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DESIGN AND CHARACTERIZATION OF BUCCAL FILMS OF TRAMADOL HYDROCHLORIDE

Padmaja Chimmiri^{*1}, R. Rajalakshmi¹, G. Ramesh², K. Rajesh¹, B. Mahitha¹,
G. Kapilraj Bharat³

Department of pharmaceutics,

¹Sree Vidyanikethan College of pharmacy, A. Rangampeta, Tirupati - 517102, AP, India.

²National institute of Pharmaceutical Education and Research (NIPER), Hyderabad, AP, India.

³Sri Venkateswara University, Tirupati, AP, India.

ABSTRACT

Opioid analgesics are important in both acute and chronic pain management. Tramadol Hydrochloride is a centrally acting analgesic having both opioid and non opioid effects, which is associated with little respiratory depression. Tramadol Hydrochloride is a water soluble drug. It is having relatively short duration of action it requires repeated dosage for therapeutic action. And it is having extensive first pass metabolism. Controlled released buccal films of Tramadol Hydrochloride were prepared and investigated using polymers HPMC K₄M, sodium carboxy methyl cellulose, carbopol 934 in different ratios. Compatibility studies were done by using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry techniques (DSC). FTIR spectra and DSC thermograph of Tramadol Hydrochloride, polymers, and all formulations indicates that there is no chemical interaction and confirmed the stability of the drug. The films were evaluated for their physical characteristics like weight variation, Thickness, folding endurance, surface pH, drug content uniformity, swelling index, *Ex vivo* bioadhesion time. *In vitro* drug release studies reveal that all films exhibited controlled release in the range of 75.87 to 91.22% for a period of 8 hours. *Ex vivo* permeation studies through sheep buccal mucosa indicate that films showed good controlled drug release in the range of 80.95 to 93.12% over a period of 10 hours.

Keywords:- Tramadol Hydrochloride, Buccal films, *In vitro* release, *Ex vivo* permeation.

INTRODUCTION

Oral mucosal route of drug delivery has attracted the attention worldwide for optimizing the drug delivery (Jain NK, 2002). The mucosa is highly permeable with a rich blood supply. Absorption through the oral mucosa overcomes drug degradation due to enzyme activity and pH of the gastrointestinal tract, avoids active drug loss due to first-pass hepatic metabolism and therapeutic plasma concentration of the drug can be rapidly achieved

(Jian-Hwa G *et al.*, 1999). The Buccal mucosa provides controlled release of drugs with the use of mucoadhesive polymers without the interference of normal activities (Swarbrick J, Boylan JC 1990).

Tramadol Hydrochloride is a centrally acting non-steroidal anti inflammatory drug with little respiratory depression. Tramadol, a synthetic opoid of the aminocyclohexanol group, with weak opoid agonist properties. Tramadol has been proved to be effective without causing serious side effects in both experimental and clinical pairs. It alters perception and response to pain by binding to mu-opiate receptors in the CNS. Tramadol Hydrochloride is used to treat moderate to severe chronic pain and is used to treat postoperative, dental, cancer, and

Corresponding Author

Padmaja Chimmiri

Email: padmajachimmiri@gmail.com

acute musculoskeletal pain. It undergoes extensive first pass metabolism by Hepatic demethylation and glucuronidation. Of a tramadol dose, approximately 60% is metabolized by the liver, including cytochrome P450 isoenzymes 2D₆ and 3A₄ and excreted.

The half life of drug is 5.5–7 hours. The drug is orally administered as 50-100 mg tablets for every 4-6 hours (Liao S, et al., 1992, Tegeder I, et al., 1999). Following oral administration, Tramadol Hydrochloride is well absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of Tramadol Hydrochloride is 68-72%. Tramadol is water soluble drug such therapy leads to poor patient compliance (Daramsi A et al., 2004). To reduce the frequency of administration and to improve patient compliance, a sustained release formulation of Tramadol is developed.

From the above points it is clear that Tramadol Hydrochloride is a suitable candidate for buccal delivery. In this study, an attempt was made to investigate the feasibility of mucoadhesive buccal films as a medium for the sustained delivery of Tramadol Hydrochloride with better bioavailability using polymers HPMC K₄M, Sodium CMC, Carbopol 934.

MATERIALS AND METHODS

Materials

Tramadol Hydrochloride was a gift sample (MMC health care limited), Hydroxypropylmethylcellulose K₄M, Sodium carboxy methyl cellulose, Carbopol 934 were obtained from Himedia labs, (Mumbai). And other chemicals used were of analytical grade.

Preparation of buccal mucoadhesive films (Balamurugan K et al., 2001)

The solvent evaporation method was used for the preparation of films. About 10 films were prepared using different composition of polymers and the films were observed for dispersion of drug, flexibility, and glossy structure. Among these four formulations were selected and used for further analysis.

Buccal films of Tramadol Hydrochloride were prepared by solvent evaporation method using film forming polymers (Devi K, Paranjothy KL 1998). Required amount of HPMC K₄M according to the formulation table-1 was weighed accurately and soaked in water and kept aside for 10min for swelling of polymer. And required amount of water was added to the above polymer solution and dispersion was stirred. Simultaneously required amount of Tramadol Hydrochloride was weighed accurately and dissolved in 5ml of distilled water in another beaker. Then drug solution was added to the polymer solution and 1ml of glycerol as plasticizer was added and mixed thoroughly with the help of magnetic stirrer. The above solution was sonicated for 20min for the removal of air bubbles. The glass mould (petridish) having diameter 9cm was placed

over a flat surface and the resulting 30 ml solution was transferred into petridish slowly drop by drop and the solution was spread uniformly. Funnel was inverted and it is placed over the petridish to get uniform evaporation. The petridish containing polymeric solution of drug was kept at room temperature for 24hours. The patch was removed carefully and circular films of 29mm diameter were punched out so that each film contained 5mg of the drug. And films were packed with aluminium foil and preserved in desiccators till evaluation tests were performed. Similarly formulations F₂, F₃, F₄ were prepared. Composition of different buccal mucoadhesive formulations containing tramadol hydrochloride was shown in the table no-1.

Evaluation of the patches

Film thickness and weight (Nafee NA et al., 2003)

For determination of weight variation three films of every formulation were taken weighed individually on digital balance then average weight was calculated. And the thickness of each film was measured using micrometer screw gauge at different positions of the film and the average was calculated.

Swelling index (Thimmasetty J et al., 2008; Semalty et al., 2005)

Drug loaded films were placed in a petridish and the increase in weight due to swelling of the film was determined by pouring 50ml of pH 6.8 phosphate buffer into the petridish. And increase in the weight of the film was noted in 15 min intervals for 60 min and the weight of film was calculated. The percentage swelling was determined by using the following formula.

$$\text{Swelling (\%S)} = (X_t - X_o / X_o) \times 100$$

X_t is the weight of the swollen film after time t,

X_o is the initial film weight at zero time.

Surface pH

The surface pH of the films was determined to estimate side effects due to change in pH *in vivo*, since any change in pH may cause irritation to the buccal mucosa. The film to be tested was placed in a Petri dish and it was moistened with 0.5 ml of distilled water and kept for 1 h and the pH was noted down after bringing the electrode of the pH meter in contact with the surface of the film (Bottenberg P et al., 1991).

Folding endurance (Gua JH, Cooklock KM, 1995)

Folding endurance of the films was calculated by folding one film at the same place repeatedly till it broke or it can also done by folded up to 300 times, which is satisfactory to reveal good film properties. The value of folding endurance was the number of times of film could

be folded at the same place without breaking. The mean value and standard deviation was calculated.

Content Uniformity (Balamurugan K *et al.*, 2001)

Content uniformity was determined by dissolving one patch of 29mm diameter contain 5 mg of Tramadol Hydrochloride in 10 ml of phosphate buffer solution (pH6.8). And the contents were stirred with the help of magnetic stirrer to dissolve the film. The contents of solution were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 271 nm using UV spectrophotometer. The experiments were carried out in triplicate for each formulation and average value was calculated.

Ex vivo mucoadhesion time (Perioli L *et al.*, 2004)

The *Ex vivo* mucoadhesive time was determined by placing the film on freshly cut sheep buccal mucosa. Using cyanoacrylate glue the tissue was fixed to the internal side of the beaker. The film was wetted with phosphate buffer pH6.8 and it was pasted to the sheep buccal tissue with finger tip by applying a light force for 20seconds. The beaker was filled with 200 ml of phosphate buffer pH 6.8 and kept at temperature of 37°C and 50 rpm stirring rate was applied to simulate the buccal cavity environment. The time taken for the film to completely erode or detach from the mucosa was observed as the *Ex vivo* mucoadhesion time.

In vitro dissolution studies (Perioli L *et al.*, 2004; Ilango R *et al.*, 1997)

The *in vitro* drug release studies were performed by using USP dissolution test apparatus (paddle method) (Doijad RC *et al.*, 2006). A film of 29mm diameter size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.8). This slide was kept at an angle of 45° in a 1000 ml beaker containing 900 ml of phosphate buffer pH 6.8 solutions. The dissolution medium was maintained at a temperature of 37 ± 0.5° C and stirred at 50 rpm. At predetermined time intervals samples were withdrawn and replaced with fresh dissolution medium. The samples were filtered through 0.45µm Whatman filter paper and made appropriate dilutions with phosphate buffer pH (6.8). Absorbance was measured using UV- VIS spectrophotometer. Drug release and the cumulative percentage of drug released were determined.

Ex vivo permeation studies (Patel MV *et al.*, 2007; Chandra Sekhar K *et al.*, 2008)

Sheep buccal mucosa was used as a barrier membrane. The buccal mucosa of freshly sacrificed sheep was procured from the local slaughter house. The buccal mucosa washed in isotonic phosphate buffer of pH 6.8 and used immediately. The permeability across the sheep buccal membrane was determined in order to evaluate diffusion studies by using Franz diffusion cell.

The buccal mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 200 ml of isotonic phosphate buffer of pH6.8 which was maintained at 37 ± 0.2° C and stirred with a magnetic bead at 50 rpm. At regular intervals of time samples were withdrawn and diluted appropriately and absorbance was analyzed using an UV-VIS spectrophotometer at 271 nm.

Table 1. Composition of different buccal mucoadhesive formulations containing Tramadol Hydrochloride

S.NO	Formulation	F ₁	F ₂	F ₃	F ₄
1	Tramadol hydrochloride(mg)	50	50	50	50
2	HPMC K ₄ M(mg)	1000	500	750	950
3	Sodium CMC(mg)	-	500	250	-
4	Carbopol 934(mg)	-	-	-	50
5	Glycerol(ml)	1	1	1	1
6	Distilled water(ml)	30	30	30	30

RESULTS AND DISCUSSION

Drug estimation

Calibration curve of Tramadol Hydrochloride was done at λ max 271 nm in phosphate buffer (pH 6.8) with a UV-VIS spectrometer (UV-1700, Shimadzu Corporation). It obeyed Beer's law. The calibration curve was done in the concentration range of 5-25 µg/ml. Analyses were done in triplicate.

Drug -polymer compatibility

Fourier transform infrared spectroscopy (FT-IR)

IR spectra of Tramadol Hydrochloride and polymers alone and the combination of drug with polymers were shown in figure 1. An IR spectrum of pure Tramadol Hydrochloride showed the peaks 3306 cm⁻¹ (Hydrogen bonding), 2929 cm⁻¹ (C-H stretching of OCH₃), 2604 cm⁻¹ (-C-H stretching of -CH₂ and CH₃ groups), 1606 cm⁻¹ (C=C ring stretching), 1288 cm⁻¹ (-C-H bending of symmetric and asymmetric of -CH₂ and CH₃). These peaks can be considered as characteristic peaks of Tramadol Hydrochloride and were not affected with polymers and prominently observed in IR spectra of Tramadol

Hydrochloride along with polymers as shown in the figure 1. This indicated that there was no interaction between Tramadol Hydrochloride and polymers.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of the pure drug showed sharp distinct exothermic peak at 187.5°C corresponding to melting point temperature. There was no appreciable change in the melting exotherms of pure drug and the physical admixtures. This indicates that there was no incompatibility between drug and polymers and confirms the compatibility of drug and the polymers as shown in the

Figure 2.

Preparation of film formulations

The films of different formulations were prepared by solvent evaporation method using Glycerol as plasticizer. The films of HPMCK₄M were prepared. Further different Copolymers like Sodium carboxymethylcellulose, Carbopol 934 were added to HPMC K₄M. Maximum drug percentage was released from HPMCK₄M films. HPMCK₄M was found to be more mucoadhesive than Sodiumcarboxymethylcellulose. The prepared films were clear and translucent.

Figure 1. FT-IR spectroscopy A: Tramadol Hydrochloride, B: HPMC K₄M C: Sodium Carboxy methylcellulose, D: Tramadol Hydrochloride + HPMCK₄M E: Tramadol Hydrochloride+Sodium carboxy methylcellulose, F: Tramadol Hydrochloride + Carbopol 934

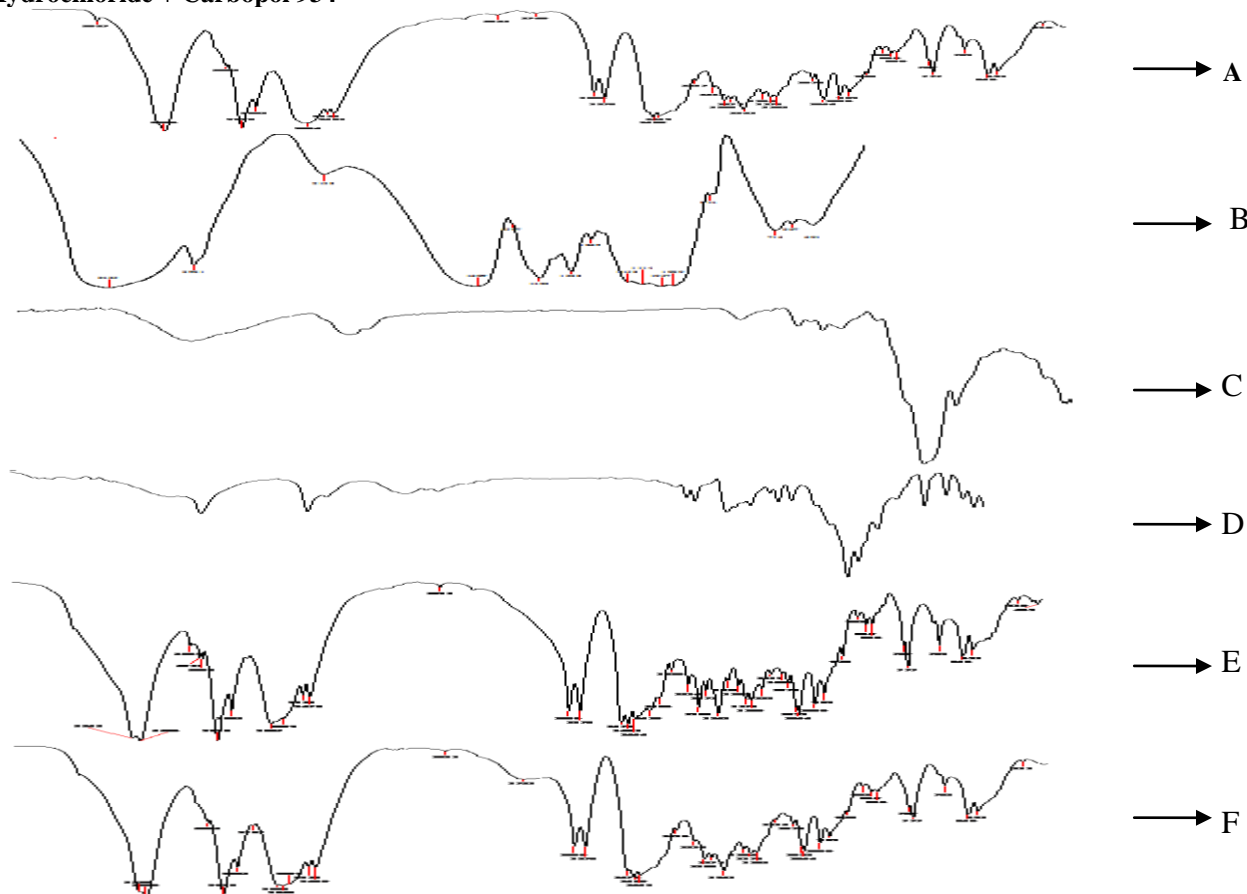


Table 2. Physical evaluation of mucoadhesive buccal films of Tramadol Hydrochloride

Formula code	Weight Uniformity	Thickness (mm)	Folding Endurance	Surface pH	Content Uniformity	Swelling index	Ex vivo bioadhesion time
F ₁	49±2.15	0.26±0.01	>300	6.51±0.02	4.64±0.008	44.4±0.33	2.28 ± 0.52
F ₂	44±0.95	0.23±0.03	>300	6.50±0.02	4.72±0.012	42.3±1.25	2.25± 0.41
F ₃	47±2.19	0.24±0.02	>300	6.45±0.03	4.66±0.037	45.2±1.16	3.00 ± 0.61
F ₄	48±1.73	0.24±0.01	>300	6.21±0.10	4.65±0.065	32.1±0.26	4.25± 0.71

All observations represent the mean ± S.D (Standard Deviation) and n=3 for all.

Figure 2. DSC thermograms A: Tramadol Hydrochloride, B: Sodium Carboxy methylcellulose, C: Carbopol 934, D: Tramadol Hydrochloride + Sodium carboxy methylcellulose, E: Tramadol Hydrochloride + Carbopol 934, F: Tramadol Hydrochloride + HPMCK₄M

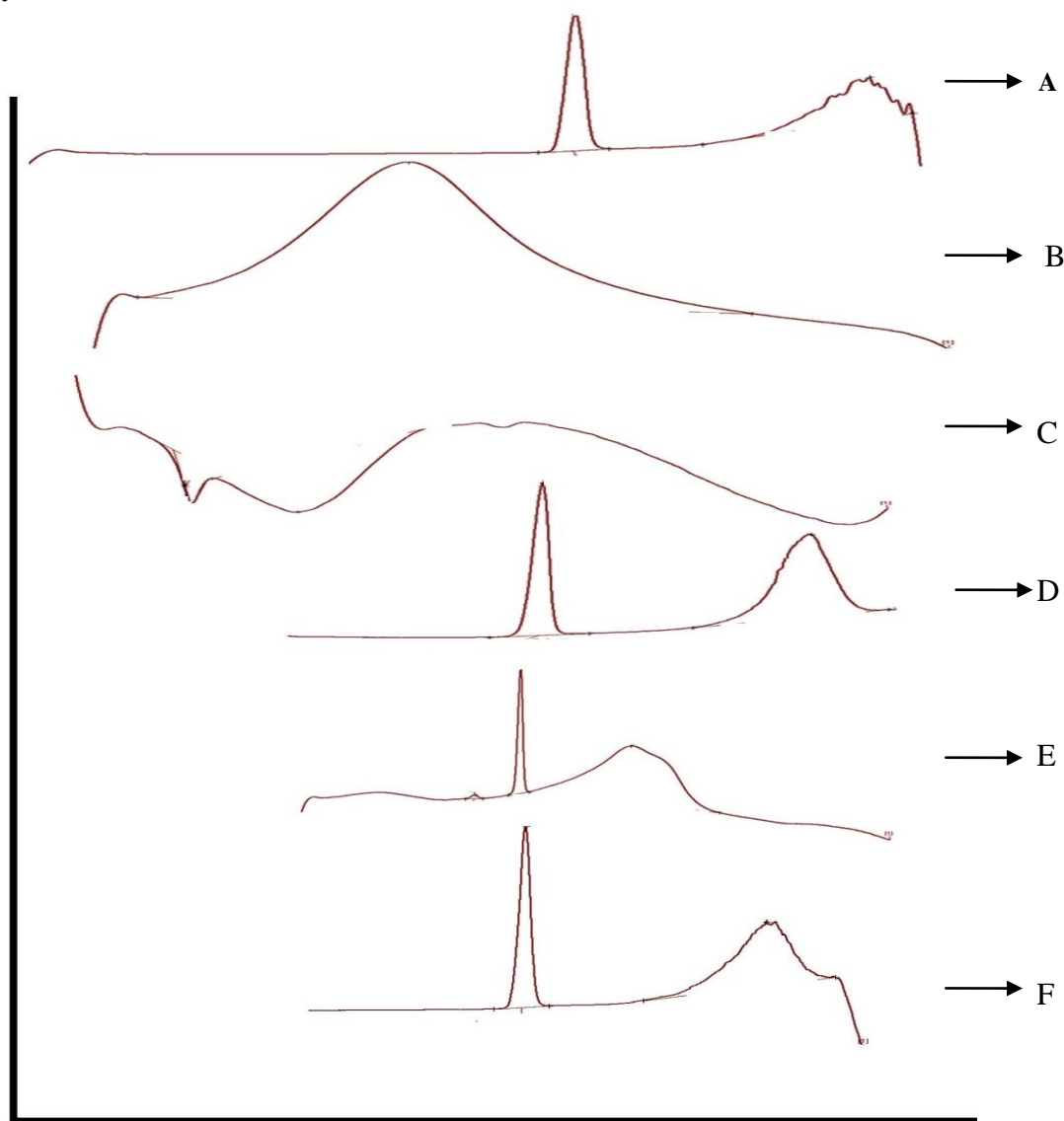


Figure 3. *In vitro* release of Tramadol Hydrochloride from buccal mucoadhesive films I to IV

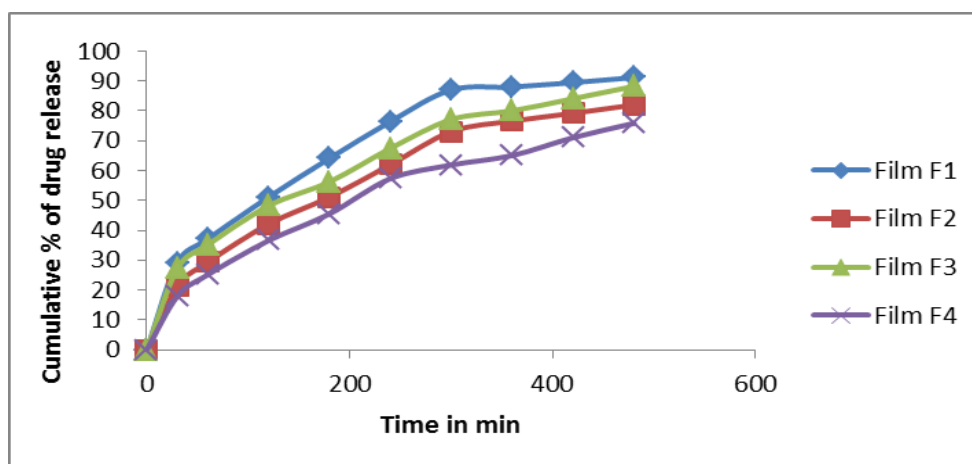
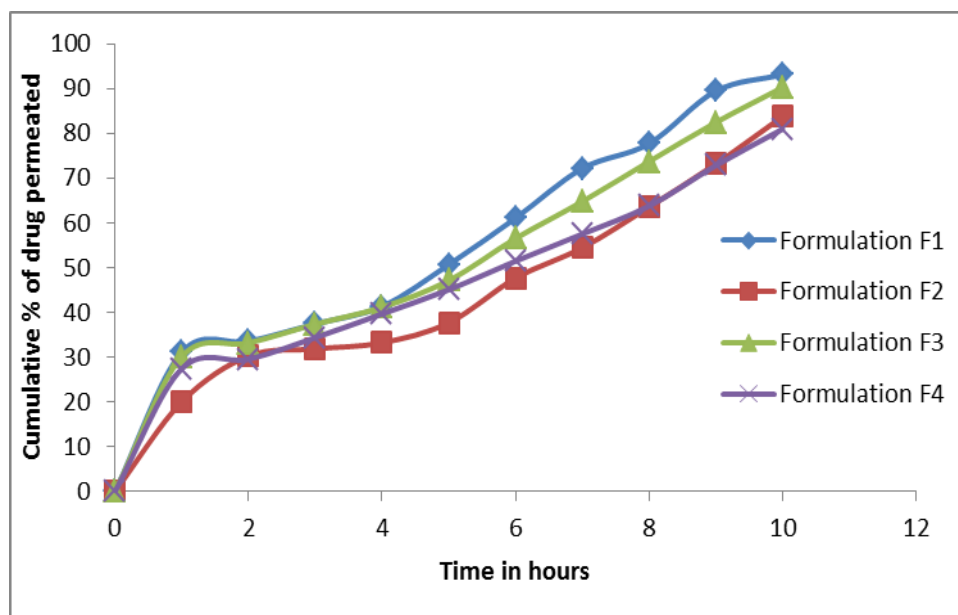


Figure 4. Ex vivo permeation studies of mucoadhesive buccal films of Tramadol Hydrochloride**Weight variation**

Drug loaded patches 29mm diameter was tested for uniformity of weight. The films weight found to be in the range of 44 ± 0.95 to 49 ± 2.15 .

Film thickness

The thickness of the films was found to be in the range of 0.23 ± 0.03 to 0.26 ± 0.01 .

Folding endurance

Films were folded for more than 300 times it did not show any sign of cracks. It was taken as end point.

Surface pH

Any change in pH of administered dosage can irritate the buccal mucosa. The surface pH of all films was found to be close to neutral in all the formulations. These formulations have less potential to irritate the buccal mucosa. The surface pH was found to be in the range of 6.21 ± 0.1 to 6.50 ± 0.02 .

Swelling index

The swelling of the patches were observed in phosphate buffer solution (pH 6.8). Swelling index was higher in film 1 and 3 which contains higher amount of HPMC K₄M. This was because of higher swelling capacity of HPMC K₄M. The swelling index was found to be in the range of 32.1 ± 0.26 to 45.2 ± 1.16 .

Content Uniformity

The drug content in all formulation was uniform and it was found to be in the range of 4.64 ± 0.008 to 4.72 ± 0.012 .

Ex vivo mucoadhesion time

The *Ex vivo* mucoadhesion time as follows $F_4 > F_3 > F_2 > F_1$. The buccal patches containing both HPMC K₄M and SCMC were found to increase the mucoadhesive

property. The mucoadhesive property was enhanced with HPMC K₄M and SCMC and was due to higher modulus of elasticity and mucoadhesive interaction may results from hydrogen bonding or other types of bonding possible by the hydrophilic nature of both polymers. *Ex vivo* permeation studies of all formulations showed in the figure no 4.

In vitro drug release studies

In vitro release studies of buccal patches were done by using pH 6.8 phosphate buffers as dissolution medium and measuring drug absorbance spectrophotometrically at 271 nm. The drug release was higher in formulation 1 and 3. The increased HPMC K₄M concentration in the film would enhance hydration this could be due to the higher rate and extent of swelling of the larger proportion of the hydrophilic polymer, HPMC K₄M leading to enhanced release of Tramadol Hydrochloride from the films. The films containing HPMC K₄M swelled during dissolution and form a gel layer on the exposed films surfaces. The HPMC K₄M molecules in these films were easily eroded, allowing release of Tramadol Hydrochloride. *In vitro* drug release of all formulations showed in the figure no 3.

Ex vivo permeation studies

Drug permeation studies were conducted through sheep buccal mucosa indicate that the Suitability of formulating Tramadol Hydrochloride for buccal delivery. *Ex vivo* permeation studies of Tramadol Hydrochloride from the film formulations indicate slow and sustained permeation of the drug for 10 h. The order of drug permeation from films was found to be $F_1 > F_3 > F_2 > F_4$.

CONCLUSION

Good results were obtained for Tramadol Hydrochloride buccal films from both *in vitro* and *ex vivo* studies. The present investigation shows that it is possible to formulate Tramadol Hydrochloride mucoadhesive buccal films for systemic drug delivery with the intention of obtaining better therapeutic efficiency by sustaining drug release thus by improving bioavailability, decreased dosing and fewer side effects with an added advantage of circumventing hepatic first pass metabolism. It may be concluded that the Tramadol Hydrochloride in Formulation

(F₃) showed good swelling, controlled release and optimum residence time, thus it seems to be a potential candidate for the development of buccal films for effective therapeutic use.

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