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# Development and characterization of cellulose–polymethacrylate mucoadhesive film for buccal delivery of carvedilol

Jaya Gopal Meher[a,1,2], Magdaline Tarai[a,2], Narayan P. Yadav[b,*], Ansuman Patnaik[a], Paresh Mishra[a], Kuldeep Singh Yadav[b]

[a] Indira Gandhi Institute of Pharmaceutical Sciences, IRC Village, Bhubaneswar 751 015, India
[b] CSIR-Central Institute of Medicinal and Aromatic Plants, PO: CIMAP, Lucknow 226 015, India

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ABSTRACT

The aim of the present work was to develop and characterize mucoadhesive film of cellulose (methyl cellulose and hydroxy propyl methyl cellulose) and polymethacrylate (Eudragit RSPO) polymers for buccal delivery of carvedilol. Drug and polymers were found to be compatible as revealed by FTIR and DSC analysis. Mucoadhesive films were prepared by solvent casting technique. Swelling studies up to 4 h did not show erosion of film, which was further confirmed by SEM analysis. New, simple and precise instrumental methods were established for the evaluation of mucoadhesive strength ($33.8 \pm 0.37$–$38.4 \pm 0.24$ g) and film strength ($331.2 \pm 0.73$–$369.0 \pm 1.00$ g) of developed films. Mucoadhesive film F5 showed $88 \pm 1.15$% *in vitro* drug release and $80 \pm 2.30$% *ex vivo* drug permeation through goat buccal mucosa in 12 h. Drug release and permeation followed Higuchi's model and mechanism was found to be Fickian type diffusion controlled.



## 1. Introduction

Since last three decades researchers have been focusing on buccal drug delivery, as it has shown ability to enhance the therapeutic efficacy of poorly effective oral drugs (Sudhakar, Kuotsu, & Bandyopadhyay, 2006). Different drug molecules such as miconazole, propranolol, salbutamol, naproxen and progesterone were formulated as mucoadhesive films/patches and found to be therapeutically more effective than conventional formulations (Abruzzo et al., 2012; Madgulkar, Kadam, & Pokharkar, 2009; Patel & Poddar, 2009; Thimmasetty, Pandey, & Babu, 2008; Vishnu, Chandrasekhar, Ramesh, & Rao, 2007). Mucoadhesive films offer many advantages viz. small size and reduced thickness, avoidance of first-pass effect or gastric degradation of drugs, systemic or local action, fast absorption of drugs through rich vasculature of buccal region, flexibility in drug release either towards oral cavity or buccal mucosa, easy removal in emergency cases, controlled or sustained release of drug, dose accuracy and comparatively better stability than other buccal drug delivery system such as gel, cream or ointment (Avachat, Gujar, & Wagh, 2012; Jug, Kosalec, Maestrelli, & Mura, 2012; Portero, Teijeiro-Osorio, Alonso, & Remunan-Lopez, 2007). Drug release from the mucoadhesive polymeric matrix depends on the nature and concentration of polymer as well as drug; hence it is an expertise as well as art to select suitable polymers (for a specific drug) in order to achieve desired release characteristics (Fuertes, Caraballo, Miranda, & Millan, 2010; Maderuelo, Zarzuelo, & Lanao, 2011).

In this study mucoadhesive films of carvedilol (one of the suitable candidates for buccal drug delivery) were formulated and the release pattern of drug from the polymeric matrix containing cellulose (HPMC), the key rate controlling polymer, was investigated. Carvedilol is a non selective beta blocker, used in the management of hypertension, angina pectoris and as an adjunct to standard therapy in symptomatic heart failure. It has high first pass effect and the bioavailability is approximately 25–35%. Oral dose of carvedilol ranges from 3.125 mg/day to 12.5 mg/day. Its physicochemical properties viz. partition co-efficient (log *P*) and molecular weight are reported to be 3.8 and 408.48, respectively (Planinsek, Kovacic, & Vrecera, 2011). Carvedilol administered by buccal route is absorbed through buccal mucosa and directly reaches the systemic circulation bypassing the liver leading increased bioavailability (Thimmasetty et al., 2008; Vishnu et al., 2007).

Two cellulose polymers viz. hydroxy propyl methyl cellulose (HPMC) and methyl cellulose were chosen for the present investigation. HPMC dissolves in cold water, and forms a colloidal solution

* Corresponding author at: Department of Herbal Medicinal Products, CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP), PO: CIMAP, Lucknow 226 015, UP, India. Tel.: +91 522 2718 657/9451244418; fax: +91 522 2716141.
*E-mail addresses:* npyadav@gmail.com, np.yadav@cimap.res.in (N.P. Yadav).
[1] Present address: CSIR-Central Institute of Medicinal and Aromatic Plants, PO: CIMAP, Lucknow 226 015, India.
[2] Equal contribution.

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whereas it is practically insoluble in hot water, dehydrated alcohol, acetone and toluene (Sweetman, 2007). It is widely used as coating agent, film former, rate controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder and viscosity modifier (Castellanos Gil, Iraizoz Colarte, Lara Sampedro, & Bataille, 2008; Huang et al., 2007; Rowe, Sheskey, & Owen, 2006; Sangalli et al., 2004). Methyl cellulose is soluble in equal volume of chloroform and ethanol whereas it swells in cold water to form a clear to opalescent, viscous, colloidal dispersion (Sweetman, 2007). In addition to cellulose polymers, polymethacrylate polymer (Eudragit RSPO) was also used for formulation of mucoadhesive films. Eudragit RSPO is poly (ethyl acrylate, methyl methacrylate, trimethyl ammoni oethyl methacrylate chloride) in the ratio of 1:2:0.1. It swells upon hydration and used as sustained release polymer (Rowe et al., 2006; Sweetman, 2007). Carbopol 940 and methyl cellulose were incorporated in the film formulation as mucoadhesive and film forming polymer (Maurya, Bali, & Pathak, 2012). Although buccal films of carvedilol are reported in literature but the combination of above mentioned polymers (HPMC, Eudragit RSPO, methyl cellulose and Carbopol) used in the present investigation exhibited better film characteristics viz. mucoadhesive and film strength, swelling and drug release/permeation, drug content as well as residence time.

The aim of the present study was to develop mucoadhesive film of carvedilol using HPMC as the key rate controlling polymer which can be a suitable alternative for effective administration of carvedilol. In addition to the formulation and evaluation of the novel mucoadhesive film; new, simple and precise instrumental methods are established for the evaluation of film strength and mucoadhesive strength of films/patches, using CT3 texture analyser with texture Pro CT V1.3 Build 1.5 software. These methods will be highly useful in optimization of mucoadhesive films/patches.

## 2. Materials and methods

Carvedilol and HPMC K15M (15 000 cP) were obtained as a gift sample from Glenmark Generics Ltd., Goa, India. HPMC K4M (4000 cP) and methyl cellulose (4000 cP) were procured from Sigma Aldrich, Mumbai, India. Carbopol 940 was obtained as a gift sample from Lubrizol Advanced Materials India Pvt. Ltd., Mumbai, India. Eudragit RSPO was supplied by Evonik Industries, Germany as a gift sample. Other excipients, chemicals and solvents were of analytical reagent grades purchased from Sigma Aldrich and Merck Chemicals. Fresh goat buccal mucosa was collected from the local slaughter house, Lucknow, India.

### 2.1. Preparation of mucoadhesive films

Mucoadhesive films were prepared by solvent casting method with slight modification (Jain, Jain, Gupta, & Kharya, 2008; Semalty, Semalty, & Kumar, 2008). Briefly, Eudragit RSPO and required quantity of carvedilol (1.56 mg drug in 1 $cm^2$ of prepared film) were dissolved in 3:2 ratio of acetone and isopropanol. HPMC K4M, HPMC K15M, methyl cellulose and Carbopol 940 were prepared as 2% solution and stirred for 2 h before adding it to the drug Eudragit mixture. 0.05% Propylene glycol was added as plasticizer. Finally the above mixture was stirred for 1 h followed by sonication for 15 min and then poured on glass petri dishes (110 mm diameter). The petri dishes were kept overnight at room temperature (25 ± 1 °C) in an undisturbed condition. After complete drying the films were removed carefully and were cut in to 1 $cm^2$ size. The samples were packed in aluminium foil and stored in a glass container at room temperature for further studies. Composition of polymer ratio of film formulations (F1–F5) is shown in Table 1.

**Table 1**
Ratio of polymers for mucoadhesive film formulation.

| Polymers | Formulation code | | | | |
|---|---|---|---|---|---|
| | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ |
| Eudragit RSPO | 5 | 5 | 5 | 5 | 5 |
| Methyl cellulose | 2 | 2 | 2 | 2 | 2 |
| Carbopol 940 | 1 | 1 | 1 | 1 | 1 |
| HPMC[a] K4M | 5 | 10 | – | – | 5 |
| HPMC[a] K15M | – | – | 5 | 10 | 5 |

[a] HPMC: hydroxy propyl methyl cellulose.

Placebo of each formulation was also prepared by the above mentioned method.

### 2.2. Physicochemical interactions studies

Physicochemical interaction between active pharmaceutical ingredient (carvedilol) and polymers were investigated by Fourier Transmission Infra Red (FTIR) Spectroscopy and Differential Scanning Calorimetry (DSC) analysis (Jug, Maestrelli, Bragagni, & Mura, 2010; Palem, Gannu, Doodipala, Yamsani, & Yamsani, 2011). Selected mucoadhesive films were cut into small pieces and subjected to crushing by glass pestle–mortar. The crushed powder was mixed with potassium bromide (1:100) and analyzed by FTIR spectrophotometer (Shimadzu 8400S).

For Differential Scanning Calorimetry, TA Differential Scanning Calorimeter (DSC-2010) filled with a thermal analyst 2100 system (Universal V3.0G TA instruments, USA) was used. Sample was placed in to pre-weighed sample pan which was then placed on the spacer insert and then sealed by a TA quick press. The reference was an empty pan sealed with a lid to give a suitable heat capacity. Triplicate sample pans were prepared and heated at a heat flow rate of 5 °C/min, from 50 °C to 300 °C in the TA pressure cell. DSC thermograms of the samples were obtained using thermal analyst software.

### 2.3. Surface morphology studies

Selected batches of mucoadhesive films were investigated for surface morphology after 4 h and 12 h of dissolution by scanning electron microscopy. Films were fixed on stubs and coated with gold palladium with the help of a gold sputter module in a high vacuum evaporator. Samples were then analyzed with LEO 420 (LEO Electron Microscopy Ltd., England) using secondary electron imaging (Abruzzo et al., 2012).

### 2.4. Evaluation of mucoadhesive films

Different evaluation of mucoadhesive films viz. film surface pH, flatness, drug content, swelling index, mucoadhesive strength, *in vitro* residence time, film strength and folding endurance were performed as pre reported methods with minor modifications (Abruzzo et al., 2012; Diaz del Consuelo, Falson, Guy, & Jacques, 2007; Nappinnai, Chandanbala, & Balaijirajan, 2008; Sekhar et al., 2008; J.D. Smart, 2005). Random sampling of films was done from each batch and different evaluations were performed in triplicate ($n = 3$).

#### 2.4.1. Surface pH

Mucoadhesive film was placed on a Petri dish containing 4 mL distilled water. It was allowed to swell for 1 h at room temperature (25 ± 1 °C). After 1 h, pH was measured by placing the electrode of pH metre (Mettler Toledo, AG) on the swelled surface of mucoadhesive film.

*2.4.2. Flatness*

Mucoadhesive film of definite size (1 $cm^2$) was taken on a plane surface, cut length wise (strips) in several pieces and the length of the cut pieces was measured. Following formula was used to calculate percent constriction. Zero percentage constriction implies 100% flatness.

$$\text{Constriction } (\%) = \frac{L_1 - L_2}{L_1} \times 100$$

where, $L_1$ = initial length of film, $L_2$ = final length of strip.

Flatness (%) = 100 − constriction (%).

*2.4.3. Drug content*

Mucoadhesive film was cut in to small pieces and dissolved in 100 mL 0.1 N NaOH with the help of magnetic stirrer. Then the solution was filtered through 0.45 μm syringe filter. From the above stock solution 10 μg/mL concentration sample was prepared and scanned at 242 nm ($\lambda_{max}$) by UV–vis spectrophotometer (SpectraMax, Molecular Devices). Placebo mucoadhesive films were used for blank control. Drug content was calculated from the measured absorbance.

*2.4.4. Swelling index*

Each film was weighed and the initial weight was denoted as $W_1$. Then film was placed in a petri plate containing 4 mL of phosphate buffer (pH 6.8). At the time interval of 1–4 h the film was removed carefully from the Petri plate and excess of solvent was soaked by a filter paper. The weight of the swelled film was measured and was denoted as $W_2$. Swelling index was calculated by using the following formula:

$$\%\text{SI} = \frac{W_2 - W_1}{W_1} \times 100$$

where, SI = swelling index, $W_1$ = initial weight of mucoadhesive film, $W_2$ = weight of swelled mucoadhesive film.

*2.4.5. Film thickness*

The thickness at three different locations (upper, middle and lower) in the same film was measured with the help of screw gauze and the mean was determined.

*2.4.6. Folding endurance and film strength*

Folding endurance of the films was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance.

Film strength, which is an advance and more precise method to evaluate mechanical strength of the mucoadhesive film, was determined with CT3 texture analyzer and data was recorded using Texture Pro CT V1.3 Build 15 software (Brookfield, 2011). Fig. 1(B) shows the photographic representation of film strength evaluation. Briefly, film was fixed on the film support fixture (TA-FSF) and cylindrical probe (TA 42, 3 mm) at a pre-specified speed was used to break the film. Force and corresponding work done required to make puncture/break on the film was recorded.

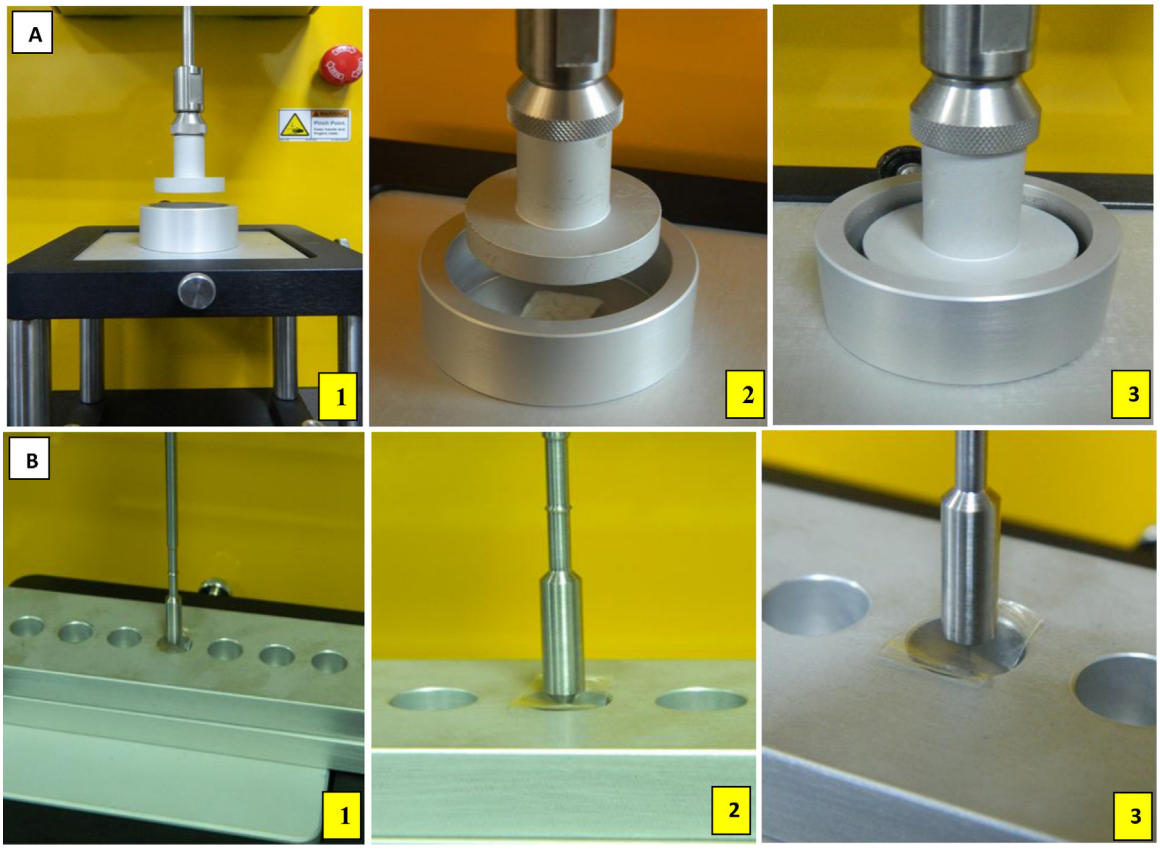


**Fig. 1.** New instrumental techniques for evaluation of mucoadhesive strength and film strength of mucoadhesive film. (A) Different stages of mucoadhesive strength test with CT3 texture analyzer. (1) Arrangement showing the stationary TA-BT KIT base where mucoadhesive film is fixed and TA-DEC probe moving down towards the film. (2) Close view of fixed mucoadhesive film and probe approaching towards the mucoadhesive film. (3) Close view of mucoadhesion test where the movable probe (glued with goat buccal mucosa) touches the film and causes mucoadhesion. (B) Different stages of film strength test with CT3 texture analyzer. (1) Arrangement showing the mucoadhesive film fixed on the stationary TA-FSF base and TA 42 probe penetrating through the mucoadhesive film. (2) A close view of film strength test where the TA 42 probe made puncture on the mucoadhesive film. (3) A close view of film strength test where the TA 42 probe moving upward (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

*2.4.7. Mucoadhesive strength*

Mucoadhesive strength of the formulated film was determined by CT3 texture analyzer with different set of accessories viz. Fixture Base table (TA-BT KIT), dual extrusion cell probe (TA-DEC) and tension type test with hold time mode (Brookfield, 2011). Fig. 1(A) shows the photographic representation of mucoadhesive strength evaluation. Briefly, upper probe (glued with goat buccal mucosa) was pressed on the mucoadhesive film (glued on the metal base plate) for at least 5 min. After 5 min at hold position, the upper probe was released at a pre-specified speed and the force required to detach both surfaces was recorded using Texture Pro CT V1.3 Build 15 software (Brookfield, 2011).

*2.4.8. In vitro residence time*

The *in vitro* residence time of mucoadhesive film was determined using a modified USP disintegration apparatus filled with 800 mL phosphate buffer solution pH 6.8, maintained at 37 ± 2 °C. The time necessary for complete erosion and/or detachment of the film from the mucosa surface was recorded.

*2.4.9. In vitro drug release*

*In vitro* drug release study was carried out with paddle over disc (65 mm) dissolution apparatus (USP 5, Electrolab India Pvt. Ltd.) (Aqil & Ali, 2002). Mucoadhesive film was placed beneath the disc in the dissolution vessel and 900 mL phosphate buffer pH 6.8 was taken as dissolution media. Dissolution test was carried out at 37 ± 2 °C with 50 RPM speed and aliquots of 5 mL were withdrawn at pre-specified time intervals for 12 h, filtered through membrane filter (0.45 μm) and equal volume of fresh pre-warmed (37 ± 2 °C) phosphate buffer media was added to the dissolution vessel. The absorbance of aliquots was taken at 242 nm by UV–vis spectrophotometer and quantity of drug released to the dissolution medium was calculated. Drug release studies were conducted in triplicates and mean values were calculated.

*2.4.10. Ex vivo drug permeability*

*Ex vivo* drug permeation study was carried out by using Franz diffusion apparatus (Desai, Mallery, Holpuch, & Schwendeman, 2011; Diaz del Consuelo et al., 2007; Maurya et al., 2012). Goat buccal mucosa (total exposed area 2.25 $cm^2$) was mounted on a diffusion cell between the donor and receptor compartment. The mucoadhesive film was fixed on the mucosal membrane. Five milliliter phosphate buffer pH 6.8 in the donor compartment and 45 mL of the same phosphate buffer in the receptor compartment was filled as dissolution fluid. The fluid was maintained at 37 ± 2 °C and stirred continuously at very low speed i.e. 50 ± 5 RPM with the help of a magnetic stirrer. The external jacket was connected with water bath so as to maintain the temperature in the Franz diffusion cell. Aliquots of 1 mL were collected at pre-specified time interval for 12 h, filtered through 0.45 μm membrane filter and the amount of drug was determined by measuring the absorbance of the aliquots at 242 nm using UV–vis spectrophotometer. Pre-warmed (37 ± 2 °C) dissolution fluid was added to the diffusion cell after each withdrawal of the sample. The experiment was carried out in triplicate ($n = 3$) and the mean value was taken for the determination of *ex vivo* drug permeation.

*2.5. Statistical analysis*

One way ANOVA test was used to check the statistical significance of drug release and permeation as well as swelling studies at $P < 0.05$ using GraphPad Prism 5 statistical software.

## 3. Results and discussions

Flexible, uniform and good quality mucoadhesive films were formulated and subjected to different physico-mechanical evaluations as well as drug release and permeation studies. Drug release/permeation mechanism was studied by fitting the drug release and permeation data to different kinetic models such as zero order, first order, Higuchi's model, Hixson–Crowell's model and Korsmeyer–Peppas's model (Bravo-Osuna, Ferrero, & JimÃ(nez-Castellanos, 2008; Mughal, Iqbal, & Neau, 2011; Vueba, Batista de Carvalho, Veiga, Sousa, & Pina, 2004).

*3.1. Physicochemical interaction and surface morphology*

Comparative FTIR spectra of carvedilol and mucoadhesive film F5 are shown in Fig. 2. FTIR spectrum of carvedilol (Fig. 2(A)) showed characteristic peaks at 3341 $cm^{-1}$ (NH stretching

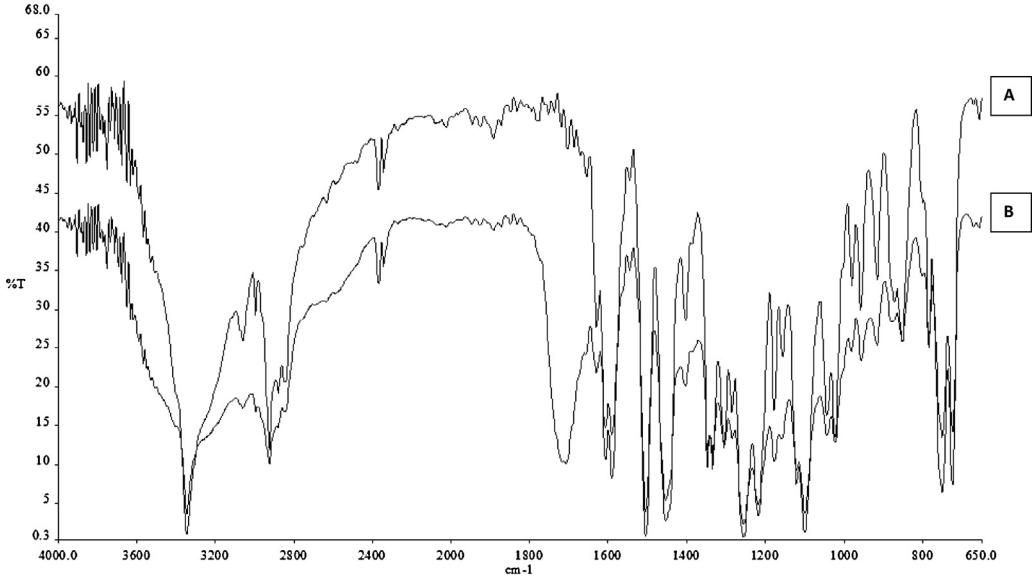


**Fig. 2.** FTIR spectra of pure carvedilol and carvedilol mucoadhesive film F5. (A) FTIR spectrum of carvedilol. (B) FTIR spectrum of carvedilol mucoadhesive film F5 (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

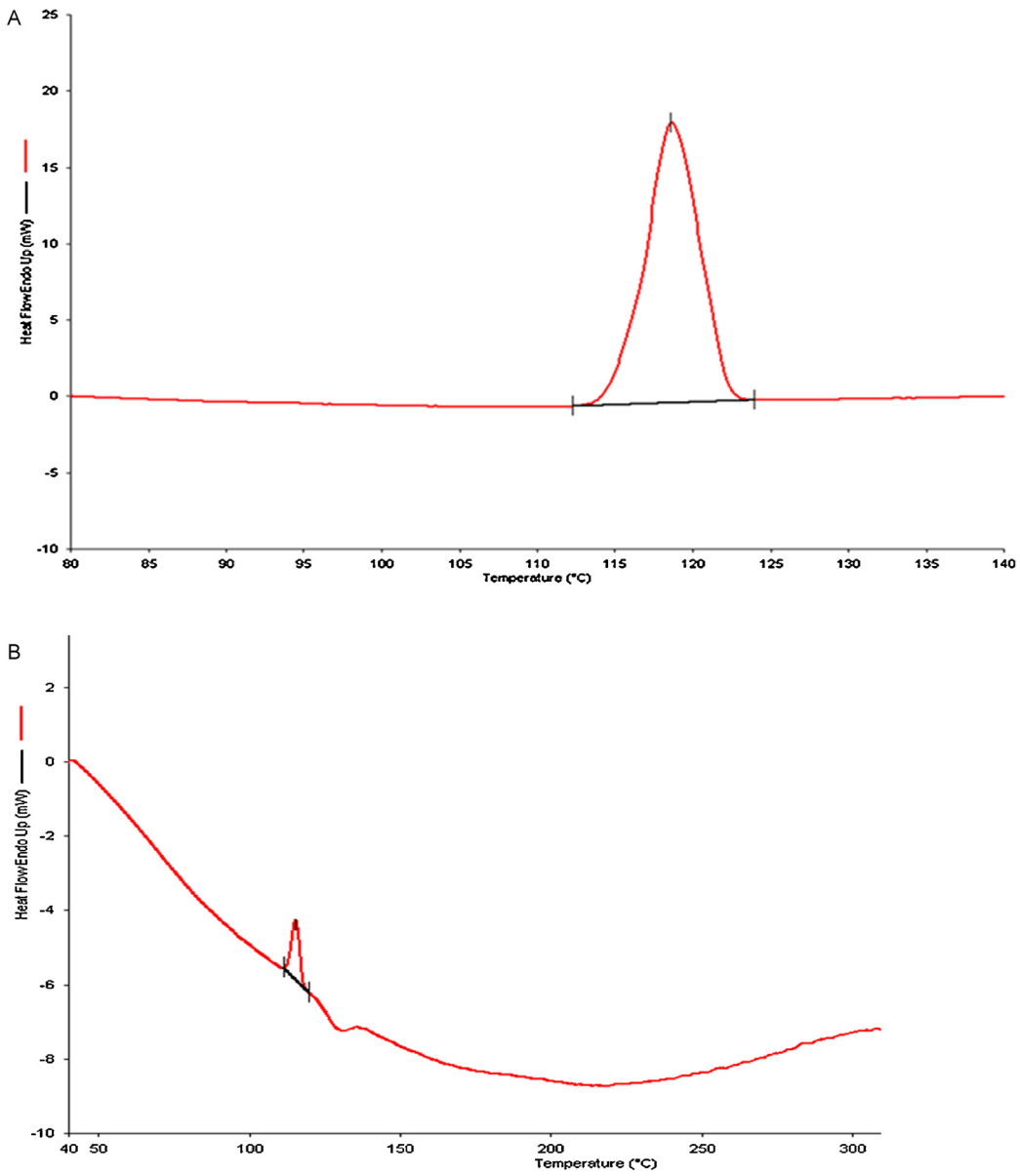


**Fig. 3.** DSC thermogram of pure carvedilol and carvedilol mucoadhesive film F5. (A) DSC thermogram of pure carvedilol. (B) DSC thermogram of mucoadhesive film F5 (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

vibration), 1591 $cm^{-1}$ (NH bending vibrations) and 1266 $cm^{-1}$ (CO stretching vibrations). In the FTIR spectrum of mucoadhesive film formulation F5 (Fig. 2(B)); characteristic peaks were observed at 3346 $cm^{-1}$, 1591 $cm^{-1}$ and 1262 $cm^{-1}$. Any interaction with these functional groups would have caused significant shift in the characteristic peaks but as revealed from Fig. 2(A) and (B) there was no significant shift in the characteristic peaks of carvedilol drug molecule. These findings suggest that carvedilol drug molecule is intact in the mucoadhesive film and there is no physical/chemical interaction between drug and polymers (Planinsek et al., 2011).

Fig. 3 depicts the DSC thermogram of carvedilol and mucoadhesive film (F5). A sharp endothermic peak at 118.56 °C (Fig. 3(A)) corresponding to the melting point of carvedilol was observed in the DSC thermogram of carvedilol. Formulation F5 showed a broad endothermic peak at 115.41 °C (Fig. 3(B)). The difference in melting point of carvedilol in free form and in polymeric matrix was insignificant, hence it was predicted that drug and polymers are compatible. The appearance of comparatively short and broad peak might be due to the conversion of crystalline drug to amorphous or disordered crystalline phase or solid solution state in the polymeric matrix (Castelli, Pitarresi, & Giammona, 2000; Hosseinzadeh, Atyabi, Dinarvand, & Ostad, 2012; Sharma & Arora, 2012).

Surface morphology of the mucoadhesive film (F5) was studied in intact form as well as at different stages of dissolution (at 4 h and 12 h). Fig. 4 shows the photographs of mucoadhesive film and SEM photomicrographs at different stages of dissolution. There was a clear difference between these stages indicating the changes in polymer matrix networking after 4 h and 12 h of dissolution. The inter-polymer matrix was swelled upon hydration and surface was observed to be less rough up to 4 h of dissolution, indicating no sign of erosion whereas after 12 h of dissolution the surface became highly rough and appeared to be macro-porous mesh. These findings are in accordance with the swelling studies (discussed in Section 3.2) of mucoadhesive films where no erosion was seen for 4 h for any of the developed films (Pendekal & Tegginamat, 2012).

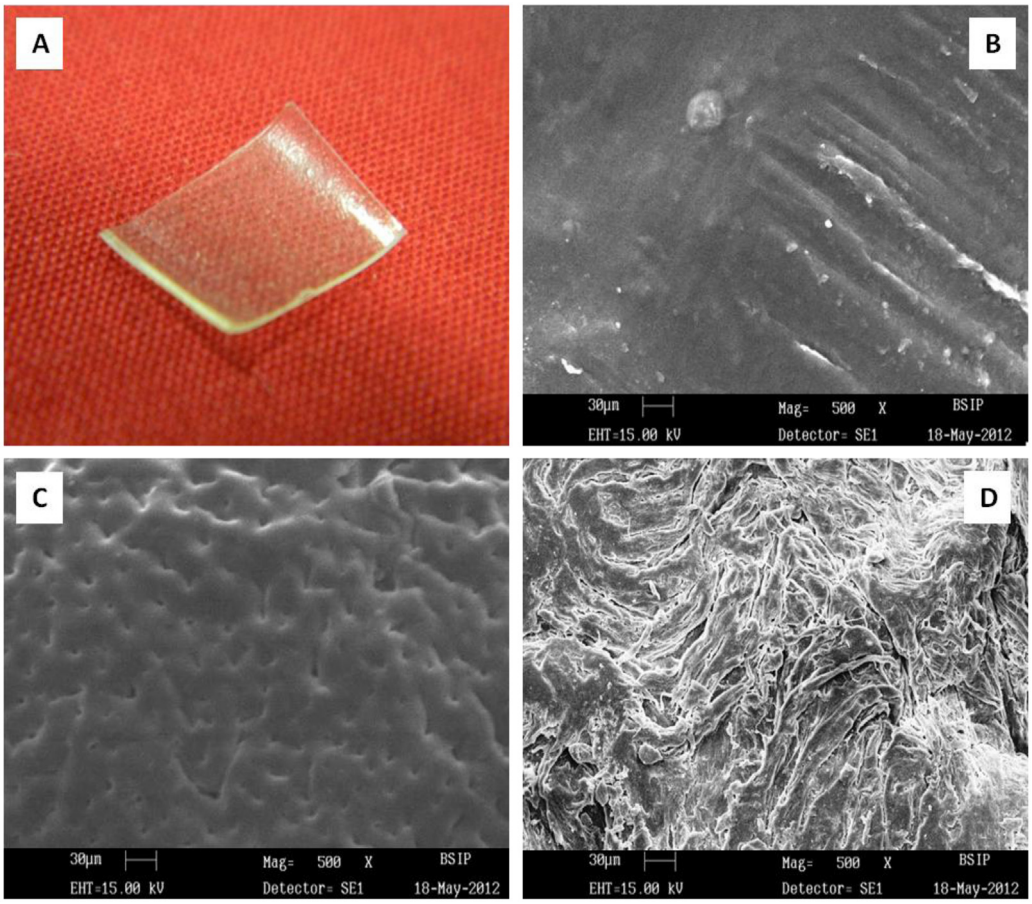


**Fig. 4.** Photographs of formulated mucoadhesive film and SEM photomicrograph of carvedilol mucoadhesive films F5 at different time intervals of dissolution. (1) Photograph of carvedilol mucoadhesive film. (2) SEM photomicrograph of carvedilol mucoadhesive film (F5) before dissolution. (3) SEM photomicrograph of carvedilol mucoadhesive film (F5) after 4 h of dissolution. (4) SEM photomicrograph of carvedilol mucoadhesive film (F5) after 12 h of dissolution (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

### 3.2. Evaluation parameters

The results of evaluation parameters of mucoadhesive films are shown in Table 2. Surface pH of mucoadhesive films was found to be in the range of $5.45 \pm 0.08$–$6.33 \pm 0.06$. All formulations were in the range of buccal pH hence it is predicted to be non-irritant to buccal mucosa. Flatness of the films was found to be within $97.5 \pm 0.56$–100%. One hundred percentage flatness ensures intimate contact to buccal mucosa and uniform drug absorption. The drug content was in the acceptable range of $97.30 \pm 0.58$–$99.68 \pm 0.86$%. This indicates the successful incorporation of carvedilol in the polymeric matrix. Thickness of the mucoadhesive films was recorded to be $0.56 \pm 0.004$–$0.67 \pm 0.002$ mm. Swelling tendency of the formulated mucoadhesive films was studied for 4 h. Percent swelling was $27.80 \pm 0.67$%, $29.98 \pm 0.55$%, $31.16 \pm 0.42$%, $34.20 \pm 0.61$% and $32.94 \pm 0.52$% for F1–F5, respectively after 4 h. Films containing exclusively HPMC K15M showed higher water uptake ($P < 0.05$) than films containing either HPMC K4M or combination of both. Researchers have studied the relaxation and erosion behaviour of cellulose polymers, where they have reported the loss of consistency of HPMC based mucoadhesive films during swelling (Chun, Kwak, & Choi, 2003; Maurya et al., 2012). In 4 h of present study no such behaviour was observed, rather it was seen that with the increase in HPMC concentration there was a non linear increase in swelling which is in agreement with Katzhendler et al. who reported higher water uptake ability of high molecular weight HPMC (Katzhendler, Mader, & Friedman, 2000). Lack of erosion behaviour of the developed films may be correlated to the presence of Carbopol which forms thick gel layer at pH of 6.0–8.0 as well as methyl cellulose which swells in aqueous medium. Formation of thick gel layer creates resistance to erosion of polymer and as a consequence drug release was retarded (Maderuelo et al., 2011). Adequate wetting and swelling is required for drug dissolution and absorption, so as revealed from swelling studies, formulation F4 and F5 showed maximum water uptake capacity which is desirable in mucoadhesive drug delivery systems. Highest water uptake by F4 is attributed to the higher concentration of HPMC K15M where as lower water uptake by F1 is due to the low concentration of HPMC K4M. This behaviour can be correlated to the presence of higher number of hydroxyl group which facilitated uptake of water into the polymer matrix (Abruzzo et al., 2012).

Mucoadhesive strength and folding endurance evaluation of films/patches are two most common but important evaluation parameters. Mucoadhesive strength suggests the feasibility of films/patches in term of its adherence to mucosal membrane. Excessive/irreversible adhesion may cause harm (irritation) to mucosa whereas inadequate adhesion will adversely affect therapeutic efficacy and at the same time it may cause patient incompliance. Hence an optimized mucoadhesion is required for a film/patch to be effectively used as drug delivery system.

Mucoadhesive strength is defined as the force required to detach the film or patch from buccal mucosal surface. Many researchers have studied mucoadhesive strength by locally modified apparatus (Abu-Huwaij, Assaf, Salem, & Sallam, 2007; Chun et al., 2003; Donnelly, McCarron, Tunney, & David Woolfson, 2007; Morales &

**Table 2**
Evaluation characteristics of carvedilol mucoadhesive films.

| Evaluation parameters | Formulation code | | | | |
|---|---|---|---|---|---|
| | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ |
| Surface pH | 6.33 ± 0.06 | 5.83 ± 0.04 | 6.0 ± 0.08 | 5.45 ± 0.08 | 6.18 ± 0.06 |
| Film flatness (%) | 98.55 ± 0.54 | 99.55 ± 0.44 | 100.00 | 97.50 ± 0.56 | 100.00 |
| Drug content (%) | 99.00 ± 0.54 | 98.46 ± 0.34 | 98.44 ± 0.65 | 97.30 ± 0.58 | 99.68 ± 0.86 |
| Swelling index[a] (%) | 27.80 ± 0.67 | 29.98 ± 0.55 | 31.16 ± 0.42 | 34.20 ± 0.61 | 32.94 ± 0.52 |
| Folding endurance (times) | 122 ± 1.09 | 138 ± 1.53 | 124 ± 0.99 | 144 ± 1.44 | 142 ± 1.32 |
| Film thickness (mm) | 0.60 ± 0.002 | 0.64 ± 0.002 | 0.65 ± 0.004 | 0.70 ± 0.006 | 0.68 ± 0.004 |
| Residence time (min) | 101.4 ± 1.32 | 96.2 ± 1.35 | 110.4 ± 0.74 | 122.4 ± 0.86 | 126.2 ± 0.58 |
| Film mucoadhesive strength[b] | | | | | |
| Mucoadhesive strength (g) | 33.8 ± 0.37 | 34.6 ± 0.42 | 34.8 ± 0.37 | 36.8 ± 0.37 | 38.4 ± 0.24 |
| Work done (mJ) | 1.40 ± 0.02 | 1.48 ± 0.02 | 1.76 ± 0.04 | 2.18 ± 0.03 | 3.76 ± 0.04 |
| Film strength[c] | | | | | |
| Film strength (g) | 331.2 ± 0.73 | 346 ± 0.70 | 361.8 ± 1.11 | 369 ± 1.00 | 362 ± 0.83 |
| Work done (mJ) | 21.92 ± 0.08 | 28.28 ± 0.26 | 30.92 ± 0.41 | 38.34 ± 0.21 | 32.22 ± 0.31 |

Mean ± SEM, $n = 3$.
[a] Swelling index after 4 h.
[b] Fixture base table TA-BT KIT, dual extrusion cell probe (TA-DEC) and compression type test with hold time mode.
[c] TA-FSF film support fixture, TA 42 (3 mm cylinder probe) and compression type test.

McConville, 2011; Patel & Poddar, 2009) that are easily available but do not meet the level of accuracy and precision. There is a need of more accurate method with high accuracy and precision for characterization of films/patches. In the present work mucoadhesive strength of the formulated films was studied with CT3 texture analyzer using Texture Pro CT V1.3 Build 15 software which is more accurate and precise instrument for mucoadhesive study. Mucoadhesive strength of all films was determined to be in the range of 33.8 ± 0.37–38.4 ± 0.24 g and corresponding work done was found to be 1.40 ± 0.02–3.76 ± 0.04 mJ. Maximum mucoadhesive strength (38.4 ± 0.24 g) was exhibited by film F5. Concentration of mucoadhesive polymer 'Carbopol' was same in all films (Table 1) but difference in mucoadhesion was seen, which might be attributed to the fact that presence of HPMC in different ratio influenced adhesive properties by interfering in hydration, flexibility and hydrogen bonding capacity (Salamat-Miller, Chittchang, & Johnston, 2005; Smart, 1999; J. Smart, 2005).

Folding endurance is popular evaluation parameters for mucoadhesive/transdermal formulations. It gives an idea about the mechanical strength as well as flexibility of the film/patch. Folding endurance of the films was found to be in the range of 122 ± 1.09–144 ± 1.44. Since folding endurance is performed manually, it may vary person to person. Therefore in the present investigation, film strength of the mucoadhesive film was estimated with the help of CT3 texture analyzer with appropriate probe, experimental conditions (Section 2.4.6) and Texture Pro CT V1.3 Build 15 Software hence film strength will be a more precise and accurate approach for evaluation of mechanical strength of the film. Film strength was in the range of 331.2 ± 0.73–369 ± 1.00 g. Corresponding work done for this phenomenon was noted to be 21.92 ± 0.08–38.34 ± 0.21 mJ. Film formulation F4 showed highest film strength, which indicates the strong internal binding of polymers. Film F5 also exhibited considerably better film strength than others. The above results suggested sufficient mechanical strength of the developed buccal films which will resist minor mechanical stress.

Both the above employed tests viz. mucoadhesive strength and film strength were conducted under specific experimental conditions (specific probe, pre-test speed, post-test speed, trigger load, hold time, motorized probe movement) (supplementary material; Table S1), hence there are least chances of error which is frequently encountered in locally designed experimental methods. Fig. 1(A) and (B) exhibits the sequential evaluation process of mucoadhesive strength and film strength respectively.

*In vitro* residence time was determined to be 96.2 ± 1.35–126.2 ± 0.58 min. Maximum residence time was noted to be 126.2 ± 0.58 min for F5. The film was completely detached from the goat buccal mucosa after 126.2 ± 0.58 min. As the experiment was carried out with USP disintegration apparatus (up and down motion causes stress condition for adhered film) residence time of F5 is considered to be adequate for mucoadhesive films. Residence of films or patches is directly related to the mucoadhesive strength which is a consequence of interaction between mucin, a negatively charged component of mucosal membrane (due to the presence of sialic acid and sulphate) and charged polymers. Further adequate hydration is required for the polymers to get charged and impart sufficient muco-residence. The residence time of F5 is supported by its water uptake behaviour (optimum swelling index) (Abruzzo et al., 2012; Palem et al., 2011).

### 3.3. Drug release and permeation (in vitro and ex vivo)

All five mucoadhesive formulations were containing Carbopol 940, methyl cellulose and Eudragit RSPO in common whereas concentration of cellulose polymers; HPMC K4M and HPMC K15M was varied and their effect on drug release behaviour was examined.

Fig. 5(A) exhibits the *in vitro* zero order drug release pattern and a comparative *in vitro* drug release kinetic data are given in Table 3. Formulation F1 showed highest drug release i.e. 98 ± 1.15%, whereas lowest was recorded for F4 i.e. 71.66 ± 1.20% in 12 h. For F2, F3 and F5 drug release was 82.66 ± 2.40%, 75.33 ± 1.45% and 88 ± 1.15% in same duration of time. Carvedilol released data was found to be best fit to Higuchi's equation as revealed by the correlation coefficients. Further from the Korsmeyer–Peppas's plot, exponent ($n$) of drug release was determined. All formulations showed '$n$' value in the range of 0.35–0.40. Fig. 5(B) exhibits the *ex vivo* zero order drug permeability pattern and a comparative *ex vivo* drug permeation kinetic data is given in Table 3. *Ex vivo* drug permeation was studied in order to understand the permeation pattern of drug through biological membrane. Highest carvedilol permeation was found to be 86 ± 3.05% shown by F1 and lowest 65.66 ± 3.48% by F4 in 12 h. F2, F3 and F5 exhibited 76 ± 4.13%, 71.33 ± 2.9% and 80 ± 2.30% drug permeation respectively in same duration of time. Drug permeation data were best fitted to Higuchi's plot. Exponent ($n$) of drug diffusion were calculated to be 0.40–0.42 from Korsmeyer–Peppas's plot.

Based on the above findings the mechanism of drug release and permeation from carvedilol mucoadhesive film was found

**Table 3**
Drug release and permeation kinetic of carvedilol mucoadhesive films.

| Code | Higuchi's model | | | Korsmeyer–Peppas's model | | | Mechanism |
|---|---|---|---|---|---|---|---|
| | $K$ | Equation | $r^2$ | $n$ | Equation | $r^2$ | |
| *In vitro* drug release kinetic | | | | | | | |
| F1 | 9.5 | $y = 9.5x + 21.5$ | 0.9544 | 0.4017 | $y = 0.4017x + 1.5555$ | 0.9881 | Fickian |
| F2 | 8.5833 | $y = 8.5833x + 20.417$ | 0.9660 | 0.393 | $y = 0.393x + 1.5250$ | 0.9808 | Fickian |
| F3 | 8.0667 | $y = 8.0667x + 14.556$ | 0.9907 | 0.4046 | $y = 0.4046x + 1.453$ | 0.9876 | Fickian |
| F4 | 7.2167 | $y = 7.2167x + 18.694$ | 0.9834 | 0.3536 | $y = 0.3536x + 1.4917$ | 0.9844 | Fickian |
| F5 | 8.5 | $y = 8.5x + 20.944$ | 0.9847 | 0.3663 | $y = 0.3663x + 1.5461$ | 0.9917 | Fickian |
| *Ex vivo* drug permeation kinetic | | | | | | | |
| F1 | 9.15 | $y = 9.15x + 21.472$ | 0.9418 | 0.417 | $y = 0.417x + 1.5325$ | 0.9650 | Fickian |
| F2 | 8.5167 | $y = 8.5167x + 15.194$ | 0.9829 | 0.4232 | $y = 0.4232x + 1.4612$ | 0.9903 | Fickian |
| F3 | 8.2167 | $y = 8.2167x + 12.583$ | 0.9837 | 0.4275 | $y = 0.4275x + 1.4249$ | 0.9982 | Fickian |
| F4 | 7.9167 | $y = 7.9167x + 12.75$ | 0.9880 | 0.4270 | $y = 0.4278x + 1.4142$ | 0.9909 | Fickian |
| F5 | 8.4833 | $y = 8.4833x + 18.917$ | 0.9660 | 0.4050 | $y = 0.4058x + 1.5014$ | 0.9871 | Fickian |

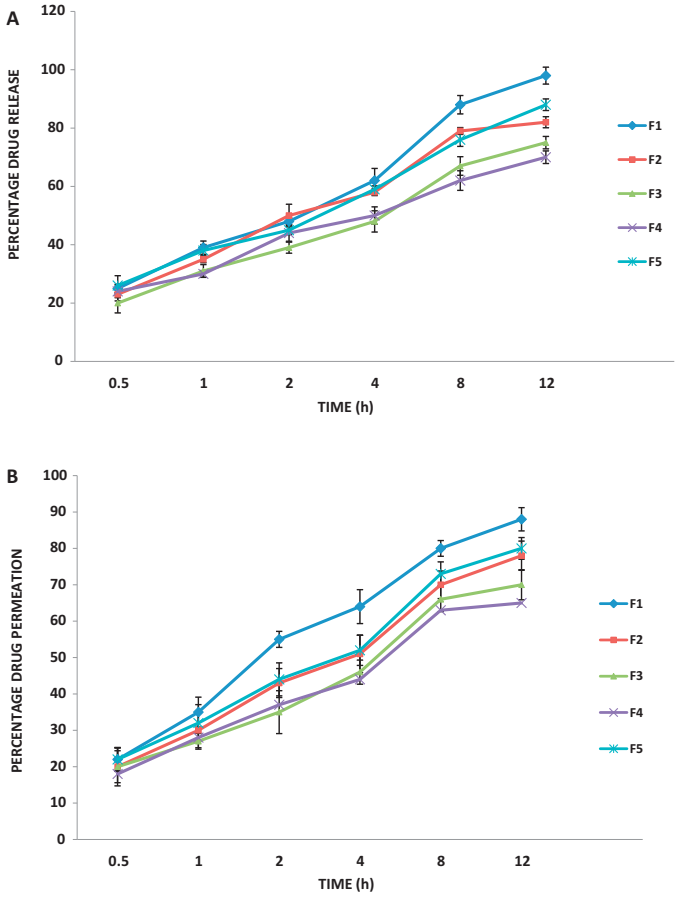


**Fig. 5.** Drug release/permeation kinetics plot. (A) *In vitro* zero order drug release plot of carvedilol mucoadhesive film F5. (B) *Ex vivo* zero order drug permeation plot of carvedilol mucoadhesive film F5 (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

to be sustained release and diffusion controlled. The exponent of drug release was Fickian type ('$n$' values below 0.5) which means release of drug is based on diffusion mechanism. Films containing different concentration of cellulose polymers exhibited different drug release/permeation ($P < 0.05$) behaviour. Decrease in drug release from formulation F4 than F1 was observed in both *in vitro* drug release and *ex vivo* drug permeation. The reason behind such behaviour is due to the higher concentration of HPMC K15M (15 000 cP) in F4. Higher concentration caused more hydration and swelling of mucoadhesive film (as discussed in Section 3.2), which consequently developed a hydrogel layer around the drug molecule. Formation of a thick hydrogel layer further increased the drug release/diffusion path length, resulting into delayed dissolution as well as diffusion of carvedilol. Additionally, presence of Carbopol 940 facilitated the formation of thick gel layer at pH 6.8 (dissolution medium) which is responsible for the delayed release of carvedilol from the polymer matrix (Maderuelo et al., 2011). However for formulation F5 an intermediate release as well as permeation characteristics were observed, which is attributed to the formation of comparatively thinner hydrogel layer as a result of equal contribution of cellulose polymers; HPMC K15M and HPMC K4M.

Sustained release formulations with only HPMC have been reported to be eroded out in due course of dissolution because of its hydrophilic nature (Mughal et al., 2011; Vueba et al., 2004) but combination with hydrophobic and swellable polymers (Eudragit RSPO and methyl cellulose) has potentially altered the release kinetics.

## 4. Conclusion

Mucoadhesive films of carvedilol were successfully developed with the combination of cellulose (HPMC, methyl cellulose) and polymethacrylate (Eudragit RSPO) polymers. Drug release/permeation were found to be Fickian type diffusion controlled which is desirable in sustained drug delivery. Hydroxy propyl methyl cellulose has shown a substantial role in controlling drug release from polymeric matrix. Formulation F5 exhibited optimum characteristics of a mucoadhesive film and can be successfully used for effective delivery of carvedilol. Equal ratio of HPMC K4M and HPMC K15M was found to be relevant for an appropriate mucoadhesive formulation in combination with methyl cellulose, Eudragit RSPO and Carbopol 940.

Simple, reproducible and precise instrumental methods were established for the evaluation of mucoadhesive strength and film strength which can be adopted as a reliable technique in the development and optimization of mucoadhesive formulations.

## Conflict of interest

All authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2013.03.076.

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