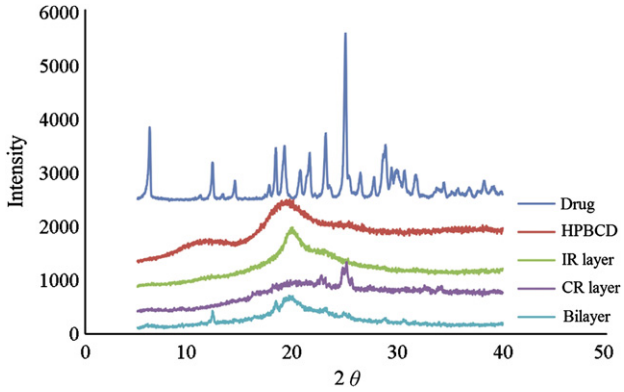

Figure 13 X-ray diffraction patterns of furosemide, HPBCD and the IR, CR and bilayer films.

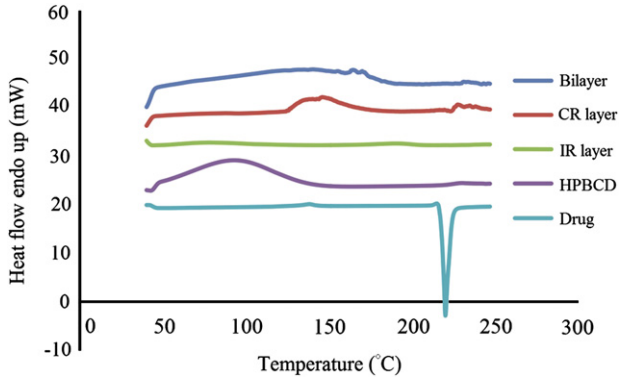

Figure 14 DSC thermograms of furosemide, HPBCD and the IR, CR and bilayer films.

Higuchi model. The release exponent n of 0.414 indicates release occurs by Fickian diffusion [20].

3.3.2. *SEM*

Both layers of the bilayer film were macroscopically homogeneous and fairly transparent with no crystals on either surface of the film (Supplementary Fig. 4). The presence of streaking may be due to high consistency of the dispersion or to problems with the casting procedure. The lateral view of the film (Fig. 12) clearly shows the presence of both the IR and CR layers.

3.3.3. *XRD*

The XRD pattern of furosemide displays crystallinity whereas the diffractogram of HPBCD shows an amorphous pattern. The diffractograms of the IR layer, CR layer and bilayer film (Fig. 13) show amorphous characteristics with drug crystallinity decreasing from 57.2% to 10.7% in the IR layer, to 8.77% in the CR layer and to 9.42% in the bilayer film. These changes indicate uniform molecular dispersion of furosemide in the polymer matrices.

3.3.4. *DSC*

The DSC of furosemide exhibits a sharp exothermic peak at 220.8 °C corresponding to its melting point which is usually

associated with decomposition of the drug. The peak did not appear in the thermograms of any of the polymeric films (Fig. 14) again indicating that drug is uniformly entrapped in the polymeric matrices.

4. Conclusions

A gastroretentive dosage form for controlled release of furosemide, a drug with a narrow absorption window, has been developed and characterized. It consists of a drug loaded polymeric film with immediate (IR) and controlled release (CR) layers folded inside a hard gelatin capsule. The optimized film formulation showed satisfactory controlled release, mucoadhesion and integrity during the release period. The presence of Carbopol® 971P NF in the CR layer and HPBCD in both layers was crucial to provide good dissolution, bioadhesion and mechanical performance of the film. The film with zig-zag folding undergoes appropriate unfolding and expansion in acidic media which, combined with good bioadhesion, indicates the gastroretentive potential of the dosage form. The combination of these favorable characteristics suggests the dosage form is worthy of further development through its evaluation in *in vivo* studies.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.apsb.2012.05.004.

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