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Formulation and Evaluation of Controlled-Release Diltiazem Hydrochloride Buccoadhesive Tablets

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Abstract

Diltiazem HCl (DTZ) is a calcium channel blocker used in the treatment of hypertension and angina (variant & classical angina). Diltiazem HCl was selected as a model drug for investigation because of its suitable properties like half-life of 4.5 hrs, optimum partition coefficient (158) and molecular weight (450.98), was formulated onto buccoadhesive tablets to overcome the limitations in the currently available dosage and routes of administration which in sequence will increase patient's compliance. Mucoadhesive buccal tablets of Diltiazem hydrochloride were prepared using carbopol-934, Sodium carboxy methyl cellulose (SCMC), Hydroxy propyl methyl cellulose (HPMC) and sodium alginate as mucoadhesive polymers. Ten formulations were developed with varying concentrations of polymers. Each formulated batch was subjected to various evaluation parameters. The physical appearance of buccal patch was examined by scanning electron microscopy. The release behavior was non-Fickian controlled by a combination of diffusion and chain relaxation mechanisms and best fitted zero-order kinetics. All tablets were acceptable with regard to thickness, weight variation, hardness, and drug content. The maximum bioadhesive strength was observed in tablets formulated with a NaCMC followed by CP and CP-NaCMC. Formulation F10 showed maximum release of 79% in 8hours. Formulation F8 showed maximum swelling index of 3.7 after 8hours. Formulation F10 follows zero order drug release. FTIR studies show no evidence on interaction between drug and polymers. The results indicate that suitable mucoadhesive buccal tablets with desired properties could be prepared.

Key Words: Mucoadhesive, Buccal patch, Diltiazem hydrochloride, mechanical properties, *in vitro* studies, ex *vivo* studies.

Introduction

Conventional routes of drug administration such as oral, intramuscular and intravenous have, in many cases, been supplanted by the advent of new, novel drug delivery systems. The systemic delivery of drugs through novel methods of administration is one area in which significant changes and improvements have been made. Consequently, precise control of drug input into the body by a variety of routes is now possible. Controlled and sustained release formulations have been developed and are gaining in popularity and medical acceptance[1]. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectables and enterable methods[2]. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug.

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route[3-5]. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore mucoadhesive dosage forms were suggested for oral drug delivery which includes adhesive tablets[6-8], adhesive gels[9-10] and adhesive patches[11-12].

Diltiazem HCl (DTZ) is a calcium channel blocker[13-14] used in the treatment of hypertension and angina (variant & classical angina)[15]. Diltiazem was selected as a model drug for investigation because of its suitable properties like half-life of 4.5 hrs, optimum partition coefficient (158) and molecular weight (450.98) make it suitable for administration by buccal route[16]. A suitable buccal drug delivery system should posse's good bioadhesive properties. So, that it can retain in oral cavity for desired duration and localize the dosage form in a specific region and control the release rate of drug[17].

In present study, the mucoadhesive tablets were developed using hydrophilic polymers (carbopol-934, HPMC, SCMC and Sodium alginate) to get controlled and zero order drug release.

The aim of this study was, design, development and characterization of a buccoadhesive controlled-release tablet of DTZ using some selective polymers like carbomer 934P (CP), hydroxypropylmethyl cellulose K4M (HPMC), sodium alginate and sodium carboxymethyl cellulose (NaCMC). Also the interaction between polymers and drug-polymers, bioadhesion and *in vitro* release characteristics of DTZ from different buccoadhesive matrix tablets was evaluated to assess the suitability of such formulations.

Material and Methods

Materials

The following materials were used:

Verapamil hydrochloride (Torrent Pharmaceuticals Ltd, Ahmedbad), Carbopol 934P (S.D.Fine chemicals Ltd, Mumbai.), Methocel K4M (Loba Chemie Pvt. Ltd, Mumbai), Sodium carboxymethyl cellulose (Loba Chemie Pvt. Ltd, Mumbai), Sodium alginate (Loba

Chemie Pvt. Ltd, Mumbai). All other chemicals, reagents and solvents were used are of A.R. grade.

Methods

Diltiazem hydrochloride calibration curve

Calibration curve of Diltiazem HCl was prepared using buffer pH 7.4 in the concentration range of 1–15µg/ml. The drug was analyzed spectrophotometrically (UV 1601 Shimadzu, Japan) at 237 nm (regression coefficient r2 = 0.9994 in buffer pH 6.8).

Drug-excipient interaction studies

Preformulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy studies and HPTLC were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, diluents and lubricants used in case tablet formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. It is observed that 1:1 ratio of drug excipients maximizes the possibility of interaction and helps in easier detection of incompatibilities[18]. Therefore, in the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies.

Differential scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The instrument is very versatile as far interaction and compatibility studies at pre-formulation stage was concerned and used to evaluate melting point, enthalpy changes and glass transition temperatures of drug with excipients and polymers. Diltiazem Hydrochloride was mixed with the excipients and the DSC analysis of each sample under the analogous conditions of temperature range 40 –300º C, heating rate 10ºC/min, nitrogen atmosphere (20ml/min) and alumina as reference. Differential Scanning Calorimetry (DSC) was performed on pure drug, excipients and composition of final formulation. DSC measurements were done on a Shimadzu DSC-60 and samples were heated at the rate of 10ºC min-1.The samples were heated in an aluminum cup up to 300ºC.

Fourier transform infrared (FTIR)

FTIR studies are very helpful in the evaluation of drug–polymer interaction studies. If there is any incompatibility between the drugs and excipients, these can be predicted by changes in the functional peaks (characteristic wave numbers). Diffuse reflectance technique was used(400 to 4000 cm-1), drug and various polymers were thoroughly mixed with 300mg of potassium bromide, compressed and the spectrum was obtained by placing the thin pellet in light path.

HPTLC technique[19]

TLC technique is a non thermal technique very helpful in the evaluation of drug polymer interaction studies. If there is any interaction between the drug and excipients, there can be determined by change in the Rf value. High performance thin layer chromatography (HPTLC) chromatogram data's were taken on a CAMAG instrument to find out the incompatibility of the drug with excipients used in the formulation. HPTLC chromatogram of the drug and composition of final formulation were obtained by using the composition of acetic acid: water: methylene chloride: ethanol (1: 3: 10:12,v/v) as mobile phase on precoated silica gel F254 plates used as stationary phase.

Formulation of buccoadhesive tablets

Controlled-release buccoadhesive tablets were prepared by direct compression method using the formula shown in Table 1. Different ratios of carbopol-934, HPMC, NaCMC and sodium alginate fixed amount of DTZ and 1% magnesium stearate were passed through a No. 85 sieve and mixed in mortar with a pestle to obtain uniform mixing. The blended powders were compressed into tablets using 8mm flat faced punches, (Rimek Minipress, Karunavati Eng. Ltd, Ahmedabad). The mass of tablets were determined using Digital balance (Shimdazu, Japan) and thickness of tablets with a digital Screw Gauge (Mitatyo, Japan).

Table 1: Formulation of buccoadhesive Diltiazem hydrochloride tablets

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Diltiazem HCl	30	30	30	30	30	30	30	30	30	30
CP*	100	--	--	--	80	50	--	80	--	30
Na CMC*	---	100	--	--	20	---	80	--	50	40
HPMC*	--	--	100	--	---	50	--	--	50	30
Sodium alginate	--	--	--	100	--	--	20	20	--	--
Mannitol	18	18	18	18	18	18	18	18	18	18
Magnesium stearate	2	2	2	2	2	2	2	2	2	2

*HPMC:hydroxypropylmethyl cellulose; CP:carbopol 934P; NaCMC:sodium carboxymethyl cellulose

Evaluation of physical properties of mucoadhesive tablets

Assay of Diltiazem Hydrochloride

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and allowed to dissolve in 100ml of water on a rotary shaker overnight. The suspension was centrifuged and supernatant liquid was collected and the absorbance was measured using (UV 1601 Shimadzu, Japan) at 237 nm.

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually.
Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Swelling studies[20]

The tablets of each formulation were weighed individually (W1) and placed separately in Petri-dishes containing 2% Agar gel. At regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 hours) the tablets were removed from Petri dishes and excess water removed carefully using filter paper. The swollen tablets were re-weighed (W2); the swelling index of each formulation calculated by using this formula.

Swelling Index (S.I.) = W1-W2 / W1

***In-Vitro* Release Studies [21]**

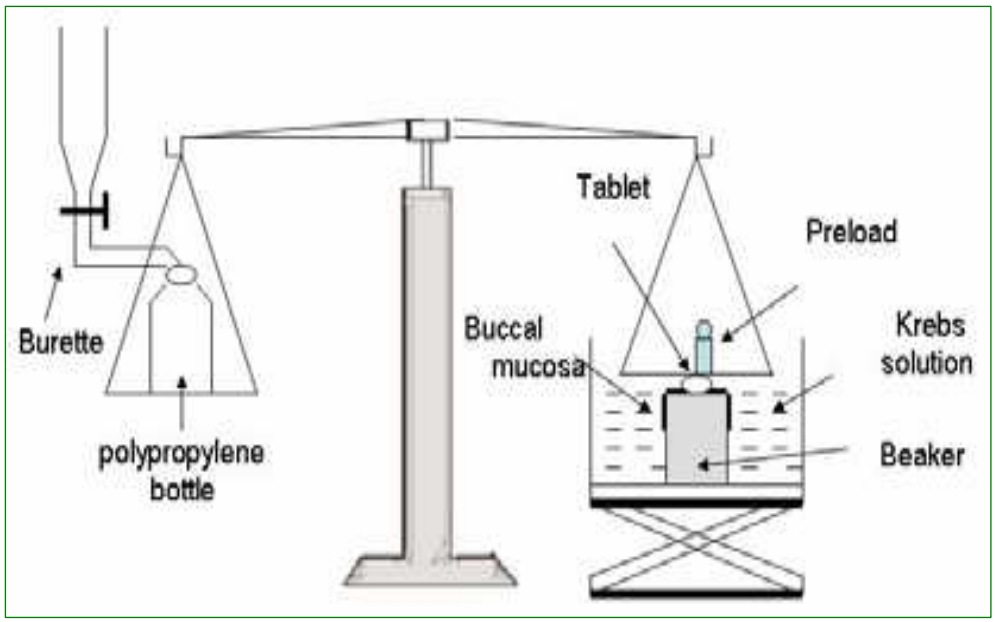
The drug release rate from buccal tablets was studied using the USP (II) dissolution test apparatus (Lab India dissolution test apparatus Disso 2000). The assembly is kept in a jacketed vessel of water maintained at 37±10C. Buccal tablet was made to stick on bottom of the flask (so as to allow one sided release from the tablet). The beaker is filled with 250ml of mixed phosphate buffer pH 6.8. The vessel maintained at 50rpm under stirring conditions by means of paddle fabricated for purpose in dissolution apparatus. At various intervals of time, samples were withdrawn and filtered through whatmann filter paper no.42. It is replaced immediately with equal amount of fresh buffer. The samples are then analyzed U.V. spectrophotometrically at 237 nm up to 8hours.

Bioadhesion experiments

Modified two-arm balance method[22]

Two-arm balance method reported by Parodi with minor modifications was also used to check and to validate the results of the aforementioned modified tensiometry method and the correlation between the results obtained from these two techniques was established. Briefly, buccal mucosa section (2-mm thick, 2×2 cm) was fixed on the bottom of smaller beaker attached to the bigger beaker. Krebs solution was added to the beaker up to the upper surface of the buccal mucosa. A tablet was attached to the upper clamp and the platform was slowly raised until the tablet surface came in contact with mucosa. After a preload time of 5 minutes, water was added to the polypropylene bottle until the tablet was detached from the buccal mucosa. The water collected in the bottle was measured and expressed as weigh (g) required for the detachment[23-24]. The schematic arrangement of the apparatus shown in figure 1.

Figure 1: Modified apparatus for *in vitro* bioadhesion test



Drug release kinetic study

To describe the kinetics of the drug release from the matrix base buccal patch of optimized batch F10, mathematical models such as zero-order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas models are were use. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Scanning electron microscopy

Optimized Tablet formulation (F10) morphology was characterized by scanning electron microscopy. Samples were mounted on round brass stubs (12mm diameter) using double-backed adhesive tape and then sputter coated for 8 min at 1.1 LV under argon atmosphere with gold palladium before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). The images were captured on an Ilford PANF 50 black and white 35mm film.

Results and Discussion

Bioadhesive delivery systems have received considerable attention to provide an attractive alternate to the oral route of drug administration, particularly in overcoming deficiencies associated with the oral administration. It has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. The direct entry of the drug into the systemic circulation avoids the first-pass hepatic metabolism leading to increase in bioavailability.

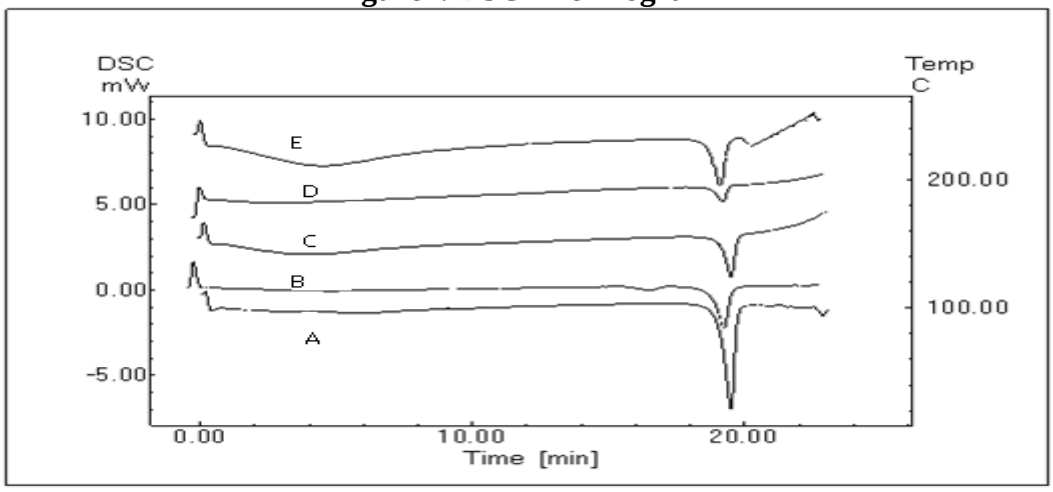
Drug excipient Compatibility study

Drug excipient compatibility studies were carried out to check whether any compatibility related problems are associated between drug and excipients used in the formulations.

Differential Scanning Calorimetry (DSC)

DSC results revealed that the physical mixture of Diltiazem with excipients showed superimposition of the thermograms. There is no considerable change observed in melting endotherm. DSC study reveals that there was no interaction took place between the drug and the polymer. The DSC thermograms are shown in Figure 2.

Figure2: DSC Thermogram

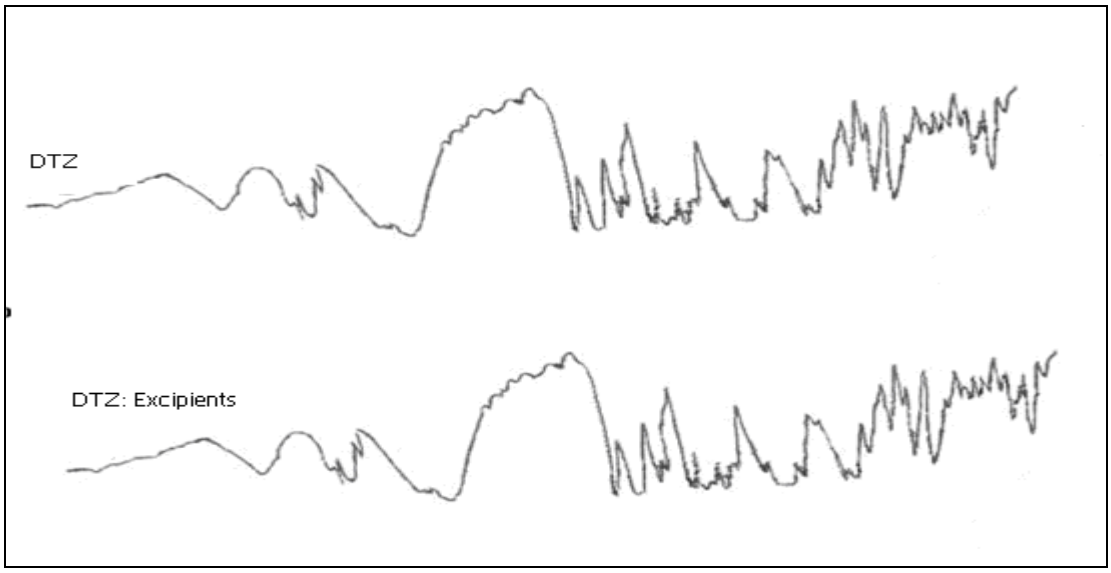


A. DSC thermogram of Pure DTZ; DSC thermogram of DTZ : Carbopol (1:1); DSC thermogram of DTZ: Methocel (1:1)
B. DSC thermogram of DTZ: sodium alginate (1:1); DSC thermogram of DTZ: sodium CMC (1:1)

Fourier transform infrared (FTIR) study

Diltiazem Hydrochloride contains two carbonyl groups, shows the values around 1679 and 1745 cm-1. Infrared studies reveal that both characteristic bands around 1679 and 1745 cm-1 were present in all spectra. While no new bands or shift in characteristic peaks appeared. IR spectra are shown in Figure 3.

Figure 3: FTIR spectra of drug and physical mixtures of drug and excipients



HPTLC study

HPTLC technique, Rf value for the drug was around 0.75. HPTLC studies revealed that the Rf values obtained for the drug and excipient mixture were around 0.75. HPTLC chromatograms are shown in Figure 4 and 5.

Figure 4: HPTLC chromatogram of Diltiazem hydrochloride

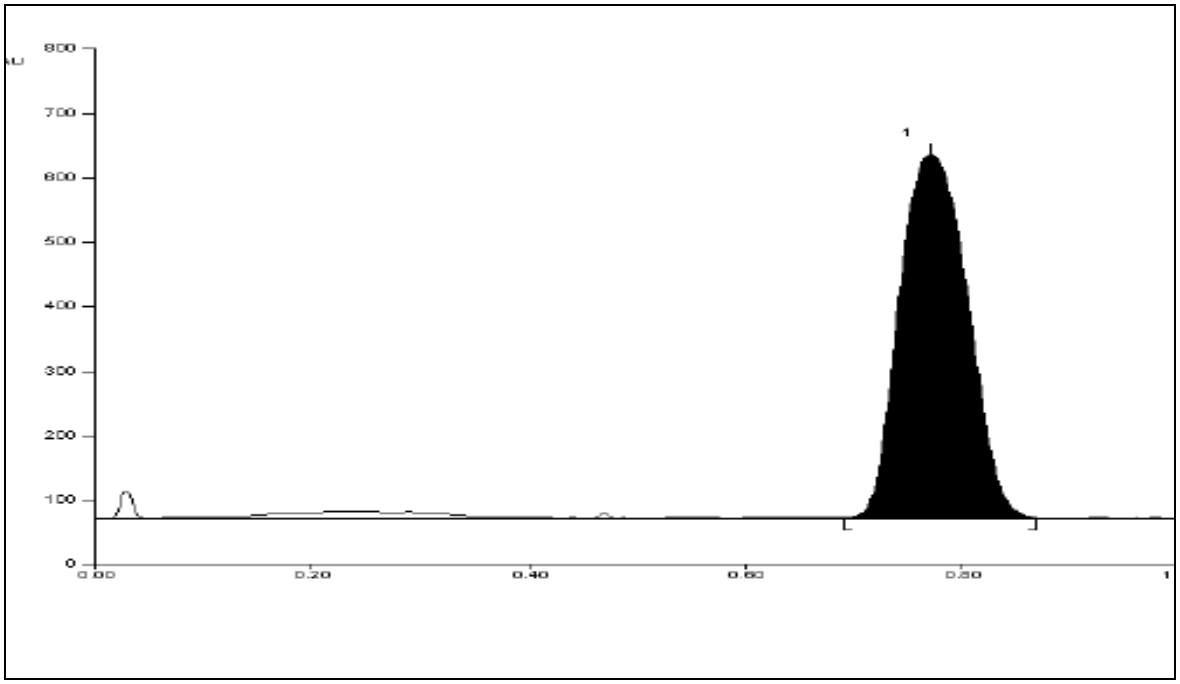
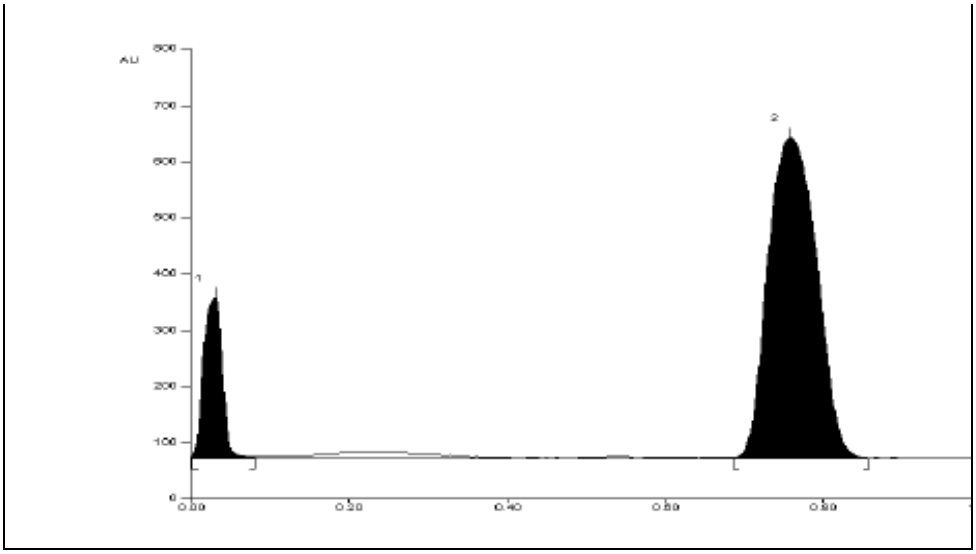


Figure 5: HPTLC chromatogram of DTZ and physical mixtures of drug and excipients



From the DSC, FTIR and HPTLC results revealed that there is no interaction between the drug and the excipients used in the formulation.

Physical characteristics of buccoadhesive tablets of DTZ

Bioadhesive polymers such as CP, HPMC, sodium alginate and NaCMC are suitable for use in buccoadhesive preparations because by uptake of water, can stick to the oral mucosa, and control the drug release while they resist salivation, tongue movement and swallowing for a significant period of time. The results of physical characteristics of prepared buccoadhesive tablets of DTZ are shown in Table2. All the tablets prepared were of good in appearance.

The buccoadhesive tablets showed uniform thickness throughout, in the range of 2.10-2.16 mm. No significant difference in the weight and content of individual formulations from the average value was observed and variations were within the limits. The drug contents in the buccoadhesive tablets were also within the limit of 98.78 -101.54%.

Table 2: Physical characteristics of buccoadhesive tablets of DTZ

Formulation Code	Thickness (mm)	Hardness	Content uniformity (mg)	Weight uniformity (mg)	% drug content (%)	Appearance
F1	2.11±0.08	6.5 ±0.15	31.2±0.56	151.1±10.8	99.23	+++
F2	2.10±0.11	4.0±0.13	30.1±0.75	149.2±11.3	100.12	++
F3	2.13±0.15	4.5±0.20	29.5±0.62	154.2±12.4	101.54	+
F4	2.15±013	4.3±0.15	28.3±0.85	152.1±17.5	98.78	+++
F5	2.10±0.15	5.8±0.16	29.5±0.81	149.3±16.2	99.65	+
F6	2.12±0.14	5.4±0.21	30.3±0.45	151.6±14.6	99.87	++
F7	2.10±0.16	4.5±0.15	29.1±0.32	150.3±12.0	101.23	++
F8	2.13±0.11	5.8±0.14	30.1±0.85	154.3±14.2	100.12	+++
F9	2.14±0.12	5.9±0.21	31.2±0.74	153.5±16.8	101.21	+
F10	2.16±0.13	6.1±0.18	30.5±0.69	149.3±17.5	99.45	+++

Hardness of buccoadhesive tablets varied with various ratios and type of polymers and was less for formulations containing NaCMC alone. NaCMC is a hygroscopic material which under high humidity conditions can absorb a large quantity (>50%) of water. In tablets, this phenomenon is associated with a decrease in tablet hardness and an increase in disintegration time (47). The hardness of tablets containing only NaCMC was lower and increased by increase in the amount of CP or HPMC in the formulation. Tablets containing CP exhibited greater hardness which decreased by increase in the amount of HPMC. The differences in the tablet hardness did not affect the release of the drug from hydrophilic matrices which is released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet [25].

Bioadhesion properties

Figure 6: *In vitro* bioadhesion study of prepared buccoadhesive tablets, using Modified balance method

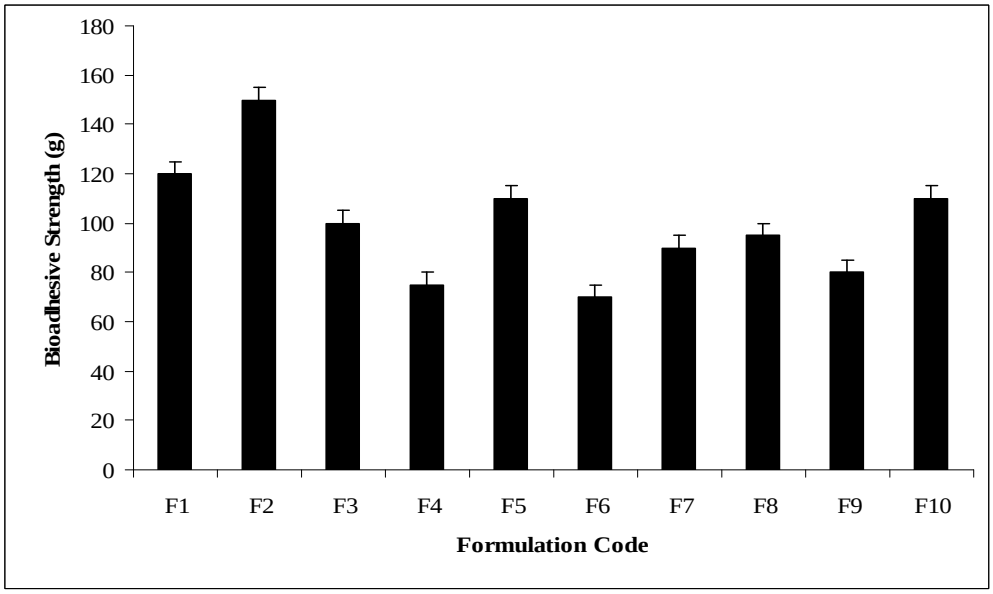
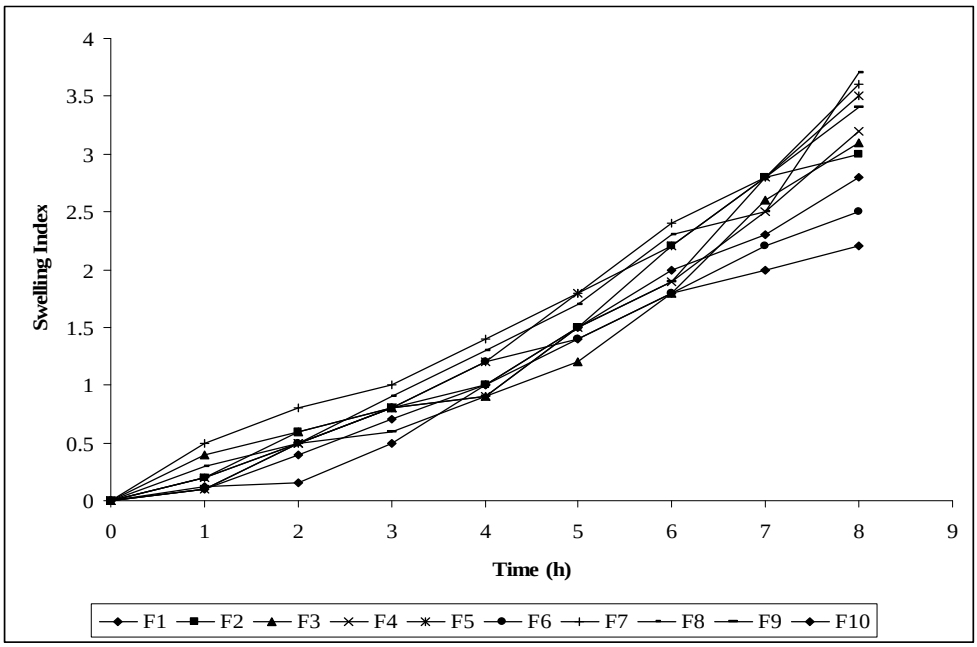


Figure 6 shows the adhesion force of CP-HPMC, CP-NaCMC and NaCMC-HPMC tablets to the bovine mucosa at various mixing ratios of the polymers. The bioadhesion characteristics were affected by the type and ratio of the bioadhesive polymers. The highest detachment force was observed with the formulation F2 followed by F1, F5 and F10 .However, the bioadhesion differences between F5 and F10 did not reach a significant level . The detachment forces of CP-NaCMC were greater than those of CP-HPMC and NaCMC-HPMC, CP-sodium alginate and NaCMC-Sodium alginate at similar mixing ratios. Decreases in the amount of CP in tablets containing CP-HPMC or NaCMC and in systems containing CP-NaCMC or NaCMC-HPMC resulted in decrease in the detachment forces[26-27]. The adhesion force in the formulation F6 at a weight ratio of 1:1 of CP-HPMC was improportionally less than those with other mixing ratios in this group. This could be attributed to a possible interpolymer complex formation between CP and HPMC which in turn inhibited, at least in part, the adhesion force of the tablet. This type of interaction results from hydrogen binding between the OH groups of HPMC and the carbonyl groups of CP in the acidic medium. The detachment forces of tablets of CP-NaCMC and Na CMC-HPMC decreased by decrease in the amount of NaCMC.

In-Vitro Swelling Studies

The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The agar plate model used in this study simulates the secreting fluid around the buccal mucosa which is required for adhesion, swelling and release of the drug from tablets. The swelling index of mucoadhesive tablets for a period of 8hours was studied. The values obtained as shown in the figure 7. It is evident that an increase in the amount of carbopol-934 causes decrease in swelling index, in case of SCMC and sodium alginate. Among all the formulations, F8 showed highest value of 3.7 and F10 with lowest value of 2.2 swelling index at end of 8hours.The polymers showed significant differences in their swelling indices in the order of NaCMC > CP > HPMC>sodium alginate.

Figure7: Swelling index of buccoadhesive tablets containing different ratios of polymers

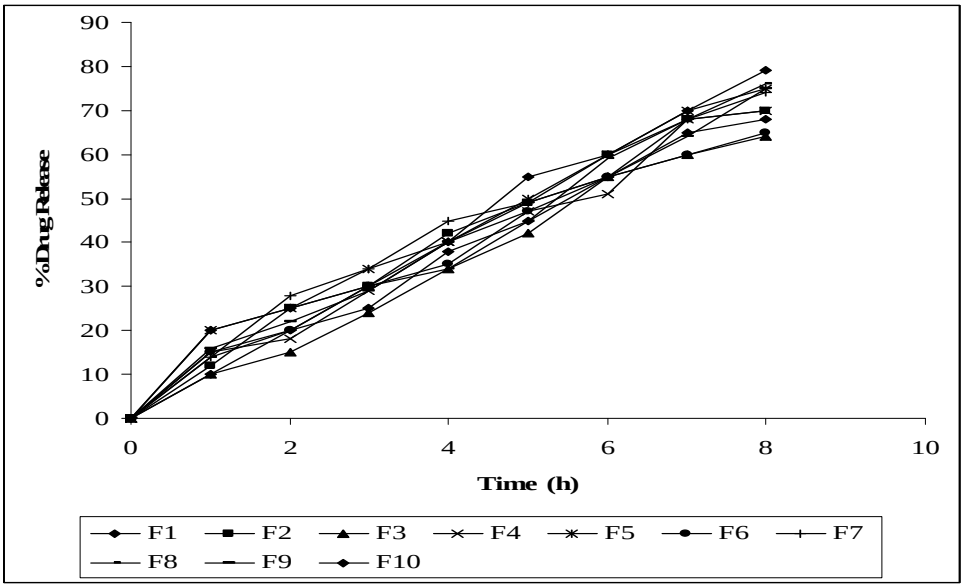


In-Vitro Drug Release Studies

The Release of DTZ from buccal tablets varied according to type and ratio of matrix forming polymers. The drug release was governed by amount of matrix forming polymers. The most important factor affecting the rate of release from buccal tablets is the drug and polymer ratio. As increase in the polymer concentration increases the viscosity of the gel as well as the formation of gel layer with longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of drug and therefore reduction in drug release rate. CP is more hydrophilic than HPMC and if it is added in high ratios causes high release rates. The swelling values and the release rate of DTZ, as indicated by greater mean dissolution time (MDT), from the matrices with CP-NaCMC or NaCMC-HPMC, increased by an increase in NaCMC content. Swelling and eroding of NaCMC explains the relatively high release rates of DTZ from formulations containing this compound. Although matrices containing CP-NaCMC exhibited maximum swelling values, they showed lower release rates which could be attributed to higher hydrophilicity and water uptake of CP and NaCMC compared to HPMC, which produces a water-swollen gel-like state that may substantially reduce the penetration of dissolution medium into the tablets and as a result the drug release rate. Among the ten formulations, F10 (SCMC, HPMC as a secondary polymer) showed highest

drug release (79% at the end of 8 hrs) and it is also highest among ten formulations. This is probably due to high gelling property of HPMC and CP. Tablets from F5 (SCMC, as a secondary polymer), F8 (sodium alginate as a secondary polymer) and F9 (HPMC, as a secondary polymer) and showed a maximum release of 75, 76 & 73 % respectively in 8hours. The results are shown in figure 8.

Figure8: *In vitro* cumulative release profiles of DTZ from sustained release buccal adhesive tablets containing different ratios of polymers



Selection of optimized formulation

Based on *in vitro* release and Bioadhesion study studies formulation F10 was selected as the best formulation. Formulation F10 showed maximum drug release (79% at the end of 8 hrs). Formulations F10 were showed the least detachment force during bioadhesion study, therefore formulation F10was selected as best formulation and subjected for further investigation.

Release kinetic analysis of optimized formulation (F10)

The release exponent (Table 3) in optimized formulation (F10) is significantly greater than 0.5, which indicates anomalous (non-Fickian) drug release. When liquid diffusion rate and polymer relaxation rate are of the same order of magnitude, anomalous or non-Fickian diffusion is considered (46). Value of n was greater than 1 for tablets containing CP-NaCMC-HPMC (F10) than the other group of polymers. This observation could be attributed to the high swelling nature of these polymers which is in accordance with the higher swelling indices observed for these formulations. To study the release kinetics of DTZ from the tablets, different kinetic equations were applied to interpret the release rate from the matrices. In the present study, the linear nature of the curves obtained for zero-order, first order, Higuchi model and Hixon-Crowel model as demonstrated by very close and higher r squared values. When the higher correlation coefficient values are considered, the release data seem to fit better with the zero order kinetics. Therefore, the release rate is independent of its concentration or amount of drug incorporated in the formulation. There is almost a good coincidence with the results obtained from the equation of Korsmeyer-Peppas in which n value is nearly 1 and the best fitted equation forDrug release, according to the zero-order and/or first-order release kinetics. According to Higuchi model, the drug release from

insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion. Smaller correlation coefficient observed for Hixon-Crowell cube roots model indicates that the possibility of a change in surface area or the diameter of the tablets with time are less likely in the release mechanism. The results are shown in table 3.

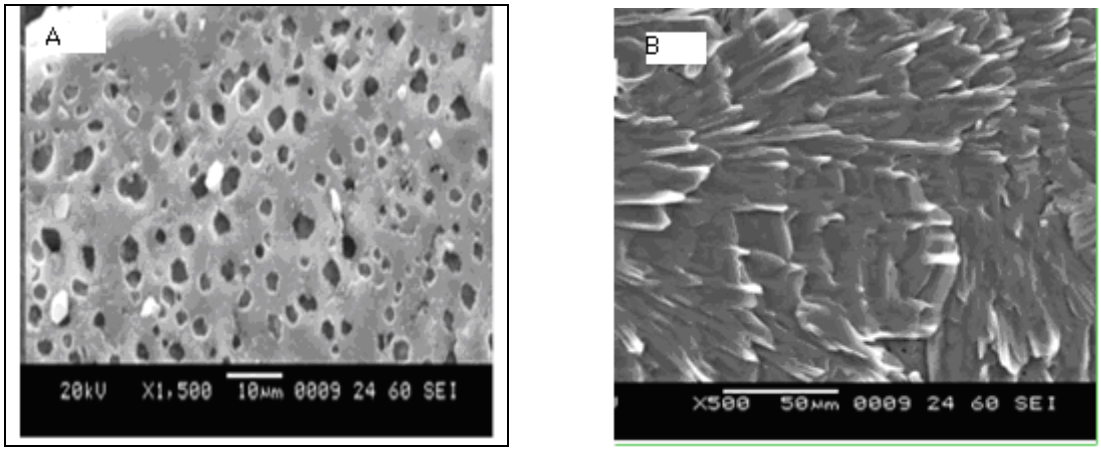
Table 3: Results of the release kinetics of optimized buccoadhesive tablets of DTZ Tablets

Formulation	n	r^2	MDT (hr)	K0 (mg/h)	r2 Zero-order	r2 First-order	r2 Higuchi	r2 Hixon-Crowel
F10	1.15	0.9968	11.4	3.20	0.9956	0.9948	0.9569	0.9943

Scanning Electron Microscopy of optimized batch (F10)

The Scanning Electron Microscopy (SEM) study of optimized batch was found at different set. The SEM photograph of optimized batch F10 were shown in figure 9. The SEM photograph (figure 9 a) indicates the uniform dispersion of polymeric solution with drug molecule and the SCMC, CP and HPMC based tablet shown porous surface, which may be suitable for the matrix system (figure 9b) .

Fig. 9: Scanning Electron Microscopy of optimized DTZ buccoadhesive tablet (F10)



(A) SEM shows uniform dispersion of drug with polymers.
(B) SEM shows porous surface on tablets

Conclusion

A new buccoadhesive system for the controlled release of DTZ was developed by using CP, NaCMC and HPMC in appropriate ratios. The release rate of DTZ from tablets was significantly affected by the type and changes in the polymer mixing ratios. F2 containing sodium CMC shows satisfactory mucoadhesive properties. Formulation F8 containing CP: sodium alginate showed significant swelling properties. Formulation F10 containing CP: HPMC: NaCMC showed optimum release profile and could be useful for buccal administration of DTZ. Based on *in vitro* release and Bioadhesion study studies formulation F10 was selected as the best formulation. Further work is recommended to support its

efficacy claims by long term Pharmacokinetic and Pharmacodynamic studies in human beings.

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