



Research Article

# Fast Dissolving Oral Thin Film Drug Delivery Systems Consist of Ergotamine Tartrate and Caffeine Anhydrous

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## ABSTRACT

**Background:** Ergotamine tartrate (ET), a serotonin 5-HT<sub>1</sub> receptor agonist, is an anti-migraine drug. Due to high first-pass metabolism, ET shows a very low bioavailability in oral administrations (<1%). Caffeine (CA) increases the rate and extent of water solubility of ET. The present study intended to investigate the possibility of developing ET fast dissolving thin films for the fast drug dissolution in the oral cavity, and thus bypassing first pass metabolism for providing quick onset of action of the drug. **Methods:** The films (ET and CA) were prepared according to solvent casting method, separately. Low viscosity grade of hydroxypropyl methylcellulose (HPMC E-15) was employed in preparation as a film forming polymer. Propylene glycol was the plasticizer used. All the films were evaluated for their thickness, weight variations, folding endurance, surface pH, disintegration, drug content, DSC, in-vitro drug release, and ex-vivo permeation. **Results:** The best polymer drug ratio in ET/CA films was 1:20 (E<sub>2</sub>) and 1:4 (C<sub>2</sub>), respectively. The films E<sub>2</sub> and C<sub>2</sub> showed 9.9, 3.2 mg weight, 74, 45 μm thickness, 120.66, up to 300 folding endurance and 0.38, 0.52 mg/cm<sup>2</sup> drug content, respectively. The DSC showed no stable characteristic for ET and CA in the drug loaded films and revealed amorphous form. The results showed that ET films prepared had faster release and CA films had slower release ( $p < 0.05$ ). Both films (ET and CA) exhibited good mucoadhesion properties and shorter retention time (36-150 s). **Conclusion:** The formulations were found to be a suitable candidate for the development of oral thin films for migraine therapy.

## Introduction

Bioadhesion is defined as a phenomenon of interfacial molecular attractive force in the middle of the surfaces of biological substrates and the natural or synthetic polymers, which permits the polymer to stick to the biological surface for an expanded period of time. Inside the oral mucous membrane cavity, the buccal area suggests an adorable path of administration for systemic drug delivery. Among different routes known in drug delivery, the oral route is possibly the most favored one by patients and clinicians in the same manner.

The mucosa is proportionately permeable, has a rich blood supply, is robust, and recovers in a short span after stress or injury. The oral cavity has been used as a space for the local and systemic drug delivery. Mucus plays an active role in the bioadhesion of mucoadhesive drug delivery system and applies it as a

lubricant. The oral mucosa in general is slightly leaky epithelium immediately between the epidermal and the intestinal mucosa. The permeability of the buccal mucosa is calculated to be 4-4000 times more than that of the skin. Usually the permeability of the oral mucosa reduces in the order from the sublingual to the buccal and then to the palatal system. Saliva preserves the liquid for total tissues of the oral cavity and hydrates oral mucosal dosage forms.

Buccal adhesive systems suggest countable benefits in terms of availability of administration and withdrawal, retentivity, low enzymatic activity, economy, and high patient compliance. Mucoadhesive buccal films are supported owing to various competencies including preventing first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract.<sup>1</sup>

A migraine is a usual headache which meaningfully influences about 15% of females and 6% of males. As a

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neurobiological syndrome, it is principally described by a unilateral throbbing headache. Other main symptoms include nausea, vomiting, and sensitivity to light.<sup>2</sup>

Ergotamine tartrate (ET), one of the alkaloids of ergot, was first shown to relieve the migraine headaches. It is "a non-sedative drug which almost always aborts even the worst of migraine headaches". ET may thus be an effective means of aborting individual attacks, but is not to be considered a "cure" for migraine.<sup>3</sup> ET is slightly soluble in water and ethanol (~750 g/l).

Fast dissolving oral thin film drug delivery systems (FDOTFs) are solid dosage forms. They can dissolve shortly when they are positioned in the mouth without drinking water or chewing. They disintegrate in the salivary fluid of the oral cavity within a minute, and release the active pharmaceutical ingredients. FDOTFs are recognized as the most advanced form of oral solid dosage forms for their flexibility and comfort. They improve the efficacy of active pharmaceutical ingredients by dissolving within one minute or even in seconds in the oral cavity after contacting saliva without chewing and no need to water for administration. They give quick absorption and immediate bioavailability of drugs due to high blood flow. The permeability of oral mucosa is counted to be 4-1000 times greater than that of skin.<sup>1,2</sup>

Orally fast dissolving sublingual films of ET prevent their first-pass metabolism and eliminate the necessity of water intake by the patient during the migraine attack and provide fast onset of action. These functions would be of extreme benefit for migraine sufferers in resuming their functional abilities for a short time.<sup>4</sup>

Thin film drug delivery was designed to be as an advanced alternative to the traditional tablets, capsules, and liquids often related with prescription and OTC medications. Thin films are similar to postage stamp in size, shape, and thickness, and typically are designed for oral administration, with the user placing the strip on or under the tongue or along the inside of the cheek.

As the film dissolves, the drug can enter the blood stream enterically and buccally.

ET drug prevents or aborts the vascular headaches (e.g., migraine, cluster headaches) when used alone. CA is a central nervous system (CNS) stimulant, which has the effect of temporarily warding off drowsiness, restoring alertness and exerting muscle relaxant properties. The solubility of caffeine anhydrous is 16 mg/ml in water at room temperature and 15 mg/ml in ethanol. Cafergot<sup>®</sup> tablet (ET and CA) narrows the vessels and relieves the pain together with other symptoms of migraine attacks. CA may increase the absorption of ET from the gastrointestinal tract and help to relieve the migraine.<sup>5</sup> The present work involves the formulation, evaluation, and characterization of mucoadhesive buccal films of ET and CA in which hydroxypropylmethylcellulose (HPMC) is used as a polymer.

### Materials and Methods

ET was obtained from Poli Industria Chimica S.P.A (Milan, Italy). Caffeine anhydrous, hydroxypropylmethylcellulose (HPMC, E-15), ethanol, dichloromethane, buffer phosphate (pH 6.8), sodium chloride, potassium chloride, sodium sulfate, ammonium acetate, urea, and lactic acid were purchased from Merck (Darmstadt, Germany). All solvents and reagents were of analytical grade.

### Experimental Methods

#### Preparation of ET and CA films

Buccal films of ET and CA were prepared by solvent casting technique using film forming mucoadhesive polymer. ET film was prepared using different ratios of drug (ET/CA) to polymer (HPMC-E15) (1:10, 1:20 and 1:30) and CA film was formulated using various ratios of drug to polymers (1:2, 1:4 and 1:6) as shown in Table 1.

**Table 1.** Ergotamine tartrate and caffeine anhydrous films prepared by solvent casting method with different drug to polymer ratios.

Formulation code	Drug to polymer ratio	Ergotamine Tartrate (mg)	Caffeine anhydrous (mg)	HPMC (mg)	PG (mg)	Ethanol (ml)	Dichloromethane (ml)
E1	1:10	10	-	100	30	5	5
E2	1:20	10	-	200	30	5	5
E3	1:30	10	-	300	30	5	5
C1	1:2	-	50	100	30	10	10
C2	1:4	-	50	200	30	10	10
C3	1:6	-	50	300	30	10	10

The beaker containing polymer and dichloromethane was kept aside for 5 min for swelling of the polymer. Further ET/CA was accurately weighed (10mg ET and 50 mg CA, separately), dissolved in ethanol, and added to the above polymer solution and then the dispersion was stirred. Next, 30 mg propylene glycol as plasticizer

was added to the polymeric solutions. The whole solution (ET or CA film) was poured into the glass petri dish (5/10 cm, respectively) separately placed over a flat surface. The inverted funnel was placed over the dish to avoid sudden evaporation. The mould containing polymeric solution of drug was kept for 12 h

at room temperature to dry. After drying, the films were observed to check the possible imperfections upon their removal from the moulds. They were covered with wax paper and preserved in desiccators till the evaluation tests were conducted.

#### **Evaluation of buccoadhesive films**

Appearance of the films was evaluated by observing the color, elegance, stickiness, and texture.

#### **Weighing uniformity of films**

Six films of size  $1 \times 1 \text{ cm}^2$  of every formulation were weighed individually in a digital balance (Sartorius, Germany) and the weight variations were calculated.<sup>3</sup>

#### **Thickness uniformity of the films**

The thickness of each film was measured by using digital vernier calipers (Mitutoyo, Japan) at five different points (at center and four corners) of film and the average was calculated.<sup>6</sup>

#### **Folding endurance**

The folding endurance of each film was determined by counting the number of times the film (size  $1 \times 1 \text{ cm}^2$ ) could be folded repeatedly or broken up to 300 times. Folding endurance was counted manually by folding the film repeatedly at a specific point till they were broken or folded. This is considered satisfactory to reveal good film properties.<sup>7</sup>

#### **Surface pH**

The surface pH was measured by placing pH paper on the surface of the swollen films. The mean of three readings was registered. The prepared buccal films were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warmed phosphate buffer of pH 6.8 under stirring and then pouring the solution into a petri dish till gelling at room temperature.<sup>8</sup>

#### **In vitro swelling studies**

The swelling rate of films was measured by placing the film in phosphate buffer solution with a pH of 6.8 at  $37 \pm 0.5^\circ\text{C}$ . The initial diameter of film ( $1 \times 1 \text{ cm}^2$ ) was  $D_1$  when placed in a 2% (w/v) agar gel plate and incubated at  $37 \pm 1^\circ\text{C}$ . At regular intervals (up to 1 h), diameter of swollen film were re-measured ( $D_2$ ) and the swelling index was calculated by the following formula:<sup>8,9</sup>

$$\text{Swelling index} = D_2 - D_1 / D_1 \quad \text{Eq.(1)}$$

#### **Moisture content loss and moisture absorption**

The films were accurately weighed and kept in desiccators containing anhydrous calcium chloride. After three days, the films were taken out and weighed. The moisture content (%) was determined by measuring moisture loss (%) using the formula:<sup>9</sup>

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \quad \text{Eq.(2)}$$

The films were accurately weighed and placed in desiccators containing 100ml of saturated solution of aluminum chloride, which maintains 86% relative humidity (RH). After three days, films were taken out and weighed. The moisture absorption was calculated using the formula:<sup>3</sup>

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{initial weight}}{\text{Initial weight}} \times 100 \quad \text{Eq.(3)}$$

#### **Drug content uniformity**

The films (six samples of each film) were analyzed for the content uniformity by dissolving  $1 \times 1 \text{ cm}^2$  sized films in 10 ml phosphate buffer at pH 6.8 with simultaneous shaking for several hours. The absorbance of the solution (ET/CA) was measured by UV spectrophotometry at 311 (ET) and 272.8 (CA) nm. All experiments were carried out in triplicate.<sup>8</sup>

#### **Differential Scanning Colorimetry (DSC)**

The physical state of drug in the microspheres was assessed by Differential Scanning Calorimeter (Shimadzu, Japan). The thermograms were obtained at a scanning rate of  $10^\circ\text{C}/\text{min}$  conducted over a temperature range of  $25\text{--}300^\circ\text{C}$ .

#### **Ex vivo bioadhesion time**

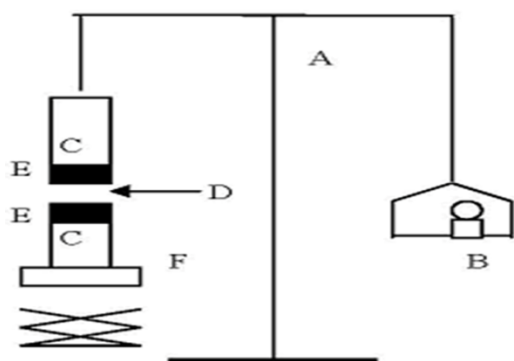
Male wistar rats ( $260 \pm 30 \text{ g}$ ) were fed in this study. The animals were given food and water ad libitum. They were housed in the Animal House of Tabriz University of Medical Sciences at a controlled ambient temperature of  $25 \pm 2^\circ\text{C}$  with  $50 \pm 10\%$  relative humidity and a 12-h light/ 12-h dark cycle. The current study was performed in accordance with Guide for the Care and Use of Laboratory Animals of Tabriz University of Medical Sciences, Tabriz-Iran (National Institutes of Health Publication No 85-23, revised 1985). The selected film was exposed to *ex vivo* bioadhesion test. The disintegration medium was composed of 50 ml phosphate buffer (pH 7.4) maintained at  $37^\circ\text{C}$ . A segment of mucosal abdominal area of rat, 3 cm long, was glued to the surface of a glass slab, vertically attached to the disintegration apparatus (Erweka, Germany).<sup>9</sup> The disintegration or disappearance time of films from mucosa surface was calculated.

The bioadhesive films were hydrated from one surface and then were brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the film could completely immersed in the buffer solution at the lowest point and go out at the highest point. The time necessary for complete erosion or detachment of the films from the mucosal surface was recorded. The experiment was carried out in triplicate.

#### **Bioadhesion strength**

The tensile strength required to detach the bioadhesive films from the mucosal surface was applied as a measure of the bioadhesive performance. The apparatus was locally assembled. The device was mainly

composed of a two-armed balance (Fig. 1).



**Figure 1.** Bioadhesive force measuring device: (A) Modified balance; (B) Weights; (C) Glass vial; (D) Films; (E) Rat tissue; (F) Height-adjustable pan.

The mucoadhesive forces of films were determined by means of the mucoadhesive force-measuring device,<sup>10</sup> using tissue cut from mucosal abdominal area of rat. The pieces of mucosa were stored frozen in phosphate buffer with pH 7.4 and thawed to room temperature before use.<sup>11</sup> At the time of testing, a section of mucosa was attached to the upper glass vial (C) using a cyanoacrylate adhesive (E). The diameter of each exposed mucosal membrane was measured to be 1.5 cm. The vials were equilibrated and maintained at 37°C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). A constant amount of films (D) was applied to exposed tissue on this vial. The height of the vial was adjusted so that the films could adhere to the mucosal tissues of both vials. Immediately, a constant force of 0.5 N was used for 2 min to ensure intimate contact between the tissues and the samples. The vial was then moved upwards at a constant speed and connected to the balance. Weights were added at a constant rate to the pan on the other side of the modified balance of the used device until the two vials were separated. During measurement, 150 µl of phosphate buffer (pH 6.8) was evenly spread onto the surface of the test membrane. The bioadhesive force, expressed as the detachment stress in g/cm<sup>2</sup>, was determined from the minimal weights that detached the tissues from the surface of each formulation using the following equation:<sup>12</sup>

$$\text{Detachment stress (g/cm}^2\text{)} = \frac{m}{A} \quad \text{Eq.(4)}$$

Where  $m$  is the weight added to the balance in grams and  $A$  is the area of tissue exposed. Measurements were repeated thrice for each of the films. All the above three experiments were conducted in triplicate.

#### Permeation studies

The *in vitro* study of ET/CA permeation through the mucosal abdominal area of rat was performed using a Franz diffusion cell at 37 ± 0.2 °C. Mucosa was obtained from mucosal area of rat in animal center.

Freshly obtained rat mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The films were placed on the mucosa and the compartments were clamped together. The donor compartment was filled with 3 ml simulated saliva with pH 6.8 (sodium chloride 4.50 g, potassium chloride 0.30 g, sodium sulfate 0.30 g, ammonium acetate 0.40 g, urea 0.20 g, lactic acid 3 g, and distilled water up to 1,000 mL, adjusting pH of the solution to 6.8 by 1 M NaOH solution). The receptor compartment was filled with 22-25 ml phosphate buffer with pH 7.4 and by stirring with a magnetic bead at 700 RPM [4]]. Three mL of samples were withdrawn at predetermined time intervals and analyzed for drugs at 311 (ET)/272.8 (CA) nm.

#### *In vitro* release studies

*In-vitro* release studies were carried out using an incubator shaker at 37 ± 0.5 °C, at a stirring speed of 50 rpm. Films were fixed on glass-slides and placed at the bottom of beaker. The studies were performed for all formulations (ET/CA) in triplicate, using 50 ml of isotonic phosphate buffer (37°C, 50 rpm, pH 6.8) as the dissolution medium. An aliquot of 3ml samples was withdrawn at regular intervals and replaced immediately with an equal volume of fresh phosphate buffer (pH 6.8). Samples were then analyzed at 311/272.8 nm with UV spectrophotometer.

#### Histopathological Evaluation of mucosa

Histopathological evaluation of tissue incubated in phosphate buffer with pH 6.8 was compared with that treated with buccal mucoadhesive films delivered from bioadhesion time test. The tissue was fixed with 10% formalin, routinely processed, and embedded in paraffin. Paraffin sections were cut on glass slides and stained with hematoxylin and eosin. A pathologist blinded to the study was assigned to detect any damage to the tissue and examine the sections on the light microscope.<sup>12</sup>

#### Results

Buccal films of ET and CA were prepared by solvent casting technique. The physicochemical characteristics and mucoadhesions of all the formulations are shown in Table 2. All of formulations were smooth, flexible, colorless (transparent) except CA films (white color), non-sticky and elegant in appearance (Fig. 2).

The cut films were 1×1 cm<sup>2</sup> in size. The weight of ET films was in the range of 6.4-12.7 mg and for CA films in the range of 2.7-4.9 mg. The thickness of ET films was observed in the range of 54-103 µm and average thickness of CA films was 29-53 µm (Table 2). The percentage of moisture absorption was shown to range between 0.77±0.05 and 1.001±0.06% for E<sub>3</sub> films while for E<sub>1</sub> and E<sub>2</sub> formulations, the uptake moisture was not observed. For C<sub>1</sub> to C<sub>3</sub> films, the uptake moisture ranged from 0.462 to 7.175%. The moisture loss was

1.82 to 0.32% for E<sub>1</sub> to E<sub>3</sub> films and 2.48 to 7.23% for C<sub>1</sub> to C<sub>3</sub> films, as shown in Table 2.

**Table 2.** Effect of drug to polymer ratio on physicochemical characteristics and mucoadhesivity of ergotamine and caffeine films.

Variables	Formulation code					
	E <sub>1</sub>	E <sub>2</sub>	E <sub>3</sub>	C <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>
<b>Drug : Polymer ratio</b>	1:10	1:20	1:30	1:2	1:4	1:6
<b>Weight variation (g ± SD)</b>	0.0064±0.0004	0.0099±0.0008	0.0127±0.0017	0.0027±0.0004	0.0032±0.0006	0.0049±0.0009
<b>Thickness (mm± SD)</b>	0.054±0.010	0.074±0.007	0.103±0.007	0.029±0.004	0.045±0.004	0.053±0.004
<b>Folding endurance (n±SD)</b>	252.66± 9.29	120.66±11.02	72.66 ±11.59	>300	>300	229.66±14.64
<b>Content (mg/cm<sup>2</sup>±SD)</b>	0.22± 0.02	0.21± 0.02	0.23± 0.02	0.60±0.05	0.30± 0.14	0.38± 0.17
<b>Absorbed moisture (% ±SD)</b>	-	-	1.001 ± 0.06	0.46±0.05	1.51±0.003	-
<b>Moisture loss (% ± SD)</b>	1.82 ± 0.06	0.72 ± 0.04	0.32±0.02	2.48±0.07	5.01±0.09	7.23±0.15
<b>pH surface (±SD)</b>	5.57 ± 0.11	5.64 ± 0.21	5.68 ± 0.19	6.47±0.27	6.26±0.34	5.26±0.23
<b>Swelling index (%±SD)</b>	8.20±1.08	8.22 ± 1.13	8.43 ± 1.43	6.53±1.50	9.3±2.94	9.21±2.8
<b>Mucoadhesive strength (g/cm<sup>2</sup>±SD)</b>	11.57±1.52	12.74±0.26	15.38±1.34	113.41±0.24	145.69± 0.56	159.24±0.34
<b>Residence time (sec±SD)</b>	135± 1.4	150± 8.74	165± 2.36	20±2.50	31± 3.10	36± 2.4



**Figure 2.** Optical microscopic photograph of mucoadhesive films of: (A) Ergotamine tartrate; (B) Caffeine anhydrous.

All formulations were of pH 5-5.78 (for E<sub>1</sub> to E<sub>3</sub>) and 5-6.7 (for C<sub>1</sub> to C<sub>3</sub>) and it may be concluded that the films are safe and non-irritating to oral mucosa (Table 2).

The ET and CA films contents were in the range of 0.21 to 0.23 mg/cm<sup>2</sup> and 0.3 to 0.6 mg/cm<sup>2</sup>, respectively.

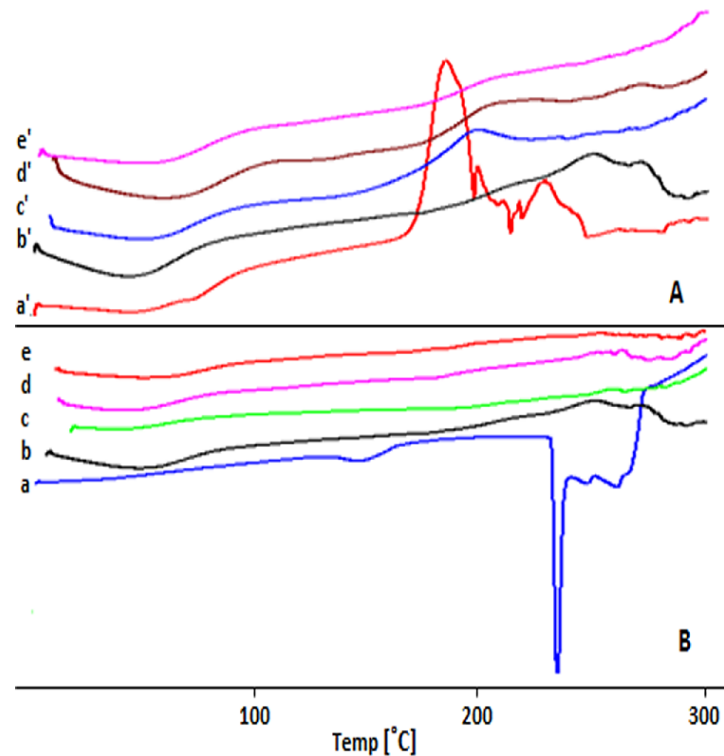
In our study, the *in vitro* residence time determined the period during which the ET and CA films adhered to the mucosa, namely, from 135±1.4 to 165±2.36 s and 20±2.5 to 36±2.4 s, respectively.

All films showed low diameter swellings. The recorded swellings after 2 h were 8.20-8.3% (for E<sub>1</sub> to E<sub>3</sub> films) and 6.53-9.30% (for C<sub>1</sub> to C<sub>3</sub> films). The best drug polymer ratios in ET/CA films were 1:20 (E<sub>2</sub>) and 1:4 (C<sub>2</sub>), respectively.

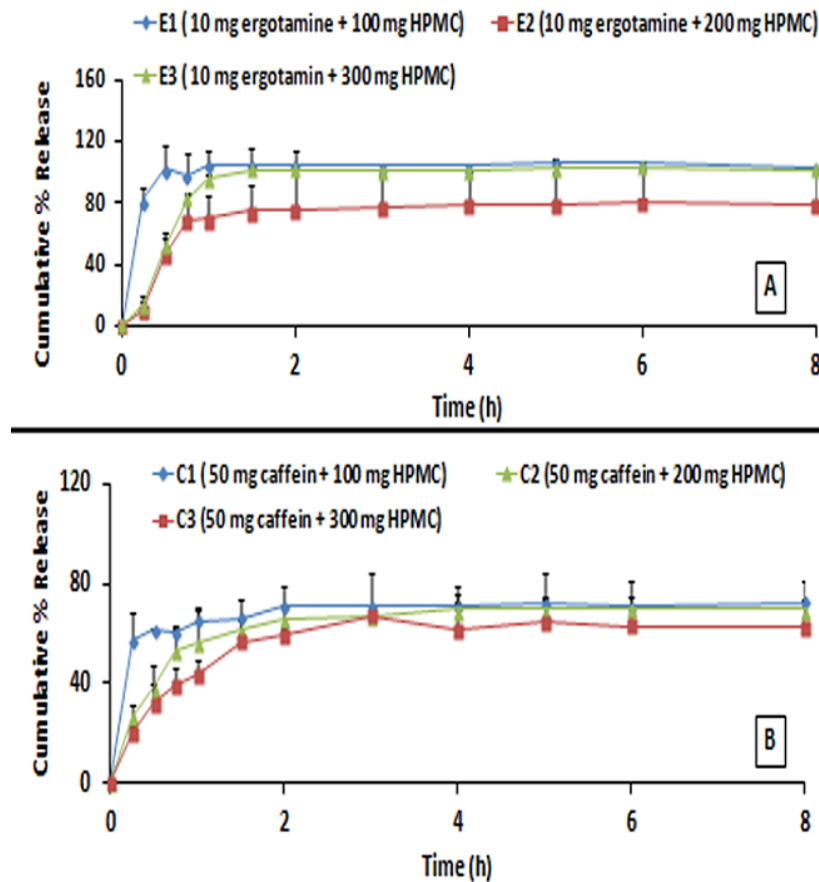
The pure ET and CA exhibited sharp melting exothermic and endothermic temperatures around 192.60 and 238.61°C, respectively (Fig. 3).

The intensity of the ET fusion peak, however, for the film formulations was lower than that for the pure drug (the melting peak of drug disappeared with increasing the concentration of HPMC from E<sub>1</sub> to E<sub>3</sub>).

The results of *in vitro* bioadhesive strength study are shown in Table 2. The bioadhesion characteristics were affected by the concentration of polymer (HPMC). The E<sub>3</sub> formulation containing a 1:30 ratio (drug: polymer) showed the highest mucoadhesivity (15.38±1.34 g/cm<sup>2</sup>). Moreover, the C<sub>3</sub> formulation containing a 1:6 ratio (drug: polymer) showed the highest mucoadhesivity (159.24±5.71 g/cm<sup>2</sup>).



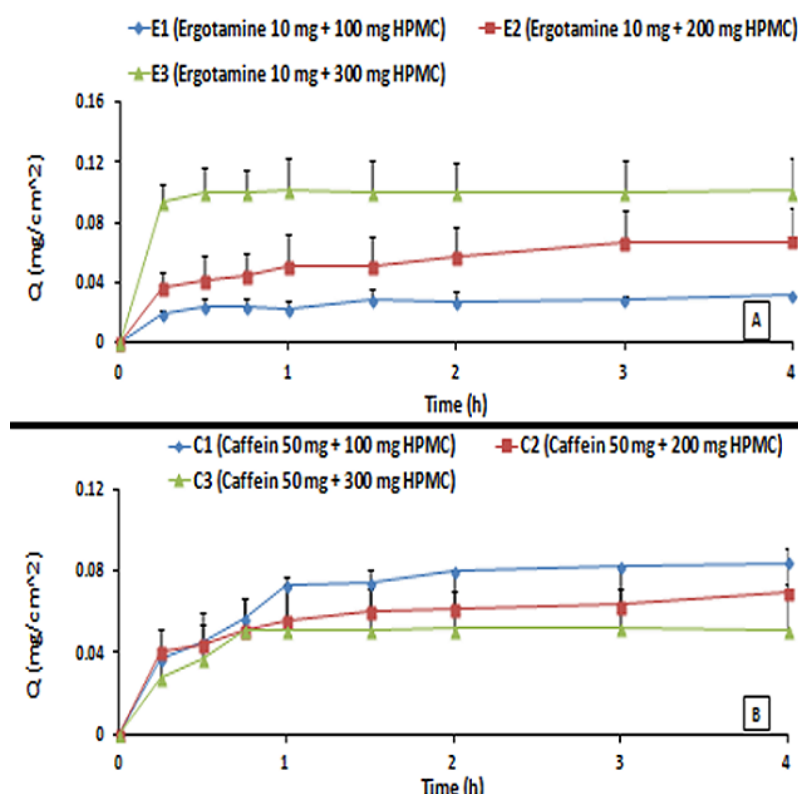
**Figure 3.** (A) DSC thermogram of caffeine (a'); HPMC (b'); C<sub>1</sub> (50 mg caffeine and 100 mg HPMC) (c'); C<sub>2</sub> (50 mg caffeine and 200 mg HPMC) (d') and C<sub>3</sub> (50 mg caffeine and 300 mg HPMC) (e'), (B) DSC thermogram of ergotamine tartrate (a); HPMC (b); E<sub>1</sub> (10 mg ergotamine and 100 mg HPMC) (c); E<sub>2</sub> (10 mg ergotamine and 200 mg HPMC) (d) and E<sub>3</sub> (10 mg ergotamine and 300 mg HPMC) (e).



**Figure 4.** Cumulative percent release of: (A) ergotamine; (B) caffeine, from films prepared with different drug to polymer ratios.

Figure 4 shows that the initial drug releases (Rel0.5) for the C1 to C3 formulations were high (57.27%, 26.85% and 19.70%, respectively) and Rel2 was 70.57%, 65.66% and 59.09%, respectively. Drug

release of ET films showed that low burst effect for E1 to E3 formulations were low (18.53%, 13.11% and 10.40%, respectively) and Rel2 was high (104.34%, 101.71% and 75.76%, respectively).



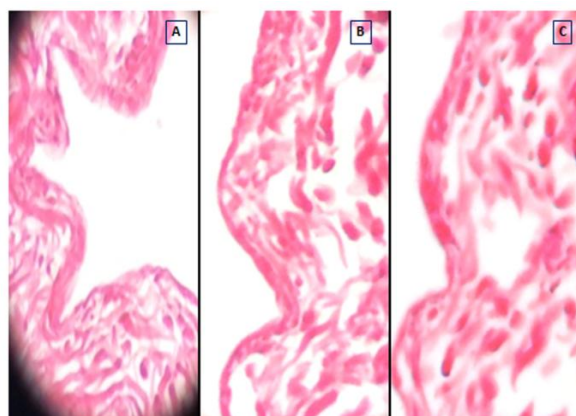
**Figure 5.**(A) Amount of ergotamine release per unit surface area after 4 h; (B) Amount of caffeine release per unit surface area after 4 h through mucosal abdominal area of rat.

Figure 5. compares the permeation of ET and CA films through rat abdominal mucosa for formulations containing different drug to polymer ratios. Slopes of the linear portion of the release profiles were calculated. These slopes represented the rate of release or flux of ET/CA from different formulations (Table 3). The highest fluxes were for formulations E2 and C2, 0.0107 and 0.0256 mg/cm<sup>2</sup>.min, respectively.

**Table 3.** Flux or amount of drug release per unit surface area after 4 h, intercept and regression coefficients for different formulations and comparison of various release characteristics of ergotamine and caffeine from different film formulations.

Formulation code	Flux (mg/cm <sup>2</sup> .min)	Intercept (mg/cm <sup>2</sup> )	r <sup>2</sup>
E <sub>1</sub>	0.0031	0.028	0.8892
E <sub>2</sub>	0.0107	0.0357	0.9642
E <sub>3</sub>	0.0025	0.0983	0.8662
C <sub>1</sub>	0.0155	0.0508	0.7452
C <sub>2</sub>	0.0156	0.038	0.9068
C <sub>3</sub>	0.345	0.02	0.9077

The microscopic observations indicated that the films had no significant effect on the microscopic structure of mucosa. As shown in Figure 6, no cell necrosis was observed.



**Figure 6.** Histopathological evaluation of sections of mucosal abdominal area of rat (A) untreated; (B) treated with film containing ergotamine; (C) treated with film containing caffeine (magnitude X).

### Discussion

The variation in weight and thickness of the formulations may be the effect of difference in molecular weight of ET/CA drugs and proportion of

polymer used in the films (Table 2). The flexibility of the ET films which was demanded for their easy handling was given by their folding endurance and was ranged from 72.66-252.66 times. All the CA films resisted the breakage upon folding for more than 300 times at the same place (Table 2). Hence it was taken as the end point. The values were observed to be optimum to reveal good film properties. Percentage moisture absorption was correlated with the capacity of excipients absorbing water in vapor form. Polymer used was hydrophilic. It is hypothesized that the initial moisture content acts as a determining factor in moisture absorption. Thus the high moisture absorbing capacity was detected in C<sub>3</sub> (7.18%) and more moisture loss was observed in C<sub>1</sub> (7.23%). The other films had high initial moisture content as was evidenced by percentage moisture loss. There was an inverse relationship between these two parameters, as the higher the percentage moisture loss, the lower the moisture absorption and vice versa.<sup>13</sup>

Though there was a little change in the loss of drug among the formulations, more uniformity was seen in ET films. The acidic or alkaline pH may cause irritation of buccal mucosa and may affect the drug release and degree of hydration of polymer. Therefore the surface pH of buccal film was determined to optimize both drug release and mucoadhesion. The surface pH of all formulations was within  $\pm 0.5$  units of the buccal pH (5.5-7) and hence no mucosal irritations were expected and ultimately achieved patient compliance.<sup>14</sup>

As the polymer particle swells, the matrix experiences an intra-matrix swelling force which promotes erosion or disintegration of the matrix, and leaching of the drug leaves behind a highly porous matrix.

Further water influx weakens the network integrity of the polymer. The structural resistance of the swollen matrices is highly affected and the erosion of loosely bound gel layer is more pronounced.<sup>9</sup> In the present study, erosion of CA films was the quickest while that of ET films (especially E<sub>3</sub>, 165 $\pm$ 2.36 s) was the slowest.

The integrity of CA films was lost soon following rapid uptake and swelling compared to ET films prepared in this study ( $p > 0.05$ ). CA drug is an anhydrous molecule, permits more water influx, and results in a quicker dissolution and erosion from the mucosal surface. HPMC is a hydrophilic polymer and may have more affinity towards mucin which is composed of 95% water. This may be the reason for the longer residence time (the films' integrity is shorter). As also reported in literature, the enhanced erosion rate was observed with the non ionic polymers as with HPMC. Evaluation of the swelling behavior was done by measuring diameter swelling. In the case of films (ET and CA) intended for buccal (local) therapy, the contact area must have been as large as possible, a requirement that must have been balanced with patient compliance. Excessive increase in film diameter might

have caused discomfort and/or dislodgment of the swollen film (lower than 10% swelling).

As the drug was uniformly dispersed in the matrix of the polymer, a significantly good amount of drug was loaded in all the formulations. The loss of drug could be related to its aqueous insolubility (ET/CA). ET/CA began settling down from medicated solutions when left non-dispersed for removal of air bubbles. Hence the solutions were casted as films containing lesser amount of drug. The viscosity of the polymeric solution may have affected the settling of drugs (ET/CA).

It is obvious from thermograms that the DSC curves of CA films showed CA was transitioning to amorphous form.

The DSC analysis of films revealed a significant change in the melting point of ET/CA drugs indicating modification or interaction between the drug and the polymer (Fig. 3).

According to *in vitro* mucoadhesion test run by Nakanishi *et al.*,<sup>11,15</sup> the mucoadhesion force depends on the hydrogen bonding between the hydroxyl group in the polymer and the mucus. It forms an ionic complex with hyaluronic acid that provides higher binding power.

No correlation was observed in this study between the bioadhesion force and the residence time of HPMC polymer. It seems the high bioadhesive polymer does not necessarily reside longer on the mucosal surface. Surface charge density and chain flexibility are regarded as prerequisites for the bioadhesion, whereas the residence time is principally dependent on the dissolution rate of the polymer.<sup>16</sup>

The release profiles for all films are illustrated in Figure 3. Films with high drug content or high drug entrapment showed a faster dissolution rate. This could be due to higher level of polymers corresponding to lower level of the drug in the formulation (E<sub>3</sub>, 1:30 drug to polymer ratio and C<sub>3</sub>, 1:6 drug to polymer ratio) which resulted in a decrease in the drug release rate ( $p < 0.05$ ). As more drugs are released from the films, more channels and pores are probably produced, contributing to faster drug release rates.

The release of drug from ET films was faster than the release of drug from CA films ( $p > 0.05$ ). During dissolution, HPMC containing films swelled forming a gel layer on the exposed mucus surfaces.

The release of drug from CA films was slow (Fig. 4) because of the formation of a loose network of HPMC which dissociates and disintegrates slowly in phosphate buffer. With an increase in HPMC concentration, the interaction between the polymer and the drug increased with the formation of a closer network, which showed a decrease in the diffusion of drug from the films. The reason for the burst release ( $Rel_{0.5}$ ) could be due to the presence of some pores and channels of polymer close to the surface of the films. When water-insoluble drugs (ET/CA) have a tendency to migrate to be removed, when left the air bubble time, thereby drug concentration increases at the surface of the films and



induces the burst effect.<sup>4,17</sup>

The pores present in HPMC polymer acted as channels for the entrance of the liquid medium through the film surface, causing it to swell. Hydrogen bonding between the hydroxyl groups of the HPMC moiety and mucus surface decreased its porosity and permeability. Thus, by varying the ratio of drug to polymer ET/CA films, the rate of release of drug can be controlled.<sup>18,19</sup>

### Conclusion

This study clearly demonstrated that ET/CA drugs could be successfully delivered through buccal route. The fast dissolving thin films (ET and CA) were successfully formulated using HPMC E<sub>15</sub> formulations. The best drug of polymer ratio in ET/CA films was 1:20 (E<sub>2</sub>) and 1:4 (C<sub>2</sub>), respectively. Moreover, the film had acceptable physical properties and drug content. The average disintegration time for the optimized film was within 26-165 s and the amount of 59.09-101.34% of the drug was released within 2 h. The films were nonirritating with favorable film properties and showed sufficient mucoadhesive potential until the drug was absorbed from the formulation. Further, it was confirmed that the combination of ET and CA films for a buccal delivery was a cure for migraine headaches that avoided the disadvantages of oral routes.

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### Conflict of Interest

The authors report no conflicts of interest.

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