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Formulation and Optimization of Novel Bilayer Mucoadhesive Polymeric Films: Defolding and Gastroretention

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ABSTRACT
The aim of the present study was to develop a novel gastrorentative dosage form (GRDF), as drug loaded polymeric film folded in hard gelatin capsule. The proposed mechanism for gastroretention was expansion (unfolding as well as swelling) and bioadhesion to gastric mucosa. Furosemide was selected as model drug. The dosage form was developed as bilayer film having combination of immediate (IR) and controlled release (CR) layer. The optimum formulation of GRDF was obtained on the basis of folding patterns, in-vitro drug release profile, in-vitro bioadhesion, swelling and mechanical performance. The developed formulation was studied via Scanning Electron Microscopy (SEM), X-Ray Diffractometry (XRD), and Differential Scanning Calorimetry (DSC). The obtained data presented that the developed formulation exhibited favorable gastrorentative properties.

KEYWORDS: *Gastroretention, Unfolding, Swelling, Bioadhesion, Bilayer film*

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I. INTRODUCTION

Oral controlled release (CR) dosage forms (DFs) have developed from last 3 decades due to their considerable therapeutic advantages. The drugs having narrow absorption window have gain importance in development of controlled release dosage forms. However, a problem frequently encountered with such a developed dosage forms is the inability to increase residence time in the stomach and proximal portion of the small intestine. To achieve more residence time of dosage forms in this region, many strategies have been developed based on the following approaches (1): (a) low density form of the DF that floats on gastric fluid (2); (b) high density DF that is retained in the bottom of the stomach; (c) bioadhesion to the mucosa (3); (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs and excipients; (e) expansion by swelling or unfolding to a large size which limits the emptying of the DF through the pyloric sphincter.

Above approaches have their own merits and demerits. Hence we developed such formulation which combines basic principles of bioadhesion and physical property such as expansion by unfolding as well as swelling of dosage form. The said formulation has been designed in such a way that it contains a drug loaded polymeric film which is to be folded in hard gelatin capsule. After ingestion the drug loaded polymeric film get defolded in the stomach and swells to a large size which limits its emptying through pyloric sphincter. The swelled film also has bioadhesion so that it adheres to the stomach mucosa.

Furosemide (4-chloro-2-furfurylamino-5-sulphamoyl benzoic acid) is a widely used “high ceiling” loop diuretic which acts on the ascending limb of the loop of Henle (4). Apart from a strong, rapid and short diuretic action it has a haemodynamic effect on the heart. The onset of diuresis by oral dosing commence within 20 minutes and lasts for 4-5 hours (5). The drug has extensive application in oedema of pulmonary, cardiac or hepatic origin as well as in the treatment of hypertension and in the chronic treatment of cardiac infarction. Furosemide is BCS class IV drug having poor aqueous solubility and poor permeability. Furosemide is acidic in nature with pKa value of 3.9, due to which the major absorption site is upper gastrointestinal tract. Furosemide has short half life of less than 2 hours. It has pH dependent solubility. It is practically insoluble in acidic pH and solubility increases with increase in pH (6).

The conventional dosage form of Furosemide shows erratic absorption which results in poor bioavailability i.e. 30-60% and is needed to administer 3-4 times a day which presents the issue of non-compliance (5). These dosage forms are also associated with peak diuresis effect. The peak diuresis causes weakness and fatigue symptoms particularly in elderly patients.

Hence there is a strong need to develop a controlled release formulation for drug like furosemide. Controlled release formulation of furosemide with reduced side effects will be more efficient than presently available conventional dosage forms. Generally these formulations are comprises with loading dose which

achieves the therapeutic drug concentration within short period of time and maintenance dose to maintain the same for desired period of time. In said formulation, the dose has been decided on the basis of in-vitro release of marketed formulation Lasix Retard 60mg. It was found that marketed formulation has tremendous difference in the drug release pattern in different pH buffers as shown in fig. 1. Lasix Retard 60 mg have good controlled release pattern in pH 6.8 buffer. While in that of pH 1.2, pH 4.5 and pH 5.8 the in-vitro drug release was less. In pH 6.8 buffer, there was about 30% drug release in first hour followed by remaining drug release up to 12 hours. By considering biopharmaceutical parameters viz. oral bioavailability, half life, plasma steady state concentration (7), it has been found that for 60 mg of total furosemide dose; loading dose should be 30%. Hence said dosage form has been designed containing combination of immediate release (IR) formulation as a loading dose and controlled release (CR) formulation as maintenance dose.

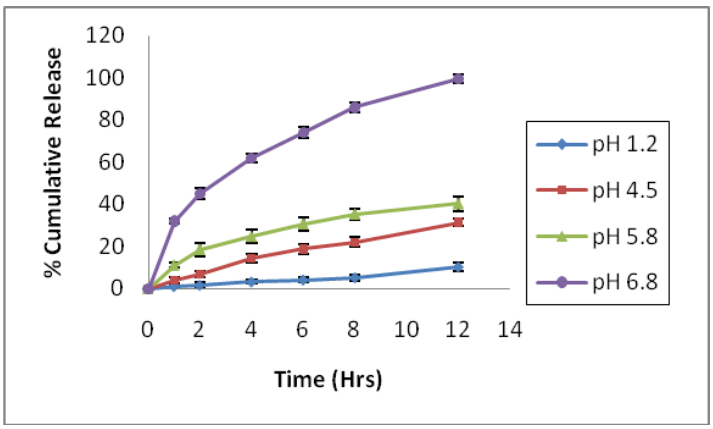

Figure1: In-vitro drug release profile of marketed drug Lasix Retard 60 mg

Hence the purpose of the present research work was,

- To develop the controlled release Furosemide formulation 60 mg and to achieve gastro-retention with desired drug release for the maximum absorption.
- To prepare the formulation containing combination of immediate release (IR) film as a loading dose and controlled release (CR) mucoadhesive film as maintenance dose to be folded and filled in capsule so that after ingestion it will get defolded in gastric region and achieve the objective of gastro-retention.

II. MATERIALS AND METHODS

2.1. Materials

Furosemide was procured from Ipca labs, Mumbai. Ployvinyl alcohol, Hydroxypropylmethylcellulose (HPMC) (E4M grade), Eudragit RLPO and Carbopol 971P NF, provided by Nippon Gohsei, Japan; Colorcon, India; Degussa-Evonik, Germany; and Noveon, India respectively, were used as polymers for the film dosage forms. Polyehtylene glycol 400 was procured from Merck India, used as a plasticizer. Cremophore RH 40, Soluphor P and HPBCD, were supplied by BASF Ltd., Germany; Colorcon, India; and respectively, used as a solubilizers. All other reagents and chemicals used were of analytical reagent grade.

2.2. Fabrication of film dosage forms

Films with single or double layer were prepared by the solvent casting method on Mathis labdryer and labcoater using knife over roll assembly. The optimized formulation was prepared using following method.

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

Polymeric dispersion was prepared using HPMC E4M, Eudragit RLPO, Carbopol 971P NF (5:0.95:0.05) in isopropanol:water (3:1) solvent system. Furosemide was dissolved in soluphor P and cremophore RH 40 with proportion of 1:1.75:1.75 respectively. Furosemide solution was mixed with polymeric dispersion followed by addition of HPBCD (1:1.5 M with respect to drug) with vigorous stirring.

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

Polyvinyl alcohol was dissolved in distilled water to yield solution of 15% w/w. PEG 400 was added (5% of the PVOH) to the PVOH solution as plasticizer. Furosemide was dissolved in 0.05N NaOH solution. Furosemide solution was then mixed with polymer solution followed by addition of HPBCD (1:1.5 M with respect to drug) with vigorous stirring.

2.2.3. Bilayer film

Initially solution A was casted on release liner and allowed to dry at 40^0C for at least 90 mins. Then solution B was casted over the formed controlled release layer and allowed to dry at 40^0C for at least 60 mins initially, followed by 60^0C for at least 30 mins. The films were observed and checked for possible imperfections upon their removal from the release liner. The prepared bilayer films were cut into size of dimensions of 4×2 cm^2 and filled in hard gelatin capsule of size "00" with zigzag folding.

2.3. In-vitro film defolding study

In this study comparison of two cases has been performed. In one case two layers were taken separately. CR layer folded in zig-zag manner and IR layer was rolled over CR layer as shown in Fig. 2A. Then this was filled in capsule. In another case bilayer film was prepared and folded in a zig-zag manner as shown in Fig. 2B. and filled in capsule. For carrying out this study 8 capsules were taken of each case. The films to be folded in capsule were subjected to in-vitro dissolution study in 900ml in pH 1.2 buffer at 37.5 ± 0.5^0C using USP XXIII Apparatus 1 (Basket) at 50 rpm. At time intervals of 5, 15, 30, 60, 120, 240, 480 and 720 mins baskets were removed and films were observed for their defolding performance.

Figure2: Folding patterns of film in hard gelatine capsule

2.4. Optimization of formulation

The formulation was optimized on the basis of drug release, mucoadhesion and film integrity during drug release.

2.4.1. Effect of HPMC E4M concentration

Different formulations of CR layer were prepared by varying concentration of HPMC E4M as shown in Table 1. The composition for IR layer was same for each formulation. The prepared formulations were tested for in-vitro drug release using USP XXIII basket method at 37.5 ± 0.5°C and 50 rpm. As dissolution medium, 900 ml phosphate buffer pH 6.8 was used. Also drug release was checked in pH 1.2 hydrochloric acid buffer and pH 4.5 acetate buffer. Samples were taken at 0, 1, 2, 4, 8, and 12h and evaluated for furosemide content by UV spectrophotometry at 274 nm. The bilayer film was folded in zigzag manner and filled into hard gelatin capsule.

Table 1: Effect of HPMC E4M concentration on release profile of Furosemide

Ingredients	**Formulations**		
	F1	**F2**	**F3**
IR Layer			
Drug	1	1	1
Soluphor P	1.75	1.75	1.75
Cremophor 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
Cremophor 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 the ingredients were taken as %w/w of solvent.)

2.4.2. Effect of HPBCD concentration

To reduce the pH dependency of the formulation HPBCD was incorporated in the formulation. Batch F2 has been selected from previous study and formulations were prepared by taking different molar ratios of drug to HPBCD as shown in Table 2. Here, HPBCD was incorporated in both layers (IR and CR). The prepared formulations were tested for in-vitro drug release using USP XXIII basket method at 37.5 ± 0.5°C and 50 rpm in pH 1.2 hydrochloric acid buffer.

Table 2: Effect of HPBCD concentration on release profile of Furosemide

Ingredients	**Formulations**			
	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
Ployvinyl 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 the ingredients were taken as %w/w of solvent. HPBCD is in molar proportion with Furosemide.)

2.4.3. Effect of Carbopol 971P NF concentration

To improve the integrity of the film during in-vitro dissolution Carbopol 971P NF was incorporated in the formulation. The composition for IR layer was same for each formulation and the CR layer varies with different proportions of Carbopol 971P NF and HPMC E4M as shown in Table 3. The prepared formulations were tested for in-vitro drug release, in-vitro mucoadhesion and swelling studies.

Table 3: Effect of Carbopol 971P NF concentration on release profile of Furosemide

Ingredients	**Formulations**			
	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
Ployvinyl 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 ingredients were taken as %w/w of solvent.)

2.4.3.1. Effect of Carbopol 971P NF concentration on in-vitro bioadhesion of CR layer

Bioadhesion study was carried out according to the procedure described as follows (8): The bioadhesion test apparatus used was working on the principle of double beam physical balance. The wistar rat stomach mucosa was excised and washed with tyrode solution. The mucosa was tied tightly with mucosal side upwards, using a thread over the protrusion in the Teflon block. This block was then placed into the glass container, which was then filled with pH 1.2 hydrochloric acid buffer kept at 37 ± 1^0C, such that the fluid just reaches the surface of mucosal membrane and keeps it moist. This was then kept below left hand setup of the balance. The film was then stuck with a little moisture, on to the lower surface of other Teflon cylinder suspended from the left hand side of the balance and was brought in contact with the mucosa placed on block by removing 5g weight from the right pan of the balance. The balance was kept in this position for 3 minutes and then slowly weights were added on the right pan, till the film separated from the mucosal surface. The excess weight on pan i.e. total weight minus 5g is force required to separate the film from mucosa. The same procedure was followed by using pH 4.5 acetate buffer in glass container. This gave bioadhesive strength of the film in 'g'. Force of adhesion in Newton was given by formula,

Force in Newton = (Biodhesive strength/100) x 9.81

The test was performed for different batches in triplicate. The schematic representation of Bioadhesion test apparatus have been shown in Fig. 3.

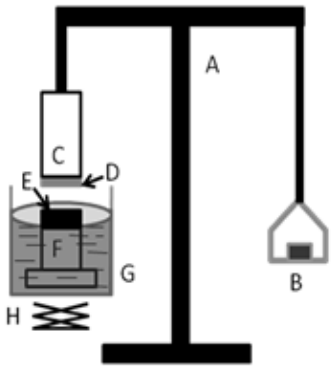

Figure3: Bioadhesive force measuring device
A-Modified Balance, B-weights, C-upper Ceramic cylinder, D-Bioadhesive film, E-Mucosal tissue, F-Lower ceramic cylinder, G- Vessel with wetting medium, H-Height Adjustable Pan

2.4.3.2. Effect of Carbopol 971P NF concentration on in-vitro residence time of CR layer

The in-vitro residence time was performed according to the procedure described as follows (9): The film was applied on freshly cut rat stomach mucosa. The rat stomach mucosa was fixed on the glass slide with cyano acrylate glue and suspended in the beaker filled with 800 ml pH 1.2 hydrochloric acid buffer. The slide allowed to reciprocate in the medium by switching on the motor. Experiment was continued till film got detached or eroded from the mucosa. Same procedure was repeated by taking pH 4.5 buffer as medium (n=3).

2.4.3.3. Effect of Carbopol 971P NF concentration on swelling behavior of CR layer

The swelling study was performed according to the procedure described as follows (10): Initially film was weighed (W_1), then it was immersed in simulated gastric fluid (pH 1.2) buffer solution maintained at 37 ± 1^0C. At the end of 360 mins, film was weighed again (W_2). Average weight of W_1 and W_2 was reported. Same procedure was carried out to study swelling of formulations in pH 4.5 acetate buffer (n=3). The swelling ratio was determined from the formula,

Swelling ratio = $(W_2 - W_1)/ W_1$

2.4.3.4. Effect of Carbopol 971P NF concentration on mechanical performance of CR layer

The prepared films were subjected for the determination of mechanical properties using Universal Testing Machine (UTM) LLOYD instrument according to the procedure described as follows (11): The films of dimensions 30 X 5 mm were cut and subjected for the analysis based on the ASTM D-882. Film specimens with physical defects were discarded. The films were carefully placed between the two vertical grips of the tester during test. The movable grip was then driven upward with a speed of 5mm/min until the rupture of film. From the recorded load-extension profiles, the tensile strength, percent elongation at break and Young's modulus were calculated (n=3).

2.5. SEM study

Morphological characteristics of films were studied using Scanning Electron Microscopy (SEM). The purpose of morphological study was to evaluate film samples for the presence of any deformities, drug crystals and

cracks. The samples were examined in a Jeol Scanning Electron Microscope (JSM-6380 LA) at an acceleration voltage of 10 kV.

2.6. DSC study

The thermal behaviour of the films was estimated in terms of its melting endotherm as determined by differential scanning calorimetry (DSC). The DSC was performed using Differential Scanning Calorimeter (Pyris 6) of Perkin Elmer with 3 mg samples in standard aluminum pans. The samples were heated at a constant rate of 5^0C/min under nitrogen. The measurements were done in the temperature range from 30 to 250^0C.

2.7. XRD study

XRD analysis was carried out to characterize the physical structure of films. In the X-ray diffractogram obtained, the peak position and their sharpness indicate the general physical properties of the films (for e.g. crystalline, amorphous etc) as well as help identifying the compound. The X-ray diffraction of the films were recorded using a X-ray diffraction meter (Rigaku miniflex, Japan) with ''Ni-filtered'' CuK radiation of wavelength λ =1.54060 A^0 ˚with a graphite monochromator. The scan was taken in the 2θ range, $5–40^0$ with a scanning speed and step size of 1^0/mm and 0.01^0, respectively. The percentage crystallinity was calculated.

III. RESULTS AND DISCUSSION

3.1. In-Vitro Defolding Study

The case in which CR layer folded in zig-zag manner and IR layer was rolled over CR layer have showed poor defolding performance as shown in Fig. 4A. In this case the IR layer gets dissolved within 10 minutes. The CR layer gets swelled as time passes but it failed to defold properly which was not desirable. In another case where bilayer film was folded in a zig-zag manner have showed good defolding performance as shown in Fig. 4B. In this case the CR layer gets swelled along with desired defolding as time passes.

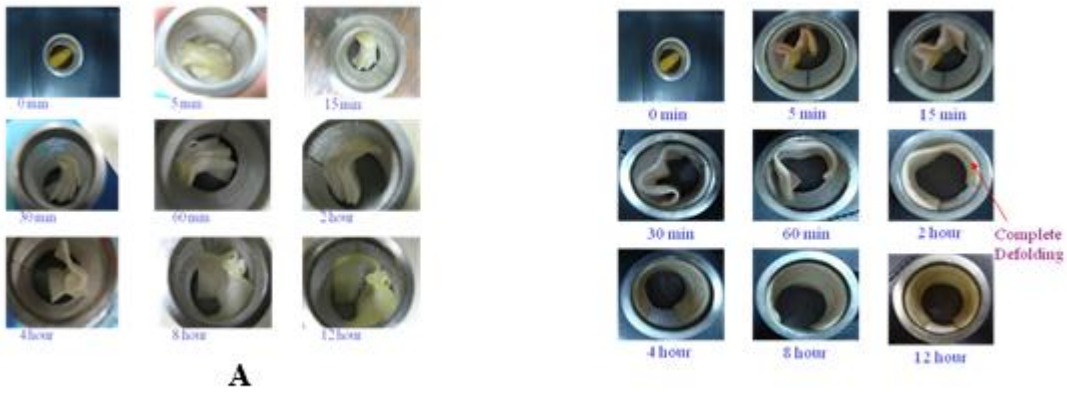

Figure 4: Defolding performance of A: Case I and B: Case II

The difficulty in defolding of film was due to the mechanical shape memory of its polymeric constitution. The prolonged stress applied during storage reduces the resiliency and ability of the films to defold in desired manner (1). The films containing the polymeric material with prolonged shape memory, used to prevent the plastic deformation and ascertain the elasticity. These polymeric materials have glass transition (T) near room temperature.

In present formulation CR layer was prepared from the polymeric materials such as Eudragit RLPO, HPMC E4M and Carbopol 971P NF. All these polymers had glass transition far away from the room temperature. IR layer was prepared from the polyvinyl alcohol which had glass transition nearer to room temperature as compared to polymers of CR layer. In case B, as the two layers were combined the IR layer helped to maintain the mechanical shape memory of the formulation which resulted in the desired defolding. But in case A, as the two layers was folded separately, the CR layer failed to defold due shorter mechanical shape memory of the polymers.

3.2. Optimization of Formulation

3.3.1. Effect of HPMC E4M concentration

As shown in fig. 5A it has been observed that increase in HPMC E4M concentration retard the drug release. Batch F2 showed desirable controlled release profile in comparison to batches F1 and F3. Batch F1 showed early release and batch F3 showed slow release.

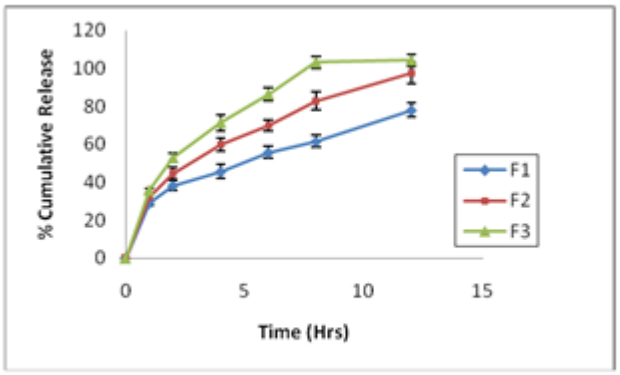

Figure 5A: Effect of HPMC E4M concentration on in-vitro release of furosemide
(HPMC E4M concentration; F1:1:5, F2:1, F3:0:5, W/W of solvent)

HPMC builds up an excessively viscous gel after its dissolution. This gel is more resistant to water penetration. Dissolved drug is released by diffusion through the viscous gel. With increase in HPMC quantity, the thickness of the swollen gel layer also increases. Also, the diffusional path length for the drug increase, thus causing the release rate to decrease (12).

Although the batch F2 has given controlled drug release pattern, there was further need to optimize the formulation. As the formulation was likely to be defolded in the gastric region, its release profile in the pH 1.2 hydrochloric acid and pH 4.5 acetate buffers have been checked. Furosemide is having pH dependent solubility and is practically insoluble in acidic pH; hence batch F2 has given tremendous difference in drug release pattern as shown in Fig. 5B. To increase the dissolution rate HPBCD have been incorporated in the formulation.

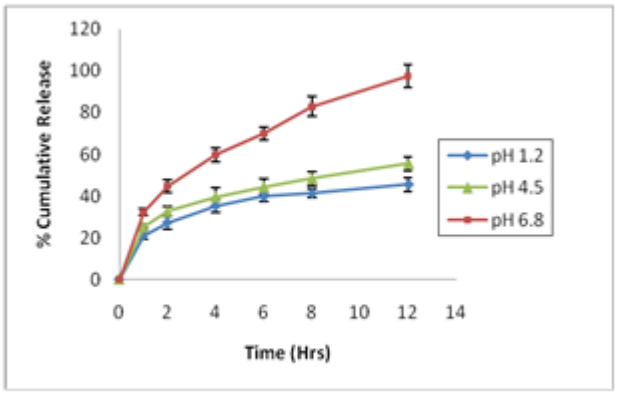

Figure 5B: In-vitro drug release of formulation F2 in different pH buffers

3.3.2. Effect of HPBCD concentration

It was found that as we go increasing the drug as to HPBCD proportion, there was increase in drug release as shown in Fig. 6. Increase in solubility of furosemide with hydroxypropyl-β-cyclodextrin and β-cyclodextrin, have been shown previously (13). HPBCD shows improved safety and solubility properties compared to the parent β-cyclodextrin.

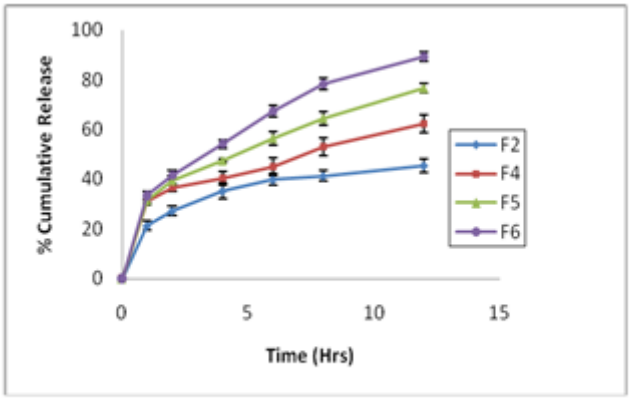

Figure6: Effect of HPBCD on drug release profile of furosemide in pH 1:2 buffer
(HPBCD concentration; F2:0, F7:0:5, F8:1, F9:1:5 in molar proportion with drug)

In case of present formulation the integrity of dosage form throughout dissolution period was very important. HPMC have higher hydration index. It formed a thick and viscous-swollen gel which was not being continuous and forms localized pockets of polymer (14). Due to which this swelled film was not so strong to withstand with peristaltic movements of the GI tract. Also the mucoadhesion offered by HPMC was not so enough which may result in dislodging of film from the stomach mucosal wall under the influence of the peristaltic movements.

3.3.3. Effect of Carbopol 971P NF concentration

To improve the integrity and mucoadhesion over a period of drug release, Carbopol 971P NF was chosen. In case of Carbopol, at lower pH less than 10% of the acrylic acid groups of carbopol will be ionized, resulting in relatively little stiffening by electroststic charge repulsion and relatively less swelling which helps to maintain the integrity of the film. Whereas on another side, the numerous proton-donating carboxylic groups of Carbopol form hydrogen bonds with the negatively charged mucus gel following the formation of physical entanglements (15), which serves the purpose of mucoadhesion.

There was decrease in drug release after addition of Carbopol 971P NF as shown in Fig. 7. The minimum concentration has been optimized which retained the integrity, Mucoadhesion and desired drug release in gastric region. As the concentration of Carbopol 971P NF decreased from batch F7 to batch F9, the drug release get increased respectively. Batch F9 contained minimum concentration of Carbopol 971P NF has shown desired controlled release pattern whereas as in batches F7 and F8 drug release was retarded due to more concentration of Carbopol 971P NF.

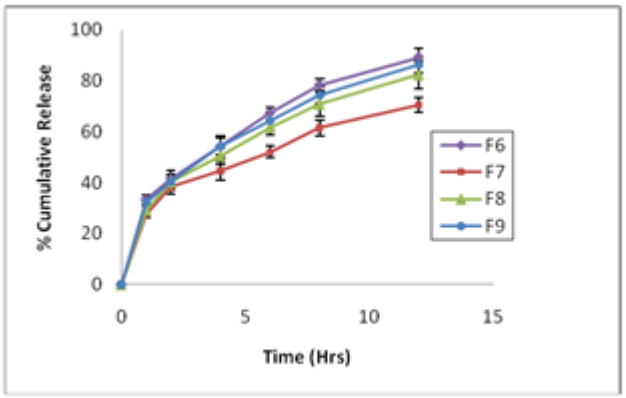

Figure7: Effect of Carbopol 971P NF concentration on release profile of furosemide in pH 1:2 hydrochloric acid buffer: (Carbopol 971P NF concentration; F6:0, F7:0:5, F8:0:1, F9:0:05%W/W of solvent)

3.3.3.1. Effect of Carbopol 971P NF concentration on in-vitro bioadhesion of CR layer

The formulations containing both Carbopol and HPMC (Batch F7, F8 and F9) have showed greater in-vitro mucoadhesion than formulation with only HPMC (Batch 6) as shown in Fig. 8. The reason behind the less in-vitro mucoadhesion of batch F6 was due to more neutral cellulose groups of HPMC which showed lesser hydrogen bonding with glycoprotein mucin and hence weaker adhesive force (16). On the other hand more mucoadhesion with batches F7 to F9 was due to Carbopol 971P NF. Carbopol has all the desirable properties such as high molecular weight, strong hydrogen bond forming groups (carboxylic acid), strong anionic nature and sufficient chain flexibility (17). Hence it proved to be a better mucoadhesive.

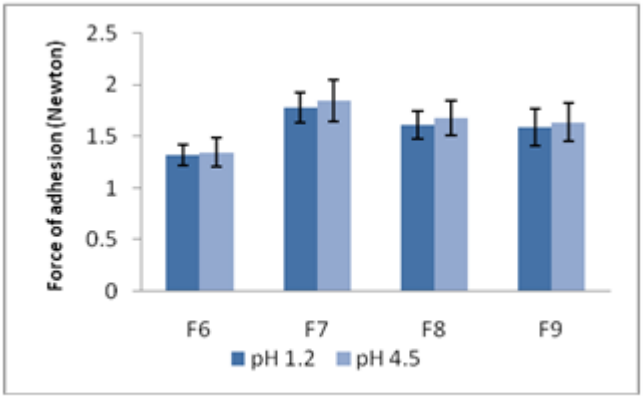

Figure 8: Effect of Carbopol 971P NF concentration on in-vitro bioadhesion of CR layer (Carbopol 971P NF concentration; F6:0, F7:0:5, F8:0:1, F9:0:05%W/W of solvent)

The results obtained by the study of in-vitro residence time as shown in Fig. 9. were complementary to the in-vitro bioadhesion study, as both studies follow the same principle. Increase in Carbopol 971P NF concentration resulted in increase in in-vitro residence time.

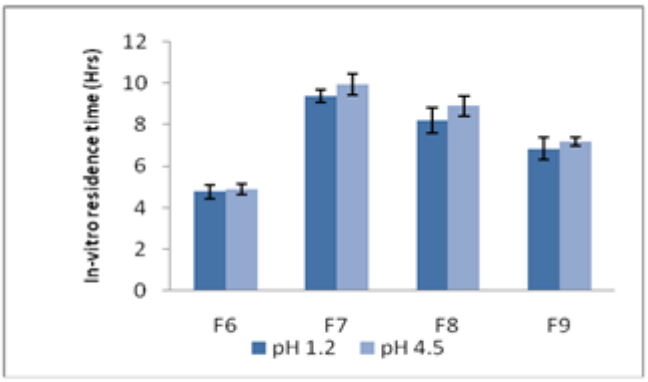

Figure 9: Effect of Carbopol 971P NF concentration on in-vitro residence time of CR layer (Carbopol 971P NF concentration; F6:0, F7:0:5, F8:0:1, F9:0:05%W/W of solvent)

3.3.3.2. Effect of Carbopol 971P NF concentration on swelling behavior of CR layer

The results obtained by swelling study were contradictory with the results of mucoadhesion. The swelling behavior of films gets decreased when Carbopol 971P NF concentration increased as shown in Fig. 10. Swelling rate of polymers plays important role in the mucoadhesion. As swelling increases mucoadhesion also get increases. But in case of our formulation, even there was little swelling, it has given better mucoadhesion. Batchs F7, F8 and F9 have shown less swelling than batch F6 but more mucoadhesion at the same time. The reason behind this contradictory result was presence of Carbopol 971P NF in the formulation.

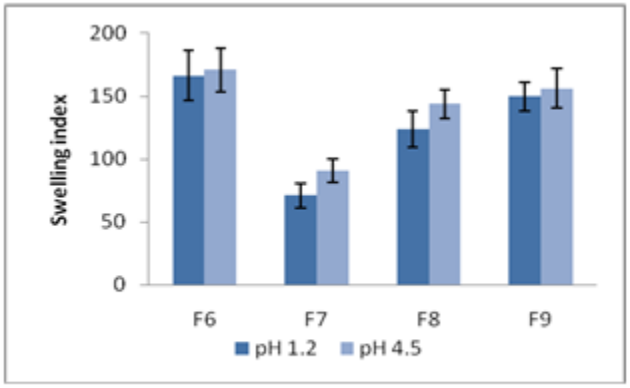

Figure 10: Effect of Carbopol 971P NF concentration on swelling behavior of CR layer (Carbopol 971P NF concentration; F6:0, F7:0:5, F8:0:1, F9:0:05%W/W of solvent)

3.3.3.3. Effect of Carbopol 971P NF concentration on mechanical performance of CR layer

The effect of Carbopol 971P NF on mechanical performance of the CR layer has been shown in fig. 11. The formulations with Carbopol have shown increase in mechanical performance of the film. Batch F6 have more tensile strength and young's modulus than batches F7, F8 and F9. The quite more film deformation at break has been occurred in Carbopol 971P NF containing batches. The decrease in tensile strength has been occurred because of Carbopol 971P NF having lower glass transition temperature as compared to HPMC E4M, due to which it is quietly more flexible.

As the final optimization of the formulation was mainly dependent on the in-vitro drug release, mucoadhesion and mechanical performance of the formulation, batch F9 was taken as optimized formulation considering all these parameters. Batch F9 has shown desired controlled drug release, mucoadhesion and integrity of the film during drug release period. The results from mechanical characterization have confirmed that the optimized batch would have sufficient strength, flexibility, elasticity while handling, packing and transport.

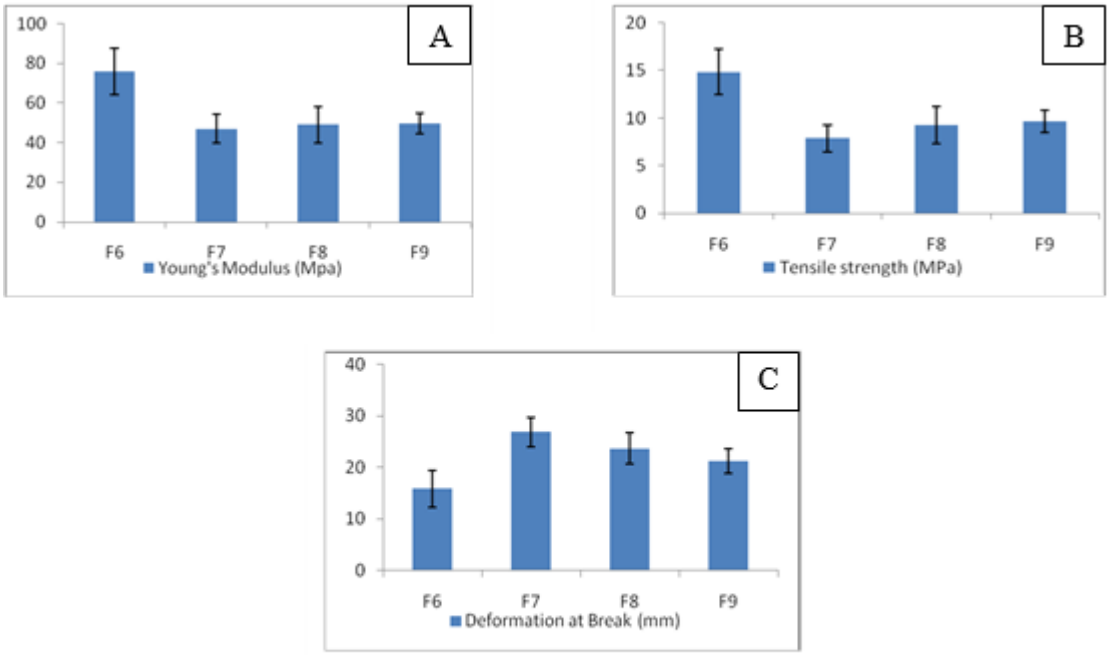

Figure 11: Effect of Carbopol 971P NF concentration on mechanical performance of CR layer; ,A: Tensile strength, B: Young's modulus, C: Deformation at break (Carbopol 971P NF concentration; F6:0, F7:0:5, F8:0:1, F9:0:05%W/W of solvent)

3.4. SEM study

The bilayer film in which both layers were macroscopically homogeneous and sufficiently transparent. The SEM microphotographs for film have shown in Fig. 12. There was no presence of any crystals on the surface of film from both sides. The presence of streaking may be due a quite high consistency of the dispersion or to a certain difficulty encountered in the casting procedure. The side view of bilayer film clearly showed the presence of IR layer and CR layer.

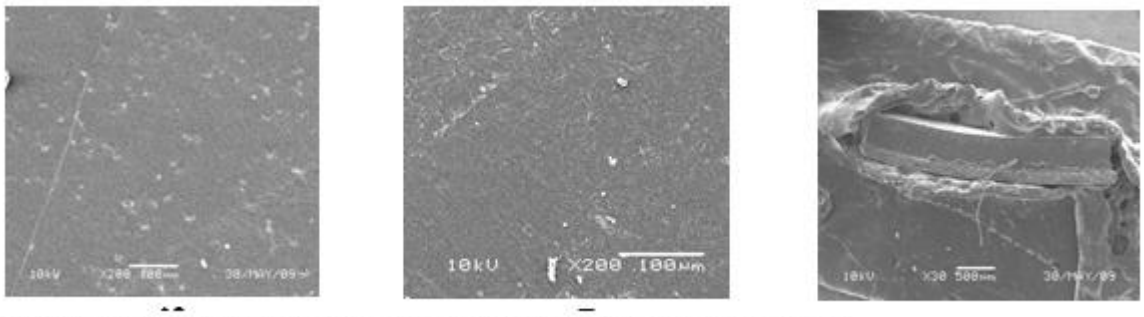

Figure 12: Scanning electron microscopy of furosemide films A) IR layer B) CR layer C)Bilayer film

3.5. XRD study

The X-ray diffractions of Furosemide, HPBCD, IR film, CR film and bilayer film are shown in Fig. 13. The X-ray powder diffraction pattern of Furosemide displayed crystallinity. The diffractogram of HPBCD showed amorphous pattern. The diffractograms of IR, CR and bilayer film showed amorphous characteristics without crystalline characteristics of Furosemide. The drug crystallinity was decreased from 57.17% to 10.74% for IR film, 8.77% for CR film and 9.42% for bilayer film. These changes probably were caused by the uniform dispersion of furosemide in the polymeric matrices.

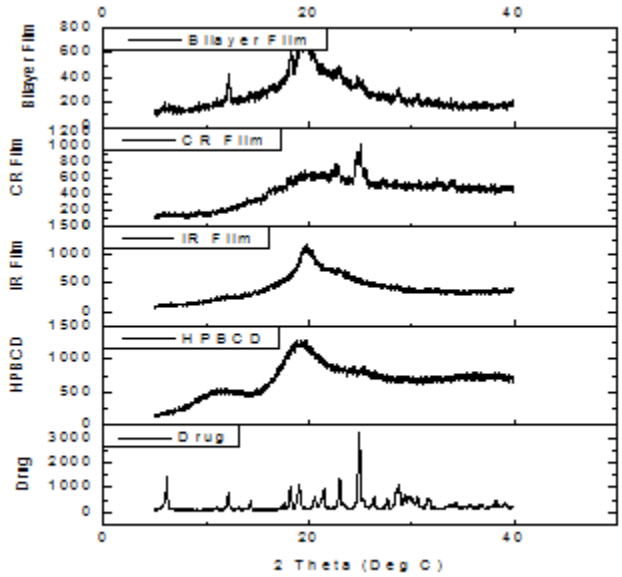

Figure13: X-ray diffraction patterns of Furosemide, HPBCD, IR, CR and Bilayer film

3.6. DSC study

The DSC thermograms of furosemide, HPBCD and drug loaded polymeric films are shown in Fig. 14. Furosemide exhibited a sharp exothermic peak at 220.8^0C corresponding to its melting point which is usually associated with the decomposition of drug. The peak of drug did not appear in the thermogram of any type of the polymeric films containing the drug. It indicates that the drug was uniformly entrapped in the polymeric matrices with change in its physical characteristics like crystalline nature.

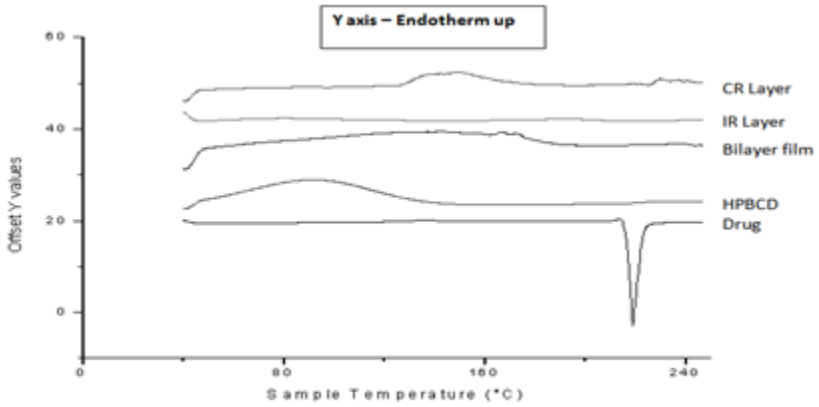

Figure14: DSC themograms of furosemide, HPBCD, IR, CR and Bilayer film

IV. CONCLUSIONS

Gastroretentive bilayer film for drugs having narrow absorption window (e.g. furosemide) has been successfully prepared and characterized. The principle of gastroretention was a combination of bioadhesion and physical property such as expansion by unfolding as well as swelling of drug loaded polymeric film. Hydroxypropyl β-cyclodextrin has significantly increased dissolution rate of furosemide in polymeric film. The performance of bilayer film was significantly altered by physical characteristics of polymer like swelling and mucoadhesion. The effects of folding patterns of film in gelatin capsule were studied and it was concluded that the bilayer film with zig-zag folding has good efficiency of defolding which is desirable for gastroretention. Carbopol 971P NF was the key ingredient of the formulation which helped to improve the bioadhesion as well as mechanical performance of the formulation.

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