



PREPARATION AND *IN VITRO* AND *IN VIVO* EVALUATION OF BUCCOADHESIVE BILAYERED TABLETS OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

In this study buccoadhesive bilayered tablets of Diltiazem HCl (DTZ) were prepared in order to improve the bioavailability by the avoidance of hepatic first-pass metabolism, and to prevent frequent administration. Bilayered Tablets containing fixed amount of Diltiazem HCl (DTZ) were prepared by direct compression method using polymers like hydroxyl propyl methyl cellulose (HPMC K4M, HPMC K15M, HPMC K100M) in combination with backing layer of ethyl cellulose and evaluated for physicochemical properties, swelling, bioadhesive strength, *in vitro* permeation studies, *in vitro* drug release and possible interaction between ingredients. The physicochemical properties, swelling index, surface pH, bioadhesive strength, *in vitro* drug release and *in vitro* permeation studies were found to be dependent on the grade and proportion of buccoadhesive material used. The dissolution of Diltiazem HCl from all the prepared tablets into phosphate buffer (pH 6.8) was controlled for 6 hrs and followed non-Fickian release mechanism. Lower release rates were observed for formulations containing higher concentration of higher viscosity grade of HPMC. FTIR and DSC studies revealed the absence of significant interaction between DTZ and the selected bioadhesive materials. *In vivo* studies of selected formulation in rabbits demonstrated significant enhancement in bioavailability of DTZ relative to orally administered drug.

Keywords: Diltiazem HCl (DTZ), Buccoadhesive bilayered tablets, Swelling index; *In vitro* drug release, bioadhesion time, HPMC.

INTRODUCTION

Diltiazem HCl (DTZ) is a non selective β -adrenergic blocker used in treatment of hypertension and myocardial infarction. DTZ is administered orally in a dose of 30-60 mg 3 times in day. From conventional tablet formulation water-soluble DTZ is completely and rapidly absorbed (80-90%) from the gastro-intestinal tract and the peak plasma concentration is reached within 2-3 hrs. However absolute bioavailability is reduced to approximately 40% with a large inter individual variation because of extensive first pass metabolism in the liver. Since this drug has a short half life of 3.5 - 4 hours and is eliminated rapidly, repeated daily administration is required to maintain effective plasma levels. These pharmacokinetic parameters make DTZ a suitable candidate for buccal delivery¹.

Buccal delivery involves the administration of the drug through the buccal mucosa membrane lining of the oral cavity. This route has a number of advantages when compared to the oral route. These advantages include the avoidance of first pass metabolism, the ability to produce systemic effect with a rapid onset of action, easy accessibility, enhanced patient compliance, rapid cellular recovery following local stress and possibility of removal of dosage form when required.

Buccal drug delivery necessitates the use of mucoadhesive polymers as a means of prolonging the residence time of the dosage form on the absorbing membrane as well as localising the drugs in the particular region. The selection of polymer and optimization of these formulation both from adhesion and controlled drug release point of view remain an important goal and challenge for development of a buccal dosage form².

The objective of the present study was to develop a buccoadhesive bilayered tablet of DTZ to prolong its residence time in buccal cavity, ensuring satisfactory

drug release in a unidirectional way to the mucosa thus avoiding loss of drug due to wash out with salivation³. The effect of polymer type and concentration was studied on the bioadhesive strength, drug release rate and release mechanism of the prepared formulation. *In vivo* bioavailability studies were carried out⁴.

MATERIALS AND METHOD

DTZ was obtained as a gift sample from Inventia Health care Pvt. Ltd. (Mumbai, India). HPMC K4M, HPMC K15M, HPMC K100M and ethyl cellulose were gifted by Colorcon Asia Pvt. Ltd., (Goa, India). Chitosan were gifted by Pelican Biotech and Chemical Labs.; (Kerala). All other excipients used were of analytical grade.

Drug Excipient Compatibility Studies

Compatibility study was carried for pure DTZ, and combination of DTZ with excipients. Fourier transform infra red (FTIR) spectroscopic (Shimadzu, Japan) studies were carried by appropriately diluting the sample with dried potassium bromide and acquiring infra red (IR) spectrum in the range of 400 to 4,000 cm^{-1} ⁵.

Preparation of the Buccoadhesive bilayered tablets of DTZ by direct compression

Buccoadhesive bilayered tablets were prepared by direct compression procedure involving two consecutive steps. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing drug, polymer, lactose and Aerosil in a glass mortar for 15 minutes. The mixture (150 mg) was then compressed using an 11 mm round shaped flat punch in a single stroke multistation tablet machine (Cadmach). The upper punch was raised and the backing layer of Ethyl Cellulose and tatrazine (75 mg) was then added on the above compact and the two layers were compressed to form bilayered tablets^{6,7}. Composition of formulation is given in Table 1.

Evaluation of Powder Blend

Blended drug/polymer mixture of all the formulations were subjected for precompressional evaluation such as bulk and tapped density, compressibility index and Hausner's Ratio and angle of repose⁸.

Evaluation of buccoadhesive bilayered tablets

Physical Characterization of the Designed Formulations

For each batch, 20 tablets were weighed for assessing weight variation. The percentage weight deviation was calculated and then checked for USP specifications. Thickness was determined using vernier caliper. Friability was determined by subjecting 20 tablets to falling shocks in friabilator (Campbell Electronics, India) for 4 min at 25 rpm. Hardness of the tablet was measured using Monsanto hardness tester and recorded as the maximum force required to break the tablet. This test was done in triplicate and average was calculated.

Drug content of each batch was determined by weighing and finely powdering 20 tablets. An aliquot of this powder equivalent to 10 mg of drug was taken into 100 ml volumetric flask and dissolved in phosphate buffer pH 6.8. 1 ml of above solution was withdrawn and made to 10 ml with phosphate buffer. Thus the corresponding concentration was determined using UV spectrophotometer at 237 nm. The test was done in triplicate and the average drug content estimated^{9,10}.

Surface pH studies

The surface pH of the buccal tablets is determined to investigate the possibility of any side effects *in vivo*. The surface pH should be close to neutral, an acidic or alkaline pH may irritate the buccal mucosa. The method used to determine surface pH of the formulation was similar to that used by Bottenberg et al.

A combined glass electrode was used to measure the surface pH. The tablet was allowed to swell by keeping them in contact with 1ml of distilled water for 2 hr. pH was noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 minute^{11,12}.

Measurement of bioadhesive strength

Bioadhesive strength of buccal tablets was measured using modified physical balance using the method described by Gupta et al (Figure 1). Sheep buccal mucosa was used as the model membrane. The mucosa was kept frozen in Krebs buffer and thawed to room temperature before use. The mucosal membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at $37 \pm 0.5^\circ\text{C}$ for 30 min in phosphate buffer pH 6.8 before the bioadhesion evaluation study. The tablet was lowered onto the mucosa under a constant weight of 5g for a total contact period of 1 min. Bioadhesive strength was assessed in terms of weight (g) required detaching the tablet from the membrane¹³.

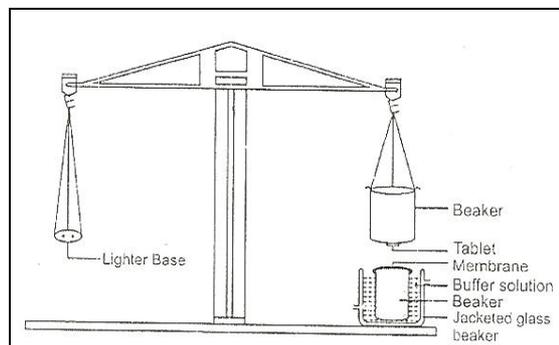


Figure 1: Bioadhesion test assembly

The swelling property of buccal tablets was evaluated by determining percent hydration. Buccal tablets were weighed individually; initial weight was considered as W_1 and placed separately in petridishes (outside dimensions: 100-mm diameter \times 15-mm height; inside dimensions 88 mm diameter \times 12-mm height) containing 15 ml of phosphate buffer (pH 6.8) solution in such a way that the side of tablet which attaches to the buccal membrane was positioned to the bottom of the petridish with the backing membrane being viewable from the top. Tablets were soaked in such a way that the core tablet remains completely immersed in the buffer solution. At regular intervals (0.5, 1, 2, 3, 4, 5, and 6 h), the buccal tablets were removed from the petridishes using cover slips and excess surface water was removed carefully using the Wattman filter paper^{11,14}. The swollen tablets were then reweighed (W_2) Percent hydration was calculated using following formula

$$\text{Swelling Index} = \frac{(W_2 - W_1)}{W_1} \times 100$$

In-vitro drug release studies

USP type II rotating paddle method was used to study the drug release from the bilayered tablet. The dissolution medium consisted of 600 ml phosphate pH 6.8. The release study was performed at $37 \pm 0.5^\circ\text{C}$, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the cyanoacrylate adhesive. The disk was placed at bottom of the dissolution vessel. 5 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through $0.2 \mu\text{m}$ Wattman filter paper and analyzed after appropriate dilution using UV double beam spectrophotometer at 237nm^{13,15-17}.

Data Analysis

To analyze the mechanism for the drug release and release rate kinetics of the dosage form, the data obtained from *in vitro* drug release studies was fitted in to zero order, first order, Higuchi's and Peppas's model¹⁸.

In-vitro permeation studies

The *in-vitro* buccal drug permeation study of DTZ through the sheep buccal mucosa was performed using Franz diffusion cell at $37 \pm 0.2^\circ\text{C}$. Fresh sheep buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and both compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment (55 ml capacity) was filled with isotonic phosphate buffer pH

7.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. 1 ml samples were withdrawn at predetermined time intervals and after appropriate dilution with isotonic phosphate buffer pH 7.4, analyzed at 237 nm using a UV spectrophotometer¹⁹.

Drug Release from backing layer

For determination of drug release from the backing layer, Franz diffusion cell was used. A bilayered buccal tablet was placed on sheep buccal mucosa placed between donor and receptor compartment in such a way that core layer of tablet faces the membrane. The complete unit was maintained at $37 \pm 0.5^\circ\text{C}$, donor compartment (3 ml) was filled with simulated saliva pH 6.8 and receptor compartment (21 ml) contained phosphate buffer pH 7.4 with synchronous stirring. At predetermined interval 2 ml sample was removed from donor compartment and analyzed at 237 nm by spectrophotometric analysis to check release of drug from the backing layer of tablet²⁰.

Differential Scanning Calorimetry

DSC thermograms of pure DTZ and its optimized formulation F1 were carried out to investigate any possible interactions between the drug and the utilized buccoadhesive materials. The sample (10 mg) was sealed in an aluminium micropan and introduced into the analytical system (DSC-50; Shimadzu, Tokyo, Japan). Thermal scanning carried out at a rate of $10^\circ\text{C min}^{-1}$ (from 0° to 300°C) and N_2 perge 30 ml/min. The instrument was calibrated with indium for temperature and energy. Thermal analysis data were obtained using a TA 501 PC system with Shimadzu software programs.

In vivo bioavailability studies

The central animal facility of the institute provided white male rabbits with mean weight of 1.79 ± 0.24 kg. The study was conducted as per CPCSEA guidelines prescribed by institutional animal ethics committee under the supervision of registered veterinarian. Animals were issued 6 days prior to experimentation for acclimatization

and were kept on standard pellet diet and water ad libitum. Food was stopped to all animals 8-10 h prior to experimentation. Food and water was not given to animals till 2 h after the start of the study.

To study the oral pharmacokinetics of DTZ, 2 ml of 15 mg/ml solution of DTZ in 40 % v/v poly ethylene glycol 400 in water was administered to rabbits (n=3) using an oral catheter. The catheter was flushed with 5ml of 40 % v/v polyethylene glycol 400 in water to ensure complete dosing. The designed tablet containing 30 mg DTZ was premoistened by dipping the tablet in distilled water for 5 seconds. The mouth of rabbit was opened using specially designed mouth restrainers and the pre-moistened tablet was pressed gently against mucosal lining of cheek using forceps for 1 min to ensure adhesion. Each rabbit was dosed with specific dose of DTZ without taking weight of the rabbit into consideration. For each study blood samples (1 ml) were withdrawn from the marginal ear vein of rabbits using a 21G needle. Samples were withdrawn before dosing and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 7.0 hour post dosing. The collected blood was harvested for 45 min at ambient temperature and centrifuged at 4000 rpm for 20 mins. The clear supernatant serum layer was collected and stored at -20°C until analysis. Frozen serum samples were thawed at ambient temperature ($25 \pm 0.5^\circ\text{C}$) for least 60 minutes. Rabbit plasma (0.1 ml) was placed in a glass tube. To this 50 μl of imipramine (2 $\mu\text{g/ml}$), as the internal standard, and 5ml of tert-butylmethylether. It was then mixed for 20 min using a rotamix and centrifuged at 5000 rpm for 10 min. 4.5 ml of the organic layer were transferred to another capped tube, 0.3 ml of 0.01N hydrochloride was added and the mixture was vortexed for 2 minutes. Fifty microlitres of the water layer were injected into the HPLC system. The serum concentration versus time data of DTZ obtained during various sets of studies was subjected to non-compartmental analysis to acquire pharmacokinetic parameters^{5, 21, 22}.

Table 1: Composition of DTZ buccoadhesive bilayered tablets

Ingredients	Formulations (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core layer									
DTZ	30	30	30	30	30	30	30	30	30
Chitosan	45	45	45	45	45	45	45	45	45
HPMC K4M	30	45	60	*	*	*	*	*	*
HPMC K15M	*	*	*	30	45	60	*	*	*
HPMC K100M	*	*	*	*	*	*	30	45	60
Aerosil	2	2	2	2	2	2	2	2	2
Lactose	48	28	13	48	28	13	48	28	13
Backing layer									
Ethyl cellulose	74.9	74.9	74.9	74.9	74.9	74.9	74.9	74.9	74.9
Tartrazine	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table 2: Physical Characterization of the Designed Formulations

Formulation Code	Weight variation test		Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	% Drug Content
	Average weight (mg)					
F1	225.05 \pm 0.35		2.00 \pm 0.01	4.2 \pm 0.60	0.080	99.225
F2	226.50 \pm 0.35		2.00 \pm 0.01	4.0 \pm 0.62	0.044	98.250
F3	225.05 \pm 0.35		2.10 \pm 0.01	4.3 \pm 0.51	0.179	96.325
F4	225.55 \pm 0.35		2.01 \pm 0.01	4.5 \pm 0.23	0.355	97.200
F5	226.05 \pm 0.35		2.00 \pm 0.01	4.1 \pm 0.41	0.178	96.000
F6	227.05 \pm 0.35		2.02 \pm 0.01	4.4 \pm 0.23	0.220	98.500
F7	226.05 \pm 0.35		2.01 \pm 0.01	4.0 \pm 0.31	0.132	95.150
F8	225.05 \pm 0.35		2.02 \pm 0.01	4.1 \pm 0.42	0.031	96.400
F9	224.05 \pm 0.35		2.00 \pm 0.01	4.3 \pm 0.21	0.045	96.675

Table 3: Kinetic data analysis

Formulation Code	Zero Order	First Order	Korsmeyer's and Peppas Model		
			Higuchi Matrix	Regression Coefficient (r ²)	Slope (n)
F1	0.876	0.963	0.982	0.925	0.685
F2	0.905	0.945	0.985	0.923	0.693
F3	0.85	0.932	0.982	0.94	0.666
F4	0.694	0.849	0.888	0.828	0.647
F5	0.686	0.854	0.914	0.848	0.645
F6	0.724	0.866	0.881	0.827	0.641
F7	0.829	0.964	0.968	0.879	0.682
F8	0.805	0.926	0.96	0.891	0.668
F9	0.815	0.923	0.968	0.904	0.664

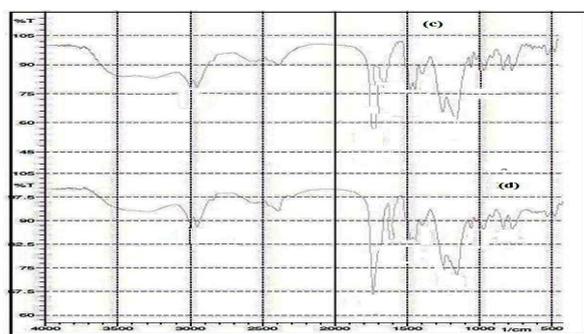
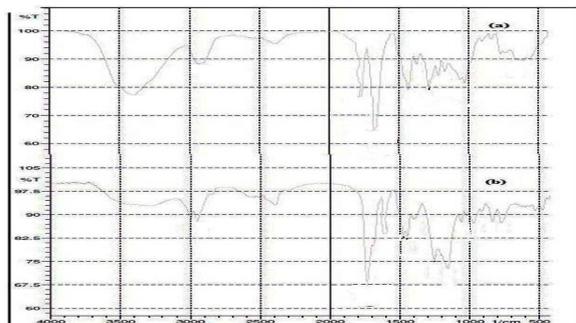


Figure 2 (A): FT-IR Spectra of (a) Pure DTZ (b) DTZ +HPMC K100M+Chitosan (c) DTZ +HPMC K15M+Chitosan (d) DTZ +HPMC K4M+Chitosan

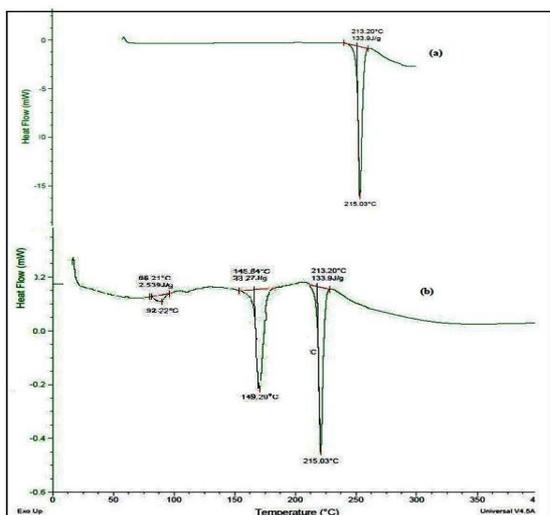


Figure 2(B): DSC thermograms (a) DTZ and (b) physical mixtures of drug and formulative ingredient (F1)

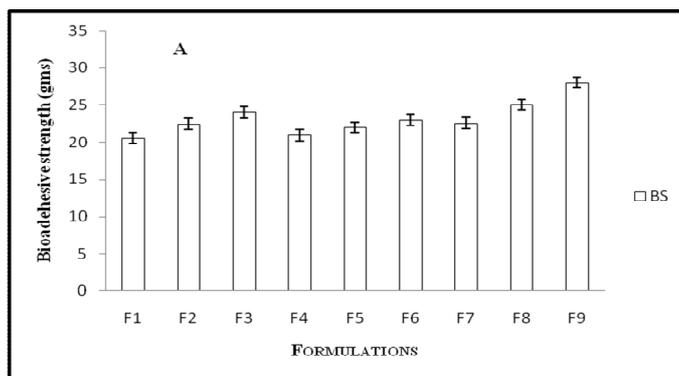


Figure 3(A): Bioadhesive strength

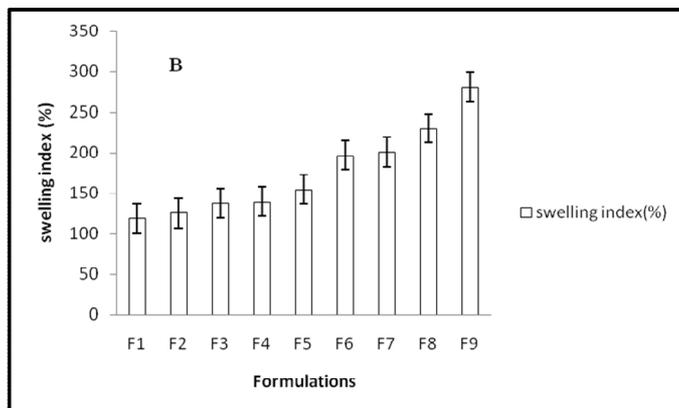
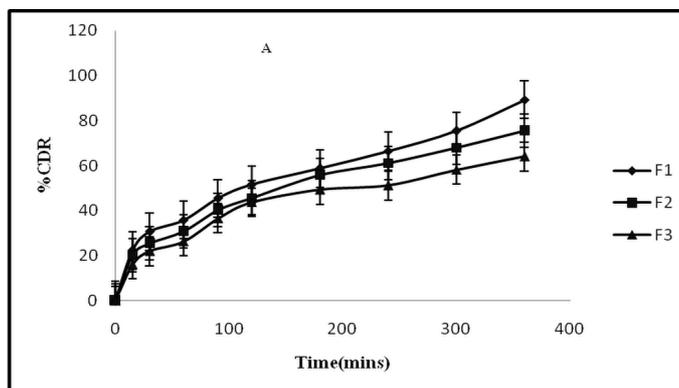


Figure 3(B): Swelling studies



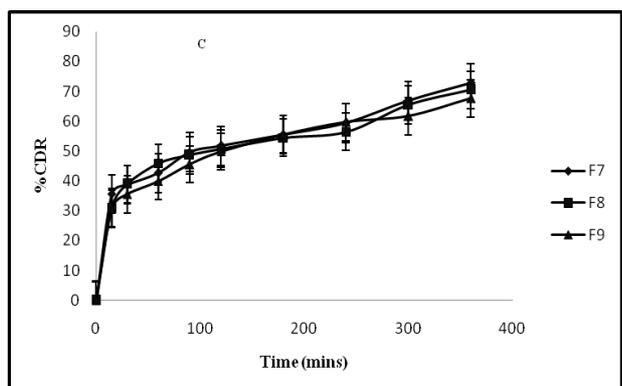
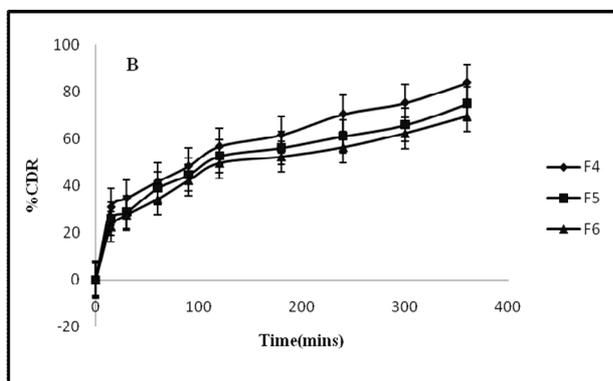


Figure 4: *In vitro* cumulative release profiles of DTZ buccoadhesive tablets containing (A) HPMC K4M (B) HPMC K15M (C) HPMC K100M

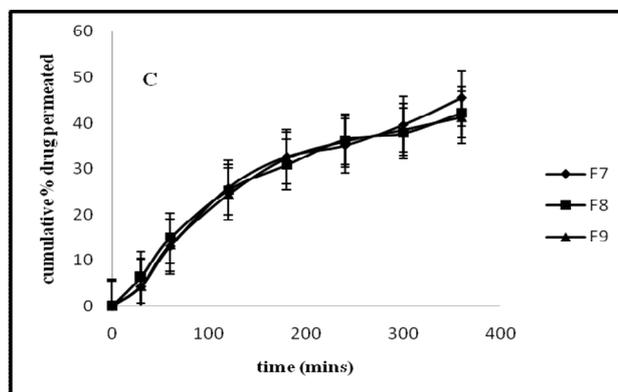
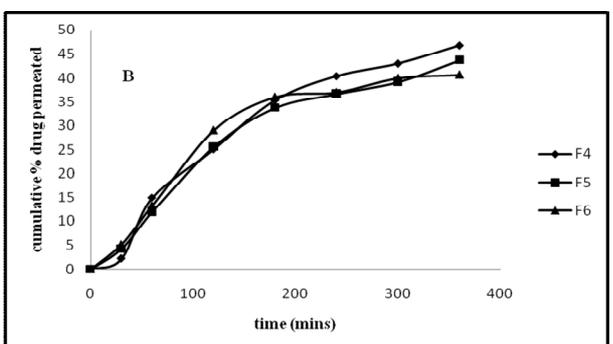
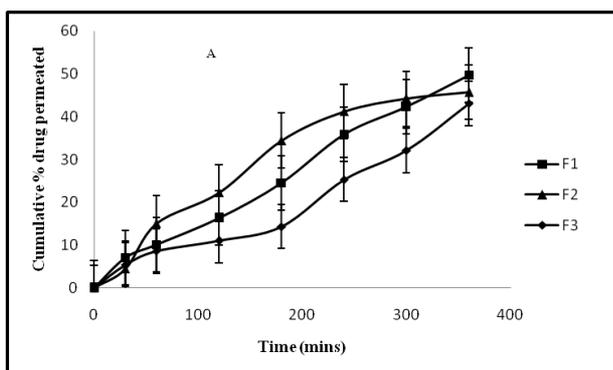


Figure 5: *In vitro* cumulative permeation of DTZ from buccoadhesive tablets containing (A) HPMC K4M (B) HPMC K15M (C) HPMC K100M

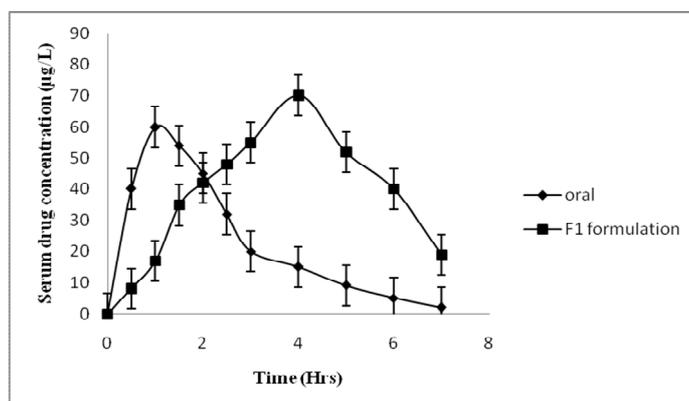


Figure 6: Time v/s Serum plasma concentration of DTZ following administration of single dose of DTZ in rabbits by oral and buccal route (Mean \pm SD of three independent determinations)

RESULTS AND DISCUSSION

DTZ is having suitable physicochemical properties for buccal delivery was selected as model drug. HPMC K4M, K15M and K100M were selected as mucoadhesive polymers. Chitosan was added as a penetration enhancer. Ethylcellulose was chosen as impermeable backing layer because of its low water permeability and moderate flexibility. Aerosil was selected as anti-adherent and lactose was included as a diluent.

Drug Excipient Compatibility Studies

In FTIR study, the IR bands that can be attributed to drug are presented in figure 2(A). In all the drug-excipient mixtures studied, these bands were retained. FTIR study further established absence of interaction between drug and excipients studied.

Differential Scanning Calorimetry

Figure 2(B) shows the DSC thermograms of pure DTZ and optimized formulation F1. A slight change in peak shape with little broadening and shifting to lower temperature was observed in thermogram of optimized formulation, which could be attributed to the mixing process that lowers the purity of each component of the mixture. These obtained results indicate that there was no positive evidence for the interaction between DTZ and formulative ingredients of F1 formulation.

Evaluation of Powder Blend

The angle of repose, compressibility index and Hausner's ratio was found to be between 23.41- 26.87, 11.4-18.1 and 1.16-1.22 for all the formulations respectively. These

results suggested that the powder blend had good flow properties.

Evaluation of prepared Tablets

Mucoadhesive bilayered tablets of DTZ were found to be satisfactory when evaluated for diameter, average thickness, weight variation, hardness, drug content (Table 2).

Surface pH studies

The surface pH of the buccal tablets is determined to investigate the possibility of side effects in vivo. The surface pH should be close to neutral as an acidic or alkaline pH may irritate the buccal mucosa. The surface pH values were found to be in the range between 6.433 ± 0.06 to 6.77 ± 0.06 for all formulations and were almost within the range of salivary pH i.e. 6.0 to 7.4. The optimized formulation F1 showed pH 6.67 ± 0.06 .

Measurement of bioadhesive strength

Figure 3(A) shows the bioadhesive strength of HPMC K4M, HPMC K15M and HPMC K100M tablets at various concentrations. The polymers show differences in their bioadhesion in the order of $K100M > K15M > K4M$.

When the concentration of polymer is low, the number of penetrating polymeric chains per unit volume of the mucus is low resulting in weaker interaction. Increase in adhesion with viscosity of polymer used can be attributed to higher strength of gel formed by HPMC K100M as compared to that of HPMC K4M and HPMC K15M resulting in stronger entanglement of polymeric chains with glycoprotein chains of mucus. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa. The bilayered tablets containing a higher proportion of HPMC K100M (F9) showed good bioadhesive strength.

Swelling studies

Swelling index is increased as the weight gain by the tablet is increased proportionally with the rate of hydration. Swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug. The comparison of swelling index of all 9 formulations is depicted in figure 3(B). The uptake of water by HPMC is a slower process compared with chitosan. HPMC is hydrophilic polymer which swells slowly to form a gel which then dissolves in the presence of water. The gelling property of this polymer will provide the binding strength to oppose bursting effect of chitosan. Hence the integrity of tablet is maintained for further period of time until HPMC dissolved. The polymers show significant differences in their swelling indices in the order of $HPMC K100M > HPMC K15M > K4M$.

In vitro drug release studies

The in vitro dissolution of all 9 formulations was studied in phosphate buffer pH 6.8. For tablets prepared using different viscosity grades of HPMC, drug release extended to 6 hours. The cumulative percentage drug released from formulations F1 to F9 is depicted in figure 4.

HPMC K4M as mucoadhesive polymer

In vitro dissolution studies revealed that formulation F1, F2, F3 showed 89.31 %, 75.44 %, 64.01% drug release in 6 hrs respectively. The plot of cumulative percentage drug released as a function of time of formulated tablets is

depicted in figure 4A. This showed that at lower concentration of polymer HPMC K4M, the release of the drug from the formulation became faster.

HPMC K15M as mucoadhesive polymer

In vitro dissolution studies revealed that formulation F4, F5, F6 showed 83.68 %, 74.84 %, 69.72 % drug release in 6 hrs respectively. The plot of cumulative percentage drug released as a function of time of formulated tablets is depicted in figure 4B. This showed that at lower concentration of polymer HPMC K15M, the release of the drug from the formulation become faster.

HPMC K100M as mucoadhesive polymer

In vitro dissolution studies revealed that formulation F7, F8, F9 showed 72.78 %, 70.45 %, 67.57% drug release in 6 hrs respectively. The plot of cumulative percentage drug released as a function of time of formulated tablets is depicted in figure 4C. This showed that at lower concentration of polymer HPMC K100M, the release of the drug from the formulation become faster. The rate of drug release was found to be inversely related to the viscosity grade of HPMC. When the viscosity of HPMC used was increased from 4000 to 100000 cPs keeping the total polymer proportion constant, the release rate was faster with lower viscosity grades of HPMC probably due to lesser polymer entanglement, lesser gel strength and larger effective molecular diffusional area when compared to higher viscosity grades.

Data Analysis

The results of in vitro dissolution studies obtained from these formulations were plotted in Zero order, First order, Higuchi and Korsmeyer Peppas's models to study the mechanism of drug release. The correlation coefficient (r) for drug release kinetic models are tabulated in Table 3. Correlation coefficient (r) value was highest for the first order release equation in all the nine batches thus indicating first order release kinetics. The obtained values of n lie between 0.641 and 0.693 for the release of Diltiazem HCl maleate from all the prepared tablet formulations, indicating non-Fickian release kinetics.

In vitro permeation studies

The prepared buccal tablet formulations were subjected for in vitro drug permeation through sheep buccal mucosa. The plot of time v/s % CDR is depicted in figure 5. Based on the in vitro drug release, bioadhesion strengths and in-vitro permeation studies using sheep buccal mucosa of all formulations the F1 formulation was selected as optimized formulation.

Drug release from backing layer

To evaluate the performance of backing membrane in avoidance of release of Diltiazem, a study was conducted using Franz diffusion cell. Results of study showed that no drug was released in 6 hrs in the donor compartment of diffusion cell. This indicated that ethyl cellulose membrane was impermeable to and the swelling of mucoadhesive layer did not change integrity of backing layer.

In vivo bioavailability studies

Buccal mucoadhesive controlled release tablets prepared using F1 were selected for in vivo bioavailability studies because of superior swelling index, bioadhesive strength, better permeability and desirable drug release. Pharmacokinetic study was conducted on male albino

rabbits (according to approved CPCSEA guidelines). DTZ was not present in the plasma samples taken prior to dosing. These samples served as negative control for the experiment. DTZ was detectable within 0.5 h of drug administration by both the routes. Drug was detectable after 6 hrs when given orally. Following oral administration of DTZ (10 mg) in solution form, average maximum serum concentration (C_{max}) of 60.58 µg/l was achieved after 1 hour. The area under the serum concentration-time curve (AUC_(0-∞)) after oral dosing was found to be 1636 µg h/L. After administration of designed formulation drug levels in serum were detectable till 6h with C_{max} 70.60 µg/L of achieved 4hrs after dosing. The AUC_(0-∞) following buccal administration of DTZ was found to be 2914 µg h/L. The relative bioavailability of buccal bilayered tablet was found to be 178.12% as given in figure 6.

CONCLUSION

It can be concluded that the designed buccoadhesive controlled release tablets can overcome the disadvantage of poor and erratic oral bioavailability of DTZ. This increased and predictable availability of DTZ from designed formulations may result in substantial dose reduction.

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