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DESIGN, DEVELOPMENT AND IN VITRO CHARACTERIZATION OF DILTIAZEM BUCCOADHESIVE TABLET

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ABSTRACT

Buccal route offer attractive route of administration for systemic drug delivery. 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 and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route.The aim of the present investigation was to develop the buccal mucoadhesive tablet of Diltiazem Hydrochloride (DIL), to enhance the oral bioavailability, to achieve good absorption of drug in treatment of hypertension and to release the drug for prolonged period of time(8hrs) so as to reduce frequency of administration of available conventional dosage form of DIL. The different batches of buccal tablet were prepared containing different grades of carbopol such as carbopol 971P and carbopol 974P.Total 6 batches were prepared. FTIR shows no evidences of interaction between drug and polymer used. Tablets were evaluated for their weight uniformity, thickness,surface pH, , drug content uniformity, mucoadhesive strength, in vitro residence time, in vitro release. Based on the evaluation of these results, it was concluded that the buccal tablet made of carbopol 971P alone in the drug :polymer ratio of 1: 0.25 showed moderate drug release for 8 hrs. The surface pH was found to be in the range of saliva pH and increase in optimum concentration of CP-971 was found to be increase in mucoadhesive strength, in vitro residence time. Data of in vitro release from tablets were fit to different equations and kinetic models to explain release mechanism.

Key Words: *Buccal tablet, mucoadhesive strength, in vitro release, Diltiazem hydrochloride*

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INTRODUCTION

Amongst the various routes of administration tried so far the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for a number of applications including the treatment of periodontal disease[1], bacterial and fungal infection[2], aphthous and dental stomatitis[3]. Over the last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining a formulation in intimate contact with the absorption site (e.g. buccal cavity)[4]. Good defined bioadhesion as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion[5]. Recently Jasti *et.al*[6], Johnston *et.al*[7], Semalty *et.al*[8] has reviewed the use of mucoadhesive polymers in buccal drug delivery and highlighted the use of novel mucoadhesive polymers. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, In addition, tablet can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva[9]. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading high bioavailability[10]. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action[11]. Therapeutically Diltiazem ia a calcium channel blocker used in the treatment of hypertension and stable angina pectoris. Diltiazem was selected as a model drug for the investigation because its oral dose is low (30 mg initialy upto 120mg).It has been reported to be rapidly absorbed from the gastrointestinaltract and to be extensively metabolized in the liver, mainly by deacetylation..The bioavailability of oral diltiazem is about 40% in humans and the absolute bioavailability of diltiazem in rabbit was reported to be 30%.(11). Because of its low bioavailability and short half life, attempts have been made to develop sustained release preparations with extended clinical effects and a reduced dosing frequency. Thus an attempt has been made to develop a buccal mucoadhesive dosage form of DIL improving and enhancing bioavailability in controlled release fashion. The present work deals with the formulation and characterization of buccal mucoadhesive tablet of DIL using mucoadhesive polymer like Carbopol-971 P and carbopol 974 P.

MATERIALS:

Materials

Diltiazem Hydrochloride was obtained as gift sample from Alkem lab ltd; Mumbai,
India.CP-971Pand 974P were obtained as gift sample from colorcon asia pacific Goa, India. Other chemicals were purchased from Samar chemical, Nagpur, India.

Drug and polymer compatibility studies:

This can be confirmed by carrying out with Infrared light absorption scanning spectroscopy (IR) studies. Infrared spectra of pure drug, polymer and physical mixture of formulations were recorded by dispersing them in a suitable solvent (KBr) using Fourier Transform Infrared spectrophotometer. A base line correction was made using dried potassium bromide and the spectra of the pure drug, polymer and the formulation mixture were recorded on FTIR at Visvesvaraya National Institute of Technology,
Nagpur.

Preparation of mucoadhesive buccal Tablet

Diltiazem hydrochloride was mixed manually in glass mortor with different ratios of carbopol 971P and carbopol 974P,(1:0.25, 1:0.5, 1:0.75), as mucoadhesive polymers and mannitol as diluent (Table I) for 10 min. The blend was lubricated with

1% magnesium stearate for 3–5 min and then compressed into tablets by the direct compression method using 6-mm flat-faced punches. The tablets were compressed using a Cadmach rotary tablet machine (Cadmach Machinery, India). The mass of the tablets were determined using a digital balance (Shimadzu Japan) and thickness with a digital screw gauge (Mitatyo, Japan).The composition of the buccal tablet was given in table I.

Table 1: Composition of mucoadhesive buccal tablets of DIL containing carbopol 971P and carbopol 974P

BATCH CODE						
Ingredient	DC1	DC2	DC3	DC4	DC5	DC6
Diltiazem hydrochloride	30	30	30	30	30	30
Carbopol 971P	7.5	15	30			
Carbopol 974P				7.5	15	30
Mannitol	61.5	54	39	61.5	54	39
Magnesium streate	1	1	1	1	1	1

EVALUATION OF BUCCAL TABLETS:

Weight Uniformity

For the evaluation of weight uniformity ten tablets from every formulation were taken and weighed individually on electronic balance. The average weights were calculated.

Thickness and Diameter Study

The thickness and diameter of three randomly selected buccal tablets from every batch was determined using a standard screw gauge. The average thickness and diameter was calculated. (Refer Table NO. 1)

Surface pH[12]

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, on the oral cavity. As acidic or alkaline pH is found to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH close to neutral p^H.A combined glass electrode was used for this purpose. Mucoadhessive buccal tablets were left to swell for 2 hours in Petri plate. The surface p^H was measured by bringing the electrode in contact with the surface of the tablet, allowing it to equilibrate for 1 min. Tablets from all batches had shown a surface pH in the range of 5 to 7.

Content Uniformity[12]

Drug content uniformity was determined by dissolving the tablet by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 8 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 10ml, and the resulting solution was filtered through a 0.45 µm Whatman filter paper. The drug content was then determined after proper dilution at 237 nm using a UV-spectrophotometer.

Swelling Study[13]

Weight in increase due to the swelling was measured (Gua and Cooklock, 1995).

Tablet was weighed on a preweighed cover slip and initial weight was recorded (W0). It was kept in a petridish of diameter 4cm and 5ml of phosphate buffer, pH 6.8 was added. At time interval of 1, 2,3,4,5,6,7,8 hr, the cover slip was removed and excess of water was carefully removed and swollen tablet were weighed (Wt). The difference in the weight gives the weight increase due to absorption of water and swelling of tablet. The experiment was repeated three times. The % swelling was calculated by following formula.

$$\% S = \frac{Wt - Wo}{Wo} \times 100$$

Where, Wt is the weight of the swollen tablet with cover slip after time t and W0 is the initial weight of tablet with cover slip, and Wt-W0 represents weight increase due to swelling.

Ex vivo Mucoadhesive Strength[12, 14]

Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with isotonic phosphate buffer pH 6.8 at 37 °C. Bioadhesive strength of the patch was measured on a modified physical balance (Fig no.5) using the method described by Parodi *et al.* Fresh sheep buccal mucosa was cut into pieces and washed with isotonic phosphate buffer pH 6.6.The instrument broadly composed of modified physical balance in which the right pan holding glass slide (3×5 cm) with the help of adhesive tape and counter balanced by water collecting plastic bottle suspended to left arm. The pan received a siphon tube from bottle, which was kept at high place in such way that water head in the bottle always remains above the water collecting bottle. At the right side, a movable platform was maintained in the bottom and above it the glass beaker of 100ml was placed in inverted position in order to fix the sheep buccal mucosa (2.4 mm thick, 3×5 cm). The mucoadhesive tablet was fixed to glass slide with cyanoacrylate glue. The exposed tablet surface was moistened with 50µl of isotonic phosphate buffer pH 6.6 for 30seconds for initial hydration and swelling. Before lifting up the platform the distance between patch and mucosal surface should be 0.5cm and both side arms should be balanced by adding weight. The platform was raised upward until in such way that the patch on glass slide was kept on the mucosal tissue and the patch remained in contact with mucosa. The preload of 50gm was placed in right pan and whole assembly kept undisturbed for 3min (preload time) to establish the adhesion between tablet and mucosal tissue. After 3min, preload was removed and water was added to bottle by siphon tube at a constant rate of 200 drops per minute until detachment of the tablet from mucosal surface took place. Water collected in bottle at the time of detachment was weighed. After each measurement the tissue was gently and thoroughly washed with IPB pH 6.8 and left for 5 minutes before taking reading. The experiment was performed in triplicate. The mass in (gm) required to detach the patch from the mucosal surface gave the measure of mucoadhesive strength. The following parameters were calculated from the bioadhesive strength:

$$\text{Force of adhesion (N)} = \frac{\text{Bioadhesive strength (g)} \times 9.81}{1000}$$

$$\text{Bond strength (N m–2)} = \frac{\text{Force of adhesion}}{\text{Disk surface area}}$$

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Determination of Residence Time[15]

The in-vitro residence time was determined using a modified USP disintegration apparatus. The disintegration medium was composed of 900 ml phosphate buffer of pH 6.8 maintained at 37^0C. A segment of goat cheek mucosa 3 cm long was glued to the surface of a glass slab, vertically attached to the apparatus. Mucoadhessive tablets of each formulation were hydrated from one surface using phosphate buffer of pH 6.8 and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for compete erosion or detachment of the tablet from mucosal surface were recorded as given in table .(18).

In Vitro Release[11, 16]

USP dissolution apparatus type 2 (paddle method) was used to study drug release from tablet formulation under sink conditions 37± 0.5^0C and stirred at rate of 50 rpm. Each tablet was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper face. Then the slide was immersed in the vessel containing 500 ml of pH 6.8 phosphate buffer

solution. The aliquots of 3 ml were withdrawn at the time interval of 1 hour up to 8 hrs and replaced with equal volume of fresh dissolution medium.The sample was diluted with buffer upto 9ml. The sink condition was maintained throughout the study. The amounts of Diltiazem hydrochloride was determined by UV-VIS Spectrophotometer at 237 nm and amount of drug release at various time intervals was calculated.(14,15)

Release kinetic of drug

To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches was fitted to zero order, first-order, Higuchi, Hixon-Crowell, Korsemeyer and Peppas, models to ascertain the kinetic modeling of drug release.

Stability study:

The optimized formulation was subjected to stability study at 40 ± 2^0 and 75±5% RH for a period of 6 months.After each month tablets were removed and analysed for bioadhesive parameters and in vitro drug release study.

RESULTS AND DISCUSSION:

Evaluation of Buccal Tablet

Weight Uniformity

The average weight of tablet was reported in Table no.2. The weight of buccal tablet ranges from 97.33±2.49 to 104.66±3.26gm.

Thickness and diameter Study

The average thickness and diameter of different formulations were reported in Table no.2 and calculated by using ten tablets for standard deviation. The thickness of formulated tablets ranges from 0.27±0.01 to 0.32±0.08 cm for batch DC1 to DC6.The diameter ranges from 0.59±0.005 to 0.61±0.004 cm.

Surface pH

The surface pH of tablets for batch DC1 to DC6 ranges from 6.23 ± 0.02 to 6.83 ± 0.126. The surface pH ranges of all batches (Table 3) were found around saliva pH range 5.6 to 7.4, which indicates no risk of mucosal damage or irritation.

Content Uniformity

Content uniformity for batch DC1 to DC6 was found to be in the of range of 97.33%±1.52 to 102.33%± 1.62. The results of content uniformity indicate that the drug was uniformly dispersed in buccal tablets and shown in Table 2.

Table 2: Postcompression parameters of buccal mucoadhesive tablets of DIL containing carbopol 971P and 974P

Batch code	Thickness(cm)	Diameter(cm)	Hardness(kg/cm^2)	Weight(gm)	Content uniformity(%)
DC1	0.29±0.01	0.59±0.005	4.83±0.28	104.33±2.0	102.33±1.52
DC2	0.27±0.01	0.59±0.01	6±0.5	102.66±3.2	97.33±1.52
DC3	0.30±0.004	0.60±0.01	5.66±0.62	104.66±2.4	98.66±0.62
DC4	0.32±0.008	0.58±0.004	6±0.40	100.66±1.2	98.83±1.24
DC5	0.27±0.01	0.60±0.004	5.66±0.84	100.33±2.0	101.16±1.24
DC6	0.3±0.02	0.61±0.004	5.5±0.81	97.33±2.49	102.33±0.62

Swelling Study

The swelling percentage for batch DC1 to DC6 was determined by measuring increased weight due to swelling after predetermined time (equn1). The swelling state of the polymer was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase with the degree of hydration until a point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. The swelling profiles of batch DC1 to DC6 are shown in Table 4. These profiles indicate the uptake of water into the tablet, producing an increase in weight.

Mucoadhesive Strength Measurement

The results of the bioadhesive strength(gm) and force of adhesion (N) of Diltiazem buccal tablets are given in Table 3. Bioadhesive strength(gm) and

force of adhesion (N) for formulationDC1 to DC6 ranges from 35.78 to 43.67gm. In all the formulations, as the polymer concentration increased, both the bioadhesive strength(gm) and force of adhesion (N) was increased. The order of bioadhesion was found to be carbopol 971P> carbopol 974P.

Determination of Ex-vivo mucoadhesion time

Ex-vivo mucoadhesion time was determined using a modified USP disintegration apparatus. Tablets containing carbopol ,971P, 974P swells slowly without formation of gel layer and remain adhered to mucosa for a period of more than 6 hrs. As the concentration of carbopol increases the residence time also increases but this exertes a retarding effect on the drug release. The residence time for batches DC1 to DC3 was found to be more than 8 hrs and for batches DC4 to DC6 , the mucoadhesion time was found to be between 6-7 hrs.

In Vitro Drug release

The release of Diltiazem from buccoadhesive tablets (Fig 2) varied according to the type and ratio of mucoadhesive polymers. The drug release was governed by the amount of mucoadhesive polymer. The most important factor affecting the rate of release from the buccal tablets is the drug : polymer ratio. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. In the present study, the results followed this predictable behaviour (Fig. 1a–c). Buccal tablets that contained lower concentrations of either Carbopol 971P or 974P , respectively, tended to release the drug in shorter time periods, while the release slowed down as the concentration of the gelling polymer increased, thus confirming the dominant role of the swellable hydrophilic polymer in the release of Diltiazem from buccal tablets. Data of the in vitro release was fit into different equations and kinetic models to explain the release kinetics of Diltiazem from buccal tablets. The kinetic models used were zero-order equation, first-order equation, Higuchi and Korsemeyer-Peppas models. .Increasing the concentration of the polymer in the formulations showed a sustained effect on Diltiazem release.The rapidly hydrating polymer dominated in controlling the release of Diltiazem from the buccal tablets, as seen from the dissolution profiles and moisture absorption data.The data for in vitro release and kinetic models was given in table III and IV

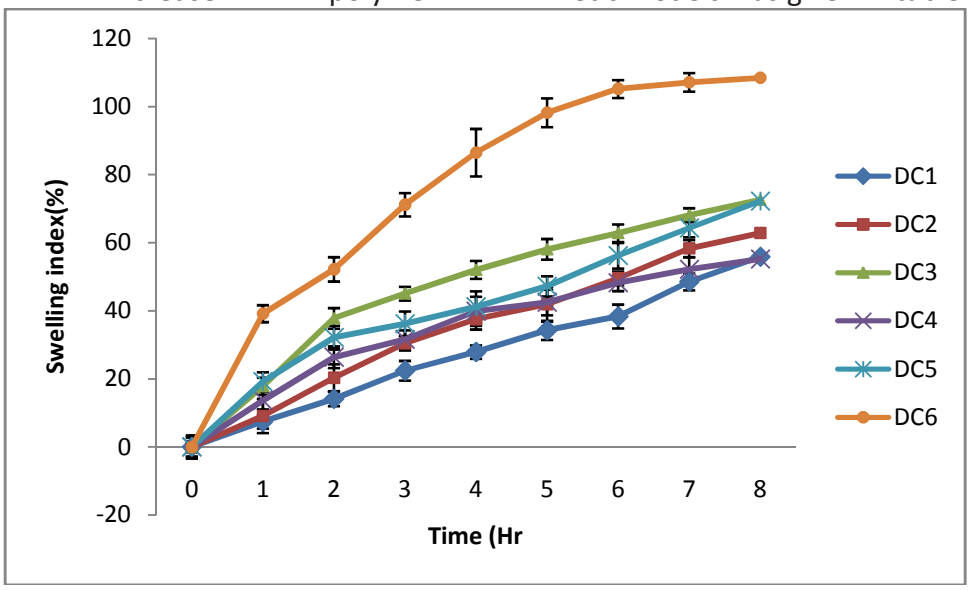

Fig 1 - Swelling index of buccal tablets of DIL containing carbopol 971P(DC1 to DC3) and carbopol 974P(DC4 to DC6)

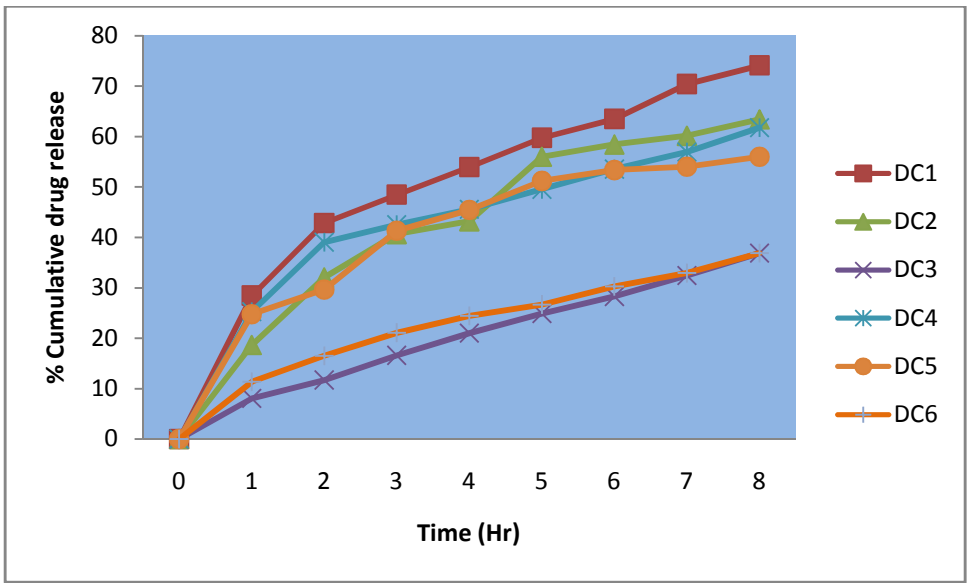

Fig 2 - In-vitro drug release profile of buccal tablet of DIl containing carbopol 971 P(DC1to DC3) and 974P(DC4 to DC6)

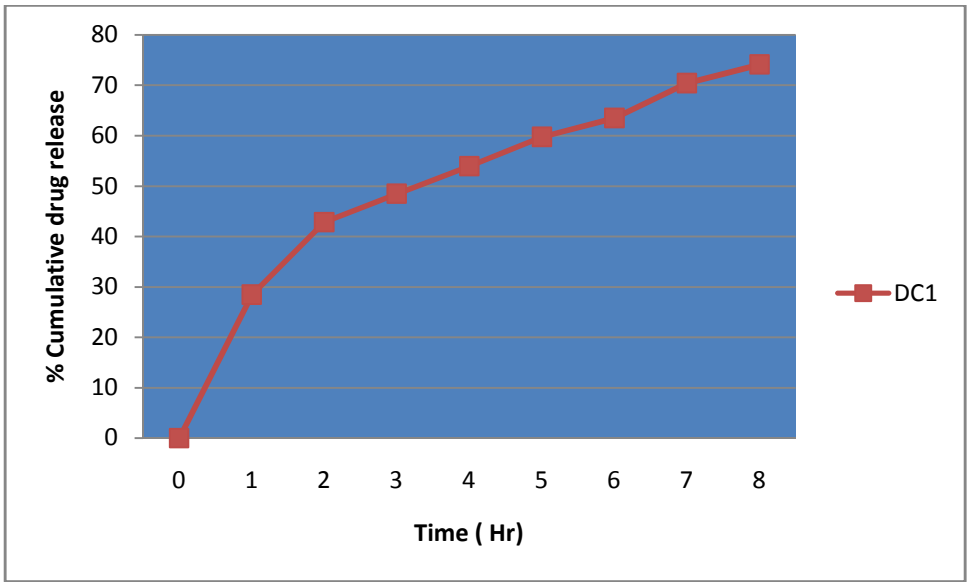

Fig 3 : In vitro release profile of optimized formulation DC1

Table 3: Mucoadhesive parameters of buccal tablets of DIL containing carbopo 971P and 974P

BATCH CODE	MUCOADHEIVE STRENGTH(GM)	FORCE OF ADHESION(N)	IN-VITRO RESIDENCE TIME	SURFACE P^H
DC1	39.12	0.383767	> 8hr	7.00±0.050
DC2	41.34	0.405545	>8hr	6.42±0.115
DC3	43.67	0.428403	> 8hr	6.23±0.029
DC4	35.78	0.351002	6-7 hr	6.48±0.058
DC5	36.23	0.355416	6-7hr	6.68±0.076
DC6	37.89	0.371701	6-7hr	6.83±0.126

Table 4 : Swelling index of buccal tablets of DIL containing synthetic polymers such as carbopol 971P and carbopol 974P

SWELLING INDEX(%)						
Time(Hr)	**DC1**	**DC2**	**DC3**	**DC4**	**DC5**	**DC6**
0	0	0	0	0	0	0
1	7.39±1.3	9.08±1.44	17.87±2.98	13.65±3.42	19.14±1.67	39.15±2.78
2	14.08±2.01	20.31±5	37.76±2.49	26.34±2.65	32.12±2.78	52.17±2.5
3	22.4±2.12	30.46±3.97	45.05±3.02	31.56±3.16	36.17±3.45	71.17±3.56
4	27.87±2.88	37.49±2.13	52.02±2.02	39.87±2.67	41.15±3.62	86.45±3.41
5	34.26±2	41.89±3	58.05±2.64	42.45±4.26	47.19±4.56	98.17±6.98
6	38.31±2.81	49.54±5.12	62.8±3.04	48.23±3.78	56.18v2.98	105.16±4.2
7	48.5±3.51	58.31±2.02	68.08±2.6	52.14±2.45	64.27±3.78	107.13±2.6
8	55.83±2.5	62.79±2.5	72.58±2.05	55.15±3.56	72.18±2.65	108.4±2.71

Drug Release Kinetic

To characterize the release mechanism of Diltiazem Hydrochloride from different formulations,different batches of mucoadhesive buccal tablet were subjected to various kinetic model fitting.The optimized formulation DC1 was best fitted to Higuchi model. The data was shown in table 6.

Table 5 - In-vitro drug release profile of buccal tablet of DIl containing carbopol 971 P and 974P

% CUMULATIVE DRUG RELEASE BATCH CODE						
Time(Hr)	**DC1**	**DC2**	**DC3**	**DC4**	**DC5**	**DC6**
0	0	0	0	0	0	0
1	28.45±3.24	18.63±2.96	8.05±2.07	25.25±3.65	24.75±3.27	11.37±3.37
2	42.83±2.56	32.04±3.77	11.7±2.31	39.01±2.84	29.64±4.66	16.49±3.71
3	48.46±3.5	40.64±2.18	16.59±3.34	42.52±1.34	41.33±2.69	21.1±2.57
4	53.94±3.58	43.18±1.54	21.01±3.44	45.56±2.66	45.47±3	24.43±2.11
5	59.74±2.04	55.97±2.76	24.89±2.36	49.54±4.66	51.21±1.17	26.68±3.05
6	63.47±2.5	58.41±2.12	28.28±2.96	53.53±2.66	53.36±1.73	30.27±2.06
7	70.39±3.16	60.11±2.71	32.44±2.28	56.92±3.68	54.03±2.5	32.92±2.38
8	74.09±3.34	63.37±3.5	36.88±3.26	61.74±3.0	55.99±3.12	36.87±3.68

Table 6- Kinetic model fitting of different batches of DIL containing carbopol 971P and carbopol 974P

Batch Code	R^2 Value						Best Fit Models
	Zero order	First Order	HIGUCHI	Hixon Crowell	Korsmeyer Peppas	n value	
DC1	0.829	0.898	0.980	0.877	0.9517	0.422	Higuchi
DC2	0.867	0.942	0.992	0.920	0.9901	0.449	Higuchi
DC3	0.985	0.992	0.966	0.990	0.9933	0.712	KorsmeyerPeppas
DC4	0.817	0.878	0.975	0.858	0.9709	0.403	Higuchi
DC5	0.904	0.955	0.992	0.940	0.9652	0.470	Higuchi
DC6	0.923	0.946	0.998	0.938	0.9976	0.540	Higuchi

Stability Study

The optimized formulation DC1 was subjected to stability study at 40 ± 2^0 and 75±5% RH for a period of 6 months.The value of all bioadhesive parameters after 6 months remain same with slight variation in invitro drug release after 8 hrs. The data was shown in table

Table 7: In vitro release profile of optimized formulation,DC1

%DRUG RELEASE	
Time(Hr)	DC1
0	0
1	28.45
2	42.83
3	48.46
4	53.94
5	59.74
6	63.47
7	70.39
8	74.09

CONCLUSION

The present work was aimed to develop the mucoadhesive drug delivery system for Diltiazem hydrochloride with prolonged effect and to avoid first pass metabolism.From the study, it is observed that formulation DC1 was best in terms of drug release, bioadhesive performance and physicochemical properties.There it can be concluded that stable formulation could be developed by incorporating carbopol 971P in the drug :polymer ratio of 1:0.25 for the controlled release of Diltiazem hydrochloride from mucoadhesive tablet with adequate bioadhesiveness and swelling properties without risk of mucosal damage.

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