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Design of Solid Dosage Form for Buccal Drug Delivery of Diltiazem Hydrochloride

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ABSTRACT

Diltiazem HCl(DIL) 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 as it has half-life of 4.5 hrs, optimum partition coefficient , log P- 158 and molecular weight 450.98 . The tablets of Diltiazem HCl were prepared using primary mucoadhesive polymers such as Carbopol-971P(CP) and secondary polymers such as Hydroxy propyl methyl cellulose (HPMCK4M) and Psyllium husk. Six formulations were developed with varying concentrations of polymers. The tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, surface pH, in vitro swelling, mucoadhesive strength, mucoadhesion time and percentage drug release. Formulation B3 containing Carbopol-971P and HPMC K4M in the ratio of 1 : 5 showed good mucoadhesive strength (51.34gm) and maximum drug release of 94.72% in 8 hrs. Swelling of tablets increased with increase in concentration of HPMC K4M . Surface pH was found to be 6.37. Drug release pattern was found to be Higuchi in formulation B3. FTIR study showed no evidence of interaction between drug and polymers.

INTRODUCTION

Mucoadhesive drug delivery systems are the ones, which utilize the property of bioadhesion of certain polymers. Bioadhesion is defined as ability of a material to adhere to a particular region of the body for extended period of time not only for local targeting of drugs but also for systemic delivery of drugs. Buccal mucoadhesive drug delivery systems offer many advantages over conventional systems such as ease of administration, rapid termination of therapy, administration to unconscious patients, bypass hepatic first pass metabolism, GI metabolism. From technical point of view, an ideal buccal dosage form must have three properties. It must maintain its position in the mouth for a few hours, release the drug in a controlled fashion and provide the drug release in a unidirectional way towards the mucosa. In regard to the first requirement, strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can be fulfilled by preparing a system having uniform adhesiveness and impermeable backing layer. Various mucoadhesive devices such as tablets, films, patches, discs, strips, ointments and gel have been recently developed[2].

Most of the mucoadhesive materials are either synthetic or natural hydrophilic or water insoluble polymers and are capable of forming numerous hydrogen bonds because of presence of the carboxyl, sulphate or hydroxyl functional groups. Various materials tested for mucoadhesion include synthetic materials such as Carbopol- 934, Hydroxy propyl methyl cellulose (HPMC), Hydroxy ethyl cellulose (HEC), Sodium carboxy methyl cellulose, Polymethyl methacrylates and polycarbophil, while natural polymers include xantium gum, sodium alginate, gelatin, acacia and tragacanth[3]. Bioadhesive polymers can not only cause the adhesion effects but can also control the release rate of drug.

Diltiazem HCl 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, log P-158 and molecular weight 450.98. The objective of present study is to design and evaluate the controlled release mucoadhesive buccal tablets of Diltiazem with a goal to increase the bioavailability, reduce dosing frequency and improve patient compliance, by employing

mucoadhesive polymers like Carbopol- 940P, Hydroxy propyl methyl cellulose (HPMC), and Psyllium husk. The buccal tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, surface pH, *in vitro* studies like swelling and drug release and *ex vivo* studies like mucoadhesive strength and time.

MATERIALS AND METHODS

Materials:

Diltiazem hydrochloride was received as gift sample from Alembic Ltd**.,** Vadodara, Gujarat. Carbopol-971P, Hydroxy Propyl Methyl cellulose (HPMCK4M), Psyllium husk were procured from S.D fine chemicals, Nagpur, India. All other reagents and chemicals used in the study are of analytical grade.

Diltiazem hydrochloride calibration curve

Calibration curve of Diltiazem HCl was prepared using buffer pH 6.8 in the concentration range of 1–15µg/ml. The drug was analyzed spectrophotometrically (UV 1601 Shimadzu, Japan) at 237 nm with regression coefficient of $r^2 = 0.9994$.

Drug-excipient interaction studies

Preformulation studies are very important for the successful formulation of any dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were carried out for checking compatibility between drug and polymers. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. It is observed that 1:1ratio of drug excipients maximizes the possibility of interaction and helps in easier detection of incompatibilities. Therefore, in the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies by FTIR.

Formulation of mucoadhesive buccal tablets

Mucoadhesive buccal tablets, each containing 30 mg Diltiazem were prepared by direct compression method. Composition of various formulations employing Carbopol 971P as a primary mucoadhesive polymer and HPMC K4M & Psyllium husk as secondary polymer was

shown in Table 1. Formulation B1, B2, B3 consist of mixture of carbopol 971P and HPMC K4M while formulation B4,B5, and B6 consist of mixture of carbopol 971P and psyllium husk. All the ingredients of tablets were blended in mortar with a pestle for 15 min to obtain uniform mixture. The blended powder was then compressed into 100 mg tablets (at 5-7 kg/cm2) on a single stoke, 10 station rotary tablet machine with 6mm round shaped flat punch.

Table 1 : Composition of Diltiazem buccal tablets

	FORMULATION CODE					
Ingredients (mg/ tablet)	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**
Diltiazem HCL (API)	30	30	30	30	30	30
Carbopol 971P Primary polymer	15	10	5	15	10	5
HPMCK4M (Secondary polymer)	15	20	25			
Psyllium husk (Secondary polymer)				15	20	25
Mannitol (Filler)	39	39	39	39	39	39
Magnesium stearate (Lubricant)	1	1	1	1	1	1
Total tablet weight	100	100	100	100	100	100

EVALUATION OF MUCOADHESIVE BUCCAL TABLET:

All the prepared mucoadhesive buccal tablets were evaluated for following official tests.

Drug Content:

Three tablets from each formulation of Diltiazem hydrochloride were taken in separate 100 ml volumetric flask. 100 ml of pH 6.8 phosphate buffer was added to volumetric flask and kept for 24 hour under constant stirring. The solution were filtered, diluted suitably and analyzed at 237 nm by UV spectrophotometer. The average of three tablets was taken as the content of drug in one tablet unit.

Uniformity of weight: [4]

Ten tablets were selected at random from each batch, weighed individually and the average weight was calculated. The batch passes the test for uniformity of weight if not more than two of the individual tablet weight deviate from the average weight by more than the 7.5 percentage. The results of uniformity of weight comply with the specifications of I.P

Hardness:

Hardness was measured using Monsanto hardness tester. Three tablets from each batch were tested. The measured hardness (kg/cm^2) of tablets of each batch are shown in Table .

Friability: [5]

Ten tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(W_t/W)\} \times 100$$

Where,

% F = Friability in percentage

W = Initial weight of tablet

W_t = Weight of tablets after revolution

Thickness uniformity:

Three tablets were selected at random from each batch and thickness was measured by using Vernier caliper.

***In- vitro* swelling study:**[6]

The swelling rate of mucoadhesive buccal tablets of Diltiazem hydrochloride were evaluated using phosphate buffer pH 6.8. Phosphate buffer was used as medium to carry out swelling studies as it resembles the secreting fluid in and around the buccal mucosa required for bioadhesion and subsequent swelling of the formulation to provide adequate release of the drug. Tablet was sticked on glass slide and weighed, (W_0) as initial weight. The tablets were placed in Petri dishes containing phosphate buffer pH 6.8 which were placed in an incubator at 37^0C. Tablets were removed at time intervals of 0.5, 1, 2, 4 and 6 hr, excess water on the surface was carefully soaked using filter paper, and swollen tablets were weighed along with glass slide on which it was sticked. The final weight (W_t) was determined and the swelling index was calculated by the formula-

$$\% \text{ Swelling Index} = \frac{(W_t - W_0)}{W_0} \times 100$$

Surface pH determination:[7]

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 pH. A combined glass electrode was used for this purpose. Mucoadhesive buccal tablets were left to swell for 2 hours in Petri plate. The surface pH 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.

***Ex Vivo* Mucoadhesive Strength:**[8]

Fresh goat 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 isotonic phosphate buffer of pH 6.8 at 37 °C. Bioadhesive strength of the tablet was measured on a modified physical balance. Fresh goat buccal mucosa was cut into pieces and washed with isotonic phosphate buffer pH 6.8.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 mucoadhessive tablet was fixed to glass slide with cyanoacrylate glue. The exposed tablet surface was moistened with 50 µl of isotonic phosphate buffer pH 6.8 for 30 seconds for initial hydration and swelling. Before lifting up the platform the distance between tablet and mucosal surface should be 0.5cm and both side arm 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 tablet remained in contact with mucosa. The preload of 50gm was placed in right pan and whole assembly kept undisturbed for 3 min (preload time) to establish the adhesion between tablet and mucosal tissue. After 3 min, 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. The 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 mucoadhessive strength. This experiment was performed in triplicate.

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

***Ex Vivo* mucoadhesion time:** [9]

The Ex-Vivo mucoadhesion 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 buccal mucosa 3 cm long was glued to the surface of a glass slab, vertically attached to the apparatus. Mucoadhesive tablet of each formulation was 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 was recorded.

In vitro drug release study [10]

USP dissolution apparatus type 2 (paddle method) was used to study drug release from tablet formulation under sink conditions at 37± 0.5^0C and stirring rate of 50 rpm. Each tablet was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be released only from upper face. The slide was immersed in 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 amount of Diltiazem hydrochloride was determined by UV-VIS Spectrophotometer at 237 nm and amount of drug release at various time intervals was calculated.

Release kinetic study: [11]

To describe kinetics of drug release from tablets of optimized batches F_{10}, mathematical models such as zero order, first order and Higuchi square root of time model were used. The criterion for selecting most appropriate model was based on goodness of fit test. The zero order kinetics (equation 1) describes system in which drug release rate is independent of its concentration, the first order kinetics (equation 2) describes the systems in which drug release rate in concentration dependent, Higuchi (equation 3) described release of drug as a square root of time dependent process on basis of Fickian diffusion.

Stability studies and storage conditions

Stability studies were carried out for optimized formulation as per ICH guidelines.

Optimized batch of mucoadhesive buccal tablet of DIL was placed in sealed vial which was then stored at 40^oC/75%RH for 6 months in stability chamber (CHM 10S, Remi Instruments, Mumbai). The physicochemical properties, *ex vivo* mucoadhesive strength, *ex vivo* mucoadhesion time, and release profile of the optimized batch was determined before keeping for stability study and then after 3 months, and 6 months.

RESULTS AND DISCUSSION

Compatibility study:

Before designing various formulations, the drug polymer-excipient compatibility studies were conducted by FTIR spectroscopy and the results are presented in Fig 3. All the major peaks obtained due to various functional groups in drug are retained in the mixture of drug, HPMC and carbopol 971P.This indicate that there was no interaction between drug and polymers. Total six different formulations (B1 to B6) of Diltiazem buccal tablets were prepared by direct compression techniques using various proportions of polymers and excipients.

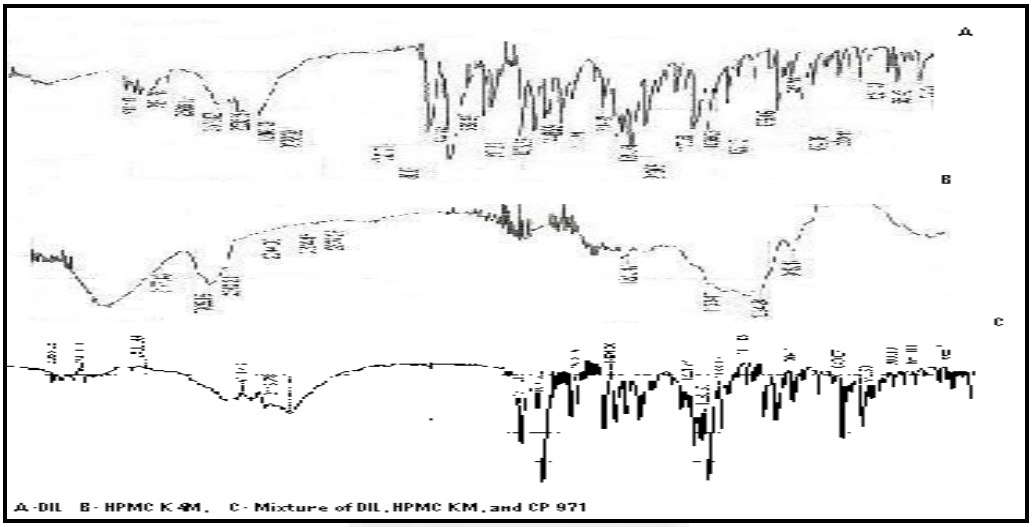

Fig 1 : FTIR spectra of A) DIL B) HPMC K4M C) Mixture of DIL, HPMC K4M, CP 971P

EVALUATION OF MUCOADHESIVE BUCCAL TABLET:

Content uniformity:

Content uniformity of all the tablets was evaluated and the results are presented in Table 3. The maximum percentage of drug content from the different formulations was found to be 104.3% and minimum percentage of drug content was found to be 99.33 %. Hence it is concluded that all the formulations are falling within the pharmacopoeial limits.

Hardness:

The hardness of tablets of different formulation (B1 to B6) was determined as per standard procedure. The average hardness of formulation B1 to B6 was in the range of 5.5 to 6.16kg/ cm^2. The results are illustrated in table 2.

Thickness:

The average thickness of tablets (B1 to B6) was determined and results are presented in Table 2.Thickness varied between 0.27cm to 0.32cm.

***In vitro* swelling:**

Swelling behaviour of buccal formulations of DIL was evaluated in phosphate buffer pH 6.8.In all the 6 formulations, carbopol 971p was used as primary mucoadhesive polymer and HPMCK4M/ psyllium husk as a secondary polymer. Carbopol 971P is a polyacrylic acid based polymer which undergoes controlled hydration and swelling. Similarly HPMCK4M, a secondary polymer undergo swelling at a controlled rate. Increase in concentration of HPMCK4M in batches B1 to B3 increases the swelling. Also increase in concentration of psyllium husk, a secondary polymer in batches B4 to B6,increases swelling. But swelling rate in batches B4 to B6 is much high as compared to batches B1 toB3. According to swelling rate theory, some degree of swelling is required for proper mucoadhesion. Excessive swelling reduces bioadhesion. Combination of carbopol 971P and HPMCK4M undergoes controlled swelling which is required for proper mucoadhesion .The results of in vitro swelling are presented in table 4 and 5.

Table 4. Swelling index of Diltiazem buccal containing HPMC K4M

Swelling index (%) Batch code			
Time(hr)	**B1**	**B2**	**B3**
0	0	0	0
1	12.12±4.21	22.58±2.89	32.43±4.78
2	21.21±5.82	25.8±3.56	36.76±5.89
3	30.32±4.65	29.03±4.28	40.65±6.34
4	33.35±3.82	38.7±5.89	46.54±5.55
5	36.39±2.74	45.16±5.76	51.32±4.45
6	39.45±2.56	48.38±3.89	±57.32±3.56
7	42.47±4.87	51.61±4.98	63.32±5.32
8	45.56±5.9	54.83±5.67	71.43±5.65

Table 5. Swelling index of Diltiazem containing Psyllium husk

Swelling index(%) Batch code			
Time(hr)	**B4**	**B5**	**B6**
0	0	0	0
1	4.44±5.43	2.43±5.87	57.89±3.41
2	8.88±6.43	4.87±4.43	86.87±4.65
3	24.44±6.22	39.02±3.87	89.47±3.67
4	42.22±4.65	58.53±6.87	92.1±2.54
5	66.67±3.87	70.73±5.32	94.73±4.21
6	91.11±4.76	82.92±5.98	99.43±3.7
7	93.33±5.32	95.12±2.76	105.26±2.8
8	97.77±6.43	107.31±3.98	123.68±5.21

Surface pH

The surface pH of tablets of each formulation (B1 to B6) was tested and the results are provided in table-3. Surface pH varies between 6.35 to 6.55.The acceptable pH of saliva is in the range of 5-7 and the surface pH of all tablets is within limits. Hence, the formulations may not produce any irritation to the buccal mucosa.

Table 2: Post compression parameters of DIL buccal tablets

Batch code	Thickness (cm)	Average weight(mg)	Hardness (kg/cm^2	Friability (%)	Content uniformity (%)
B1	0.32±0.004	101.00±0.81	6.00±0.40	0.37±0.02	104.3±2.05
B2	0.27±0.004	101.66±1.24	5.66±0.62	0.41±0.02	101.66±0.45
B3	0.27±0.004	101.66±1.24	5.66±0.62	0.4±0.008	103.33±1.69
B4	0.28±0.005	104±1	6.16±0.57	0.47±0.03	99.33±1.52
B5	0.28±0.020	99.33±1.52	5.5±0.5	0.55±0.04	102.33±1.52
B6	0.30±0.005	99.33±2.08	6±0.5	0.55±0.02	104.33±1.52

Mean ± SD., n=3

Mucoadhesive parameters:

Ex vivo mucoadhesive strength of different formulations of DIL was evaluated .Maximum strength of 51.34gm was observed in formulation B3 containing carbopol 971 and HPMC K4M.Minimum strength of 14.54 gm was observed in formulation B6 containing carbopol and psyllium husk. Maximum Mucoadhesion time was found in formulation B3.Formulations B4,B5,B6 containing husk shows less mucoadhesive strength and mucoadhesion time. The results were illustrated in table 3.Low value of mucoadhesive strength and time was found in batches containing Psyllium husk (B4-B6). This is because husk undergoes extensive swelling and hydration. This results in lowering of mucoadhesive properties such as strength and time. Mucoadhesive polymer must possess properties such as proper hydrogen bonding functional groups, suitable wetting properties, swelling/water load properties, and sufficient flexibility for entanglement with the tissue mucus network. Hydroxypropyl methyl cellulose and carbopol have been shown to possess the hydrogel-forming properties, which are necessary for mucoadhesion. Carbopol polymers readily swell in water, providing a large adhesive surface area for maximum contact with the mucin (the glycoprotein predominant in the mucus layer). Combination of HPMC and carbopol 971showed good mucoadhesive properties. Increase in the concentration of HPMCK4M increases the mucoadhesive strength but increase in the concentration of psyllium husk decreases the mucoadhesive strength as it undergoes excessive swelling and hydration. So even if carbopol shows good mucoadhesive potential but if it is combined with psyllium husk, mucoadhesive potential reduces as in batches B4, B5 and B6.

Table 3: Mucoadhesive parameters of DIL buccal tablets

Batch code	Mucoadheive Strength (gm)	Force of adhesion (N)	Mucoadhesion time (Hr)	Surface pH
B1	45.04±1.56	0.441842	10.5±1.89	6.55±0.082
B2	49.65±1.5	0.487067	10.8±0.8	6.52±0.047
B3	51.34±2.01	0.503645	10.9±0.5	6.37±0.062
B4	22.05±1.89	0.216311	1.8±1.12	6.62±0.047
B5	19.65±2.23	0.192767	1.5±1.45	6.50±0.041
B6	14.54±1.89	0.142637	1.1±1.5	6.35±0.082

mean±SD, n= 3

***In vitro* drug release study:**

In vitro drug release in all the formulations was determined by standard procedure and the release profile was given in Fig. 2. The drug release pattern of buccal mucoadhesive tablets varied according to their type and ratio of polymers. The most important factor affecting the rate of release from buccal tablet is the drug and polymer ratio. The formulation B1, B2, B3 contained, Carbopol 971p and HPMC polymers in the ratio of 1:1, 1:2, and 1:5. Among these formulations, drug release found to be maximum in formulation B3 i. e 94.72 %. Tablets of these formulations undergo controlled hydration and swelling which control the drug release. The formulation B4, B5, B6 contained, Carbopol 971p and Psyllium husk polymers in the ratio of 1:1, 1:2, and 1:5. Tablets of these formulations undergo excessive swelling. So although the polymer ratio is same but type of secondary polymer is different which is primarily responsible for controlling the drug release and optimum mucoadhesive properties. Amongst all these formulations, drug release was found to be maximum in formulation B3 i. e 94.72 %. The results were illustrated in table 6.The release profile was shown in fig 2.

Table 6 - *In-Vitro* drug release profile of Diltiazem buccal tablets

% CUMULATIVE DRUG RELEASE BATCH CODE						
Time (Hr)	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**
0	0	0	0	0	0	0
1	21.46±2.61	35.32±3	43.57±2.67	61.66±1.15	64.11±0.67	68.28±0.98
2	22.47±3.05	43.18±2.5	50.1±1.56	70.52±1.22	75.08±0.57	82.37±1.16
3	29.65±2.89	47.64±2.9	57.8±2.59	78.43±0.8	86.64±1.02	88.01±0.47
4	31.91±2.88	50.41±2.58	63.09±2.56	83.46±1.26	91.15±0.62	91.4±0.86
5	35.68±2.67	54.69±3.17	68±3.05	87.33±1.46	94.4±0.65	100.1±0.52
6	42.5±2.75	60.23±3.73	75.1±5.95	90.33±0.8	99.18±0.56	
7	46.28±3.59	66.22±4.08	86.2±4.73	93.36±0.9		
8	56.32±3.79	75.72±3.8	94.72±3.48	96.32±0.86		

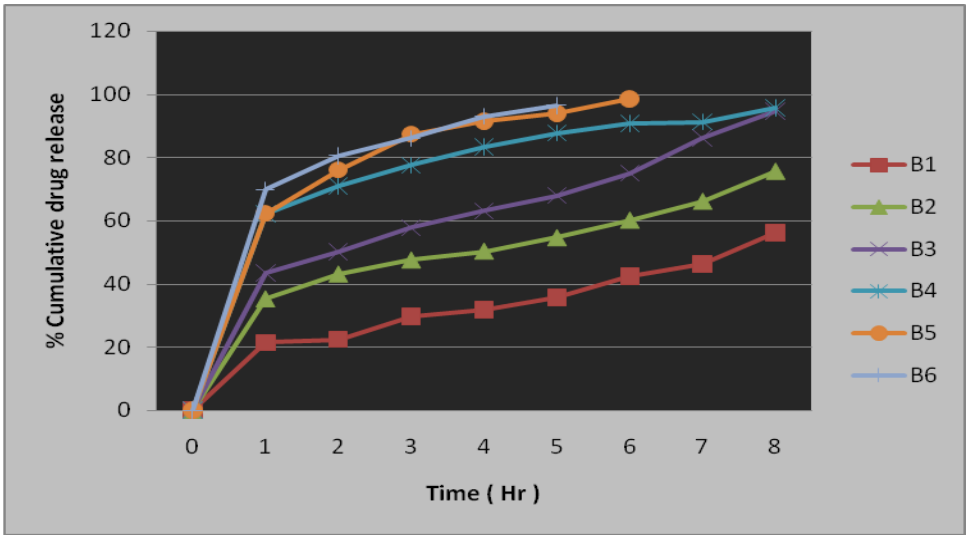

Fig 2. *In vitro* drug release profile of diltiazem buccal tablets

Optimization of formulation:

On the basis of mucoadhesive performance and in vitro drug release, formulation B3 was selected as optimized formulation and was subjected to stability analysis as per ICH guidelines. The formulation B3 was found to be stable and all the parameters were found to be within the limits.

Kinetic study:

All the formulations of Diltiazem were subjected to mathematical analysis and the results were illustrated in table 7. The optimized formulation B3 follows Higuchi kinetics.

Table 7. Correlation coefficient values of different formulations of diltiazem

Batch	R^2						Best fit model
	Zero order	First order	Higuchi	Hixon-crowell	Korsmeyer -peppas	n- value	
B1	0.826	0.870	0.970	0.856	0.9018	0.331	Higuchi
B2	0.745	0.831	0.947	0.803	0.9439	0.264	
B3	0.774	0.895	0.959	0.857	0.9402	0.280	
B4	0.702	0.919	0.922	0.852	0.9955	0.215	Korsmeyer Peppas
B5	0.730	0.970	0.940	0.906	0.9821	0.264	
B6	0.684	0.968	0.911	0.899	0.9967	0.202	

CONCLUSION

A new buccoadhesive system for the controlled release of DIL was developed by using CP, and HPMC in appropriate ratios. The release rate of DIL from tablets was significantly affected by the type and changes in the polymer mixing ratios. Formulation B3 containing carbopol 971P and HPMCK4M in 1:5 shows satisfactory mucoadhesive properties, significant swelling properties, and optimum release profile and could be useful for buccal administration of DIL. Based on in vitro release and Bioadhesion studies formulation B3 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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