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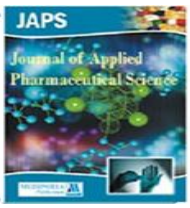

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Formulation design, in vitro evaluation and stability studies on mucoadhesive buccal films of anti-anginal calcium channel blocker

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ABSTRACT

Diltiazem hydrochloride has poor oral bioavailability, easily undergo first passage effect in the liver. Hence, an attempt was made to prepare and evaluate mucoadhesive buccal films containing diltiazem hydrochloride by employing HPMC, eudragit, ethyl cellulose alone and in combination with PVP. The I.R and DSC studies showed that there was no interaction between drug and the utilized polymer. The prepared mucoadhesive buccal films showed uniform thickness, weight, folding endurance, surface pH, drug content and swelling index. The drug content of all the formulation was found to be uniform. *In vitro* drug release studies indicated that the films prepared with HPMC (3%) and ethyl cellulose (4%) has shown fast and slow release respectively. The formulations incorporated with SLS and sodium glycocholate indicated significant drug release from F11 and F15. Later the *in-situ* diffusion studies using goat cheek pouch showed faster drug release from film with 1% (SLS). About 93.04% and 91.83% of drug release profile were observed during *in situ* diffusion studies at the end of 9hrs and 18 hrs respectively. The formulated films were stable during stability studies at 45ºC and 75%RH with respect to drug content.

Key words: Diltiazem hydrochloride, HPMC, Eudragit, Ethyl cellulose, Permeation enhancers and *In situ* diffusion studies.

INTRODUCTION

Drug delivery via the membranes of the oral cavity occurs by sublingual delivery, buccal delivery and Local delivery. The oral mucosa, mainly the buccal site rather attractive for drug delivery is the combination of several aspects like, the oral mucosa is easily accessible, so dosage forms can be easily administered and even removed from the site of application, according to is natural function the oral mucosa is routinely exposed to a multitude of different external compounds and therefore is supposed to be rather robust and less prone to irreversible irritation or damage by a dosage form, drug excipient or additive (Khanna et al., 1998). Drugs can be absorbed from the oral cavity through the oral mucosa either sublingually or buccally. In general, rapid absorption from these routes is observed. The oral cavity is lined by relatively thick, dense and multilayered mucus membrane with high vasculature. Drugs entering into the membrane can find access to the systemic circulation via network of capillaries and arteries. The arterial flow is supplied by branches of external carotid artery. The venous back flow goes via capillaries and the venous network is finally taken up by the jugular vein. The equally developed lymphatic drainage runs more or less parallel to the venous vascularization and ends up in the jugular ducts.

Thus, the buccal and sublingual routes can be used to bypass hepatic first pass elimination. (Robinson, 1987).

Mechanism of mucoadhesion

It involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface or from the swelling of the bioadhesive. In the second stage, after contact is established, penetration of the bioadhesive into the crevice of the tissue surface or interpenetration of the chains of the bioadhesive with those of the mucus takes place. Low chemical bonds can then settle.

Methods used to study bioadhesion: *In vitro* and ex *vivo* methods

Most *in vitro* methods are based on the measurement of either tensile or shear stress, Bioadhesiveness determined by measurement of stress tends to be subjective, since there is no standard test method established for bioadhesion. ***In vivo* methods:** *In vivo* techniques for measuring the bioadhesive strength are relatively few. Some of the reported methods are based on the measurement of the residence time of bioadhesive at the application site. The gastrointestinal transit time of many bioadhesives have examined using radioisotopes.

Buccal patches that are applied directly to the affected mucosal region have the potential to supply the site of action with effective drug levels and sustain these levels over a long period of time. A buccal patch for the systemic administration of a drug will, in general, be designed with much more emphasis on controlled-release rates and on achieving fairly even plasma level over a predetermined period of time. Even more than with locally active drugs, drug release from systemic buccal patches should be avoided. In general, this type of buccal patch would require relatively long adhesion times at least a few hours to achieve the desired systemic effects.

Some drugs are not absorbed from the gastrointestinal tract to a significant extent because they are degraded before they have a chance to be taken up by mucosal cells. The mechanism of degradation may be chemical, catalyzed by acid or more frequently it may be enzymatic. If a drug molecule capable of mucosal permeation is degraded in the upper gastrointestinal tract to such a degree that its oral bioavailability is too low to be acceptable, a buccal patch may be a good alternative.

Buccal absorbtion enhancers (Sevda et al., 2001)

In order to deliver broader classes of drugs across the buccal mucosa, reversible method of reducing the barrier potential of this tissue must be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restriction of the buccal mucosa. The mechanism by which the compounds enhance permeation are still not clearly defined. It is believed that the compound cause alteration of the protective permeation barrier of the mucosa either by interacting with the lipid domain of the epithelial cell without significant tissue damage or by damaging the mucosa tissue as well as perturbing the plasmatic cell membrane (Senel et al., 1998).

Buccal membrane permeation enhancers: Bile salts

Sodium glycocholate, Sodium taurocholate, Sodium taurodeoxycholate and Sodium glycodeoxycholate **Surfactants:** I) Nonionics: Poloxamer, brij, myrj, span. II) Catoinic: Cetyl pyridinium chloride. III) Anionic: Sodium lauryl Sulphate, Sodium laurate. Other enhancers: Fatty acids, Cyclodextrins and Chelators.
The buccal route as an alternative to other traditional method of systemic drug administration for the absorption of therapeutic compound from the oral mucosa provide a direct entry of the drug into the systemic circulation, therefore avoiding the first pass hepatic metabolism and gastrointestinal drug degradation which is associated with oral administration. Diltiazem hydrochloride was selected as model drug which has oral bioavailability 38± 11% and it is bound to plasma is 78 ± 3 % and having elimination half life of 4 hrs and having volume of distribution 3.3 ± 1.2 (litre/kg). The usual dosage regimen of diltiazem hydrochloride is at single oral dose of 120-300mg given to healthy adults. Therefore, in the present study buccal dosage forms of diltiazem hydrochloride films were prepared with various polymers and permeation enhancers. The formulated films are studied for physicochemical characteristics, *in vitro* diffusion studies, *in situ* drug release and stability studies to explore the polymers and permeation enhancers use in diltiazen hydrochloride buccal films.

Fourier Transform Infrared spectroscopy (FTIR) (Fergany et al., 2003).

To investigate any possible interaction between the drug and the utilised polymers under investigation FT-IR spectrophotometer method was used. The IR spectra of pure drug (diltiazem hydrochloride) and its physical mixture were carried out by using FTIR spectrophotometer on perkin elmer 1600 series USA. The folowing range was selected for IR spectra : 400cm^{-1} to 4000$cm^{-1.}$

Differential scanning calorimetry (DSC)

The DSC thermograms (Fergany A. et al., 2003) of pure drug diltiazem hydrochloride and its physical mixture were carried out to investigate any possible interaction between the drug and the utilized polymers and 50 ^{0}C to 300 ^{0}C heating rate was selected at an increase in 10^{0}Cper minute.

Preparation of Buccal Films of Diltiazem Hydrochloride

The films were prepared by using various polymers HPMC, eudragit and ethyl cellulose alone and in combination with PVP. Glycerol and dibutyl phthalate were used as plasticizers. Sodium lauryl sulphate and sodium glycocholate were employed as permeation enhancers. Among the various substrates for film formation including mercury, Teflon, glass and aluminium foil as substarate, mercury was found to give best result. The weighed quantity of polymer was taken and added to magnetically stirred

solvent system chloroform, ethanol and dichloromethane. Diltiazem hydrochloride 30mg was dissolved in 1 ml of ethanol and it was added to the polymer mixture with constant stirring Glycerol 30% w/w of polymer was added as a plasticizer in case of film contained HPMC and eudragit and Dibutyl phthalate 30% w/w of polymer was added as a plasticizer in case of film contained ethyl cellulose. This solution was stirred up to 30 min by using a magnetic stirrer. Then the mixture was poured in to a glass bangle of 18.08 sq cm area which was previously placed over mercury substrate in a petridish. The cut funnel was inverted over the Petridish for the controlled evaporation at 35º C. After 12 hrs the dried patches were collected and stored in the desiccator. Different permeation enhancers sodium lauryl sulphate and sodium glycocholate were added in the formulations and studied their effect on drug release. Two different concentration of sodium lauryl sulphate (0.5% and 1% w/w of the drug) and two different concentration of sodium glycocholate (0.5% and 1% w/w of the drug) were added in the polymer mixture and films were prepared as per the above procedure. (Khanna et al., 1998).

Evalution of buccal films of Diltiazem hydrochloride: Physical appearance

The films were observed visually for their physical appearance such as colour and transparency.

Surface texture **:** The surface texture of the films were evaluated by pressing the film with finger.

Weight variation: Four films of each formulation were taken weighed by using single pan balance and average weight films were calculated and standard deviations were computed. (Amin 2003).

Thickness and size: Four Films of each formulation were taken and the thickness of the film was measured using screw gauge at different places. The average film thickness and standard deviation were computed. (Pavankumar et al., 2003).

Folding Endurance: The folding endurance was measured manually. A small strip of film 2 cm^2 of each formulation was taken and folded at the same place till it breakes. The number of times a film could be folded at the same place gave the value of folding endurance.Average of three determination were calculated and standard deviation were computed. (Pavankumar et al., 2003).

The surface pH: The surface pH of the film was determined by allowing the film to swell by keeping them in contact with 0.5 ml of distilled water (pH 6.5±0.05) for 1 hour in 50 ml glass beaker. The surface pH was noted by bringing a combined glass electrode near the surface of the film for 1 min using pH meter. The pH was recorded and average of three determination and standard deviation was computed. (Khanna R. et al., 1998).

Drug content: Drug content uniformity was determined by tacking film area of 1.5 cm^2 from each formulation and it was placed in 50 ml of volumetric flask contained 50 ml of phosphate buffer of pH 6.6. It was kept aside for 6 hours and volume was made up to 100 ml with the buffer of pH 6.6. The content of (drug) diltiazem hydrochloride was calculated using standard graph. Average of three determinations was calculated. (Fergany A. et al., 2003).

Swelling studies: Buccal films of 2 cm^2 area from each formulation were taken accurately weighed by using single pan balance (w_1 gms) and it was placed in a petridish contained 50 ml distilled water. After different time interval 5 min, 10 min and 12 min film was removed and blotted with filter paper and weighed again. The weight of the film was noted (W_2). The swelling index was calculated by the formula. Swelling index = $(W_2\text{-}W_1) / W_2 \times 100$. Where W2 is Wet weight of the film and W1 is Dry weight of the film. (Pavankumar et al., 2003).

***In vitro* bioadhesion test:** A double pan physical balance was taken and both the pans were removed. The left pan was replaced with a brass wire. The right pan was replaced with a lighter pan. In the left pan polypropylene block was placed. The goat cheek pouch was carefully excised without removing connective and adipose tissue and stored in saline solution. The left side pan was placed in the beaker contained phosphate buffer of pH 6.6 and kept at 37 ± 1^0 C. The film was taken and attached to upper polypropylene cylinder and goat cheek pouch was attached on the lower polypropylene block. A preload weight of (30gms) was placed on the left pan of the balance for 10 min. The weights were then removed slowly and weights were added slowly in increasing order to the right pan till the patch separates from the mucosal surface. The weights required for complete detachment of the film from mucosal surface was noted. Average of three determinations was calculated. (Saisivam et al., 2000 and Khanna et al., 1998).

***In vitro* drug release evaluation**: *In vitro* diffusion studies were carried out in fabricated diffusion tube of surface area 1.5 cm^2 through sigma dialysis membrane. The sigma dialysis membrane was hydrated by addition of distilled water and fixed to one end of the tube which act as a donor compartment. The assembly was placed in the beaker contained 50 ml of phosphate buffer of pH 6.6. The teflon coated magnetic bead was placed in the beaker and rotated at 100 rpm using magnetic stirrer and the temperature was maintained at 37 ± 1^0 C. Samples of 1 ml were withdrawn at regular intervals and replaced the volume with same buffer and maintained sink condition through the studies. The absorbance was measured at 235 nm for quantifying the drug released. The same study was conducted for drug devoid film as control. (Raghuraman. et al., 2003).

***In situ* studies:** *In situ* drug release studies were carried out for the selected formulation by using goat cheek pouch membrane. In this method goat cheek pouch was attached to one end of donor compartment of the area of 1.5 cm^2 was selected and the above procedure was repeated. (Saisivam et al., 2000).

Stability studies: The stability studies were conducted for all the formulations at 40ºC and 75% RH to investigate the effect of temperature on the drug content in different film formulations. The films were removed from the oven at the end of 0, 7, 14, 21 and 28

days and they were analysed for drug content. Average of triplicate readings was taken. (Khanna et al., 1998).

Scanning electron microscopy (SEM): The surface morphology of the selected film (F1) was characterized by scanning electron microscope before and after the diffusion study and determined the drug distribution and the drug remained in the film after diffusion at 2.51 Kx. Magnification respectively. (Pongjanyakul et al., 2003).

Kinetics of drug release: The kinetics of drug release from films was studied by treating the data with first order equation. First order release would be linear as predicted by equation. Log C = Log Co - Kt / 2.303. Where, C is Amount of drug left in the matrix, Co is Initial amount of drug in the matrix, K is First order rate constant, (time $^{-1}$) and t is time, either in hours or minutes. The *in vitro* drug release data obtained from all the batches was treated to study the drug release is by diffusion as proposed by Higuchi. $Q=[De/T(2A-ec_s)c_st]^{1/2}$, Where, Q is Weight in grams of drug released per unit surface area, D is Diffusion co-efficient of drug in the release medium, e is Porosity of the matrix, Cs is Solubility of drug in the films expressed as grams per ml. Precisely, to know the exact mechanism of drug release, whether it is by diffusion or with combination of diffusion and erosion control, the data has also been plotted according to equation as suggested by Korsemeyer. $M_t / M\infty = Kt^n$ ....Where $M_t / M\infty$ is the fraction of drug release, K is Kinetic rate constant, t is Release time and n is Diffusional exponent for drug release. The value of 'n' gives an indication of the release mechanism. When n=l the release rate is independent of time and is a desirable mechanism in oral controlled drug delivery, when n=0.5 for fickian diffusion and when 0.5 < n < 1, the diffusion and non fickian transport are implicated. (Korsmeyer et al., 1983).

RESULTS AND DISCUSSION

A series of polymers like HPMC, eudragit, EC alone and in combination with PVP were used for the preparation of buccal films contained diltiazem hydrochloride as a model drug. The IR spectral studies indicated that there was no interaction between drug and the utilized polymers and copolymer (figure 1). The results showed that the usefulness of the polymers HPMC, eudragit, ethyl cellulose and PVP for preparation of various mucoadhesive buccal films contained diltiazem hydrochloride. DSC studies showed that there was no interaction between the drug and the selected polymer HPMC (figure 2). All the films were flexible with smooth surface texture and transparent and opaque in appearance. The formulations were uniform in their weight , thickness and almost uniform in their drug content with low SD value. The films contained HPMC has highest folding endurance than the films contained eudragit, ethyl cellulose alone and in combination with PVP. The surface pH values were found to be between 6.1 to 6.5 in all the formulations which indicated that all the formulations were compatible with the buccal surface. The eudragit contained buccal fims showed highest swelling index. The HPMC contained buccal films showed highest bioadhesive strength than that of other films. The drug content of all the films was found to be uniform with low SD values, which indicates that the drug was distributed uniformly in all the films (table 1).

Table 1. Characterisation studies of buccal films of diltiazem hydrochloride.

Formulation Code	Average weight (mg± SD)	Thickness (μm)	Folding endurance	Surface pH	Drug content	Swelling index	Bioadhesive strength (gm)
F1	225.11 ± 0.66	88.09 ± 0.35	488 ± 0.004	6.50 ± 0.05	98.09 ±0.3	eroded	4.85
F2	290.05 ±0.41	140.9 ± 0.32	522 ± 0.005	6.40 ± 0.05	98.29 ±0.2	eroded	6.24
F3	225.16 ± 0.64	88.12 ± 0.59	508 ± 0.005	6.20 ± 0.05	98.84 ±0.4	eroded	5.52
F4	225.21 ± 0.52	87.99 ± 0.50	105 ± 0.005	6.50 ± 0.05	98.57 ±0.2	33.47	2.74
F5	290.28 ± 0.59	141.1 ±0.48	128 ± 0.005	6.20 ± 0.05	98.06 ±0.3	44.70	3.80
F6	225.17 ± 0.46	88.41 ± 0.60	115 ± 0.040	6.10 ± 0.05	98.07 ±0.3	37.80	3.00
F7	224.58 ± 0.51	90.13 ± 0.57	458 ± 0.004	6.20 ± 0.05	98.27 ±0.2	23.14	2.10
F8	290.28 ± 0.59	141.1 ± 0.57	467 ± 0.004	6.30 ± 0.05	98.43 ±0.4	27.38	2.70
F9	224.59 ± 0.50	89.92 ± 0.44	464 ± 0.040	6.10 ± 0.05	98.28 ±0.3	22.72	2.30
F11	225.17 ± 0.50	87.99 ± 0.50	458 ± 0.004	6.50 ± 0.05	98.43 ±0.2	eroded	4.96
F15	290.28 ± 0.59	140.9 ± 0.32	521 ± 0.005	6.30 ± 0.05	98.07 ±0.3	27.20	3.10

Table 2. Kinetic assessment of Mucoadhesive Films Containing Diltiazem Hydrochloride.

Formulation Code	First order equation			Higuchi's equation		Korsmeyer's equation	
	Slope (n)	First order rate constant	Regression coefficient (r^2)	Slope (n)	Regression Coefficient(r^2)	Slope (n)	Regression Coefficient(r^2)
F1	-0.0032	0.00615	-0.99156	5.3505	0.97540	0.71361	0.96485
F2	-0.00226	0.00556	-0.97326	4.8671	0.97533	0.70387	0.96482
F3	-0.00258	0.005835	-0.97807	5.0671	0.97672	0.70046	0.96218
F4	-0.00194	0.005329	-0.98506	4.5955	0.99015	0.70632	0.97781
F5	-0.00165	0.00471	-0.98228	4.3053	0.98850	0.70342	0.98850
F6	-0.00222	0.00576	-0.99072	4.6877	0.98439	0.70171	0.96979
F7	-0.00146	0.00475	-0.98831	3.9905	0.99603	0.67707	0.99603
F8	-0.0012	0.00428	-0.97778	3.6368	0.99260	0.68846	0.97921
F9	-0.0015	0.00525	-0.98507	4.0635	0.99334	0.68188	0.97606
F11	-0.00163	0.00375	-0.98486	3.99534	0.98441	0.51251	0.96145
F15	-0.00155	0.00356	-0.98926	4.18222	0.99246	0.69028	0.96349
F18	-0.00106	0.00244	-0.97896	3.37963	0.98963	0.62703	0.97630
F19	-0.00159	0.00234	-0.98564	4.2356	0.99365	0.68794	0.98457

The films were later subjected to *in vitro* drug release studies. The release of the drug from films was dependent on the nature and proportion of the polymer. *In vitro* release studies were carried out using fabricated diffusion tube with sigma dialysis membrane in phosphate buffer of pH 6.6. The percentage release of drug from formulation F1 to F9 are as follows : 93.24, 85.34, 88.42, 80.38, 75.54, 81.41, 70.73, 64.30 and 72.38 at the end of 6hrs respectively. About 92-93 %of drug release was observed from all formulations. The films prepared with ethyl cellulose showed the drug release up to 13 hours as compared to other formulations without penetration enhancer (figure 3). In the later studies F1 and F8 formulations were selected and incorporated various concentration of penetration enhancer (figure 4). Among various concentration of SLS and sodium glycocholate only F11

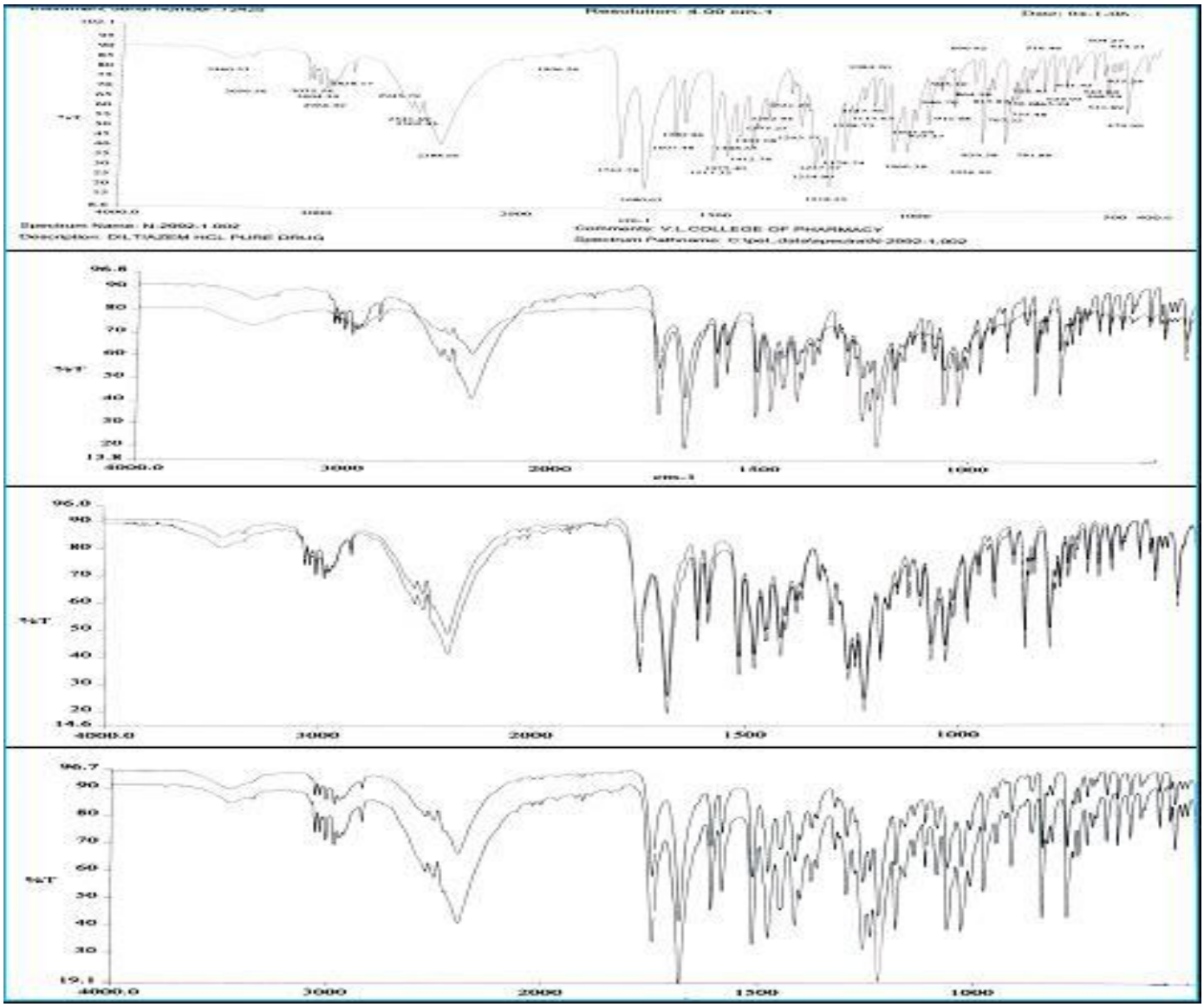

Fig 1. IR Spetrum of Diltiazem HCl, DHCl with HPMC, DHCl with Eudragit, DHCl with EC and DHCl with PVP.

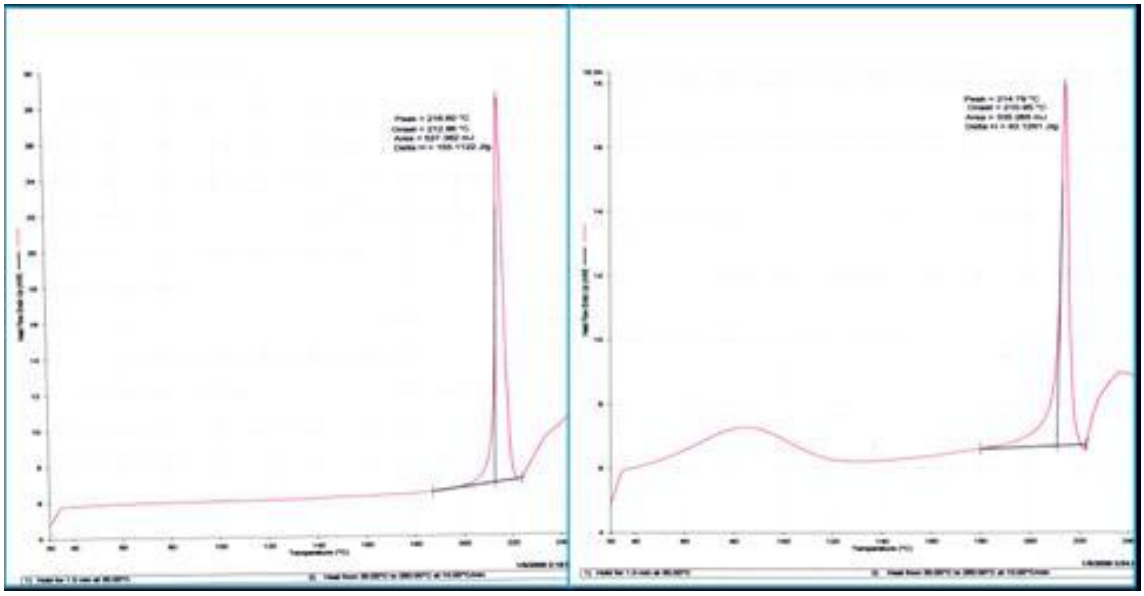

Fig 2 Differential Scanning Colorimetry of Diltiazem Hydrochloride alone and DHCl with HPMC, Eudragit, EC and PVP.

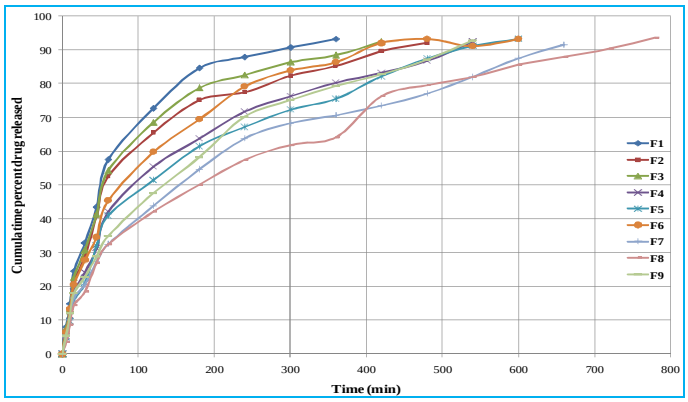

Fig 3. *In vitro* diffusion studies of Diltiazem Hydrochloride mucoadhesive polymeric buccal films.

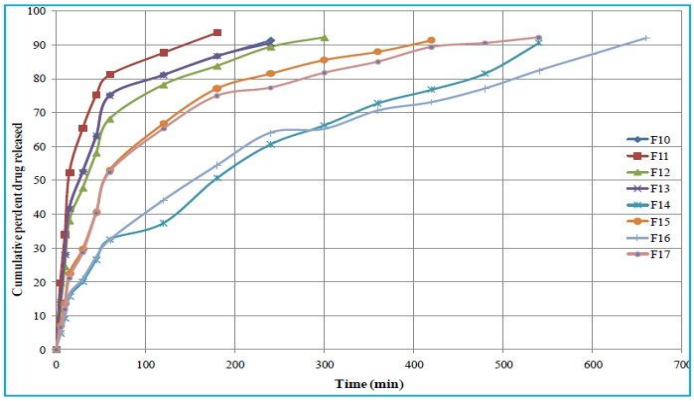

Fig 4. *In vitro* diffusion studies of Diltiazem Hydrochloride buccal films with SLS and Sodium Glycocholate.

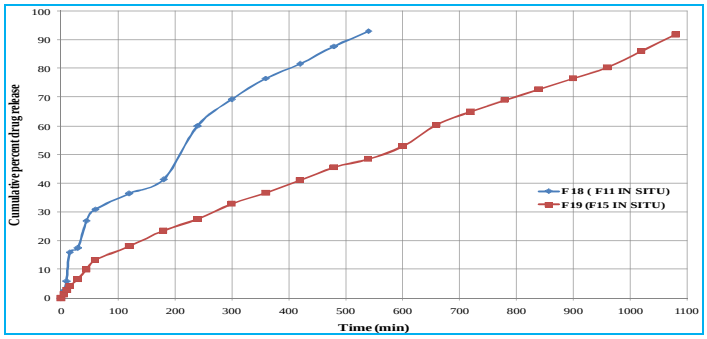

Fig 5. *In situ* diffusion studies of Diltiazem Hydrochloride mucoadhesive polymeric buccal films with permeation enhancers.

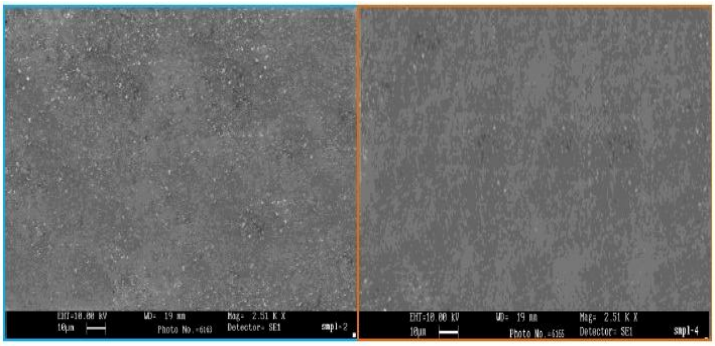

Fig 6. Scanning electron micrographs of Diltiazem Hydrochloride buccal film before and after *in vitro* diffusion studies.

with 1% w/w of SLS has shown 93.64% of drug release at the end of 3hrs. Where as in F15 formulation 91.43% of drug release was obtained with 1% SLS at the end of 7 hrs respectively. The results clearly indicated that there was an improvement of drug release in presence of penetration enhancer (SLS) which further shortened the time for drug release. Hence, SLS has shown more significant drug release ($p<0.01$) when compared with sodium glycocholate in both the formulations. Further the above two selected formulations were subjected to *in situ* diffusion studies using goat cheek pouch. The *in situ* drug release profiles from the formulations F18 and F19 showed 93.04% (9hrs) and 91.83% (18hrs) respectively (figure 5). The reason might be due to SLS acts either by perturbation of intercellular lipids or by protein domain integrity. *In vitro* and *in situ* correlation co-efficients were found to be 0.9763 and 0.9625. Further to understand the order and mechanism of drug release from buccal films the data was subjected to various kinetic equations and plotted according to first order , Higuchi and Korsemeyer's equations. The kinetic values obtained indicated that the rate of drug release was followed first order kinetics. Further the data was fitted with Higuchi equation and showed linear plots with their high regression co-efficient value between (0.97533 to 0.99603) indicated that the mechanism was diffusion controlled. Fairly linear plots were obtained for koresmeyer peppas equation with the regression co-efficient values 0.96218 to 0.99603 and slope of the plots were found to be between (0.67707 to 0.71361). The result indicated that the mechanism drug release from formulations was non-fickian and by diffusion controlled release. All the formulations were found to be stable with respect to the drug content and physical parameters during stability studies. Scanning electron micrographs indicated that the drug was uniformly distributed and released (about 93%) from the selected formulation (figure 6).

CONCLUSION

The buccal films of diltiazem hydrochloride were prepared using various polymers like HPMC, eudragit and ethyl cellulose alone and in combination with PVP by solvent casting technique. All the films were flexible with smooth surface texture transparent and opaque in appearance and they were uniform in their weight and thickness, and almost uniform in their drug content with low SD value.The surface pH values were found to be 6.1 to 6.5. The swelling index was more with eudragit contained films and the bioadhesive strength was more with HPMC contained films. *In- vitro* diffusion for F1 and F8 (fast release and slow release) with SLS and sodium glycocholate , 0.5% and 1% w/w of drug. SLS (1% w/w of drug) has shown significant increase on drug release. The release kinetics indicated non-fickian and by diffusion controlled release mechanism of drug release from films. The *in vitro- in situ* drug release profile were well correlated. The stress studies showed the stability of mucoadhesive buccal films contained diltiazem hydrochloride. SEM studies indicated that the drug was distributed uniformly and in the buccal film formulation.

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