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Development and Evaluation of Novel Buccoadhesive Bilayer Tablet

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ABSTRACT

This work aimed to formulate and develop a buccoadhesive bilayer tablet using bioadhesive polymers carbopol, xanthan gum along with ethyl cellulose as an impermeable backing layer. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming the problems like difficulty in swallowing. 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. Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. The formulation consists of two layers one is of drug Diltiazem HCl and another layer is of polymer ethyl cellulose. This is called a backing layer, the backing layer is added to prevent the loss of drug. This type of drug delivery system is formulated to enhance the drug bioavailability and to minimize the drug leaking into saliva. The preformulation study was performed by FTIR. The first layer which adheres to mucosa was obtained by direct compression of mucoadhesive polymers and drug. The second layer containing water-impermeable agent ethyl cellulose was compressed on the first layer. Eight formulations of Diltiazem HCl were prepared by the direct compression method. The formulations were subjected to various evaluation parameters like weight variation, hardness, swelling index, in vitro drug release, bioadhesion strength. The formulation F3 was considered as the optimized formulation based on satisfactory drug release, bioadhesion strength. The use of xanthan gum, HPMC K100, carbopol 940 showed proper sustained release of the drug.

INTRODUCTION

Oral drug delivery is the most favored route for the administration of various medications and tablets are the most widely accepted dosage form. Solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly patient compliance. But the difficulty in swallowing the conventional tablets is the main problem in generally geriatric patients, such problems led to the development of a novel type of solid oral dosage form hence, an attractive, taste masking formulations are the need of the hour. The buccoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. The buccal drug delivery system involves the administration of drugs via the buccal mucosa (lining of the cheek) to the systemic circulation. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, viscoelastic properties, flexibility for interpenetration with mucus, and epithelial tissues. The buccoadhesive bilayer tablets are prepared with the help of adhesive polymers like carbopol, xanthan gum, etc. the backing layer of ethylcellulose is added to prevent the loss of drug due to saliva. The buccal bilayer tablets involved two layers one is of Diltiazem HCl and another layer is of ethylcellulose, i.e.backing membrane main function of the backing membrane is to provide unidirectional drug flow to the buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for the backing membrane must be inert and impermeable to drugs and penetration enhancers.

MATERIALS AND METHODS

MATERIALS

Diltiazem HCL was obtained as a gift sample from Yarrow Chem Pharmaceutical Pvt, Ltd., Mumbai, and other ingredients like HPMC K100, Xanthan gum, Carbopol 940 Ethylcellulose were obtained from Zim laboratories Ltd, Nagpur, Loba Chemicals, Mumbai respectively.

METHODS

The tablets were prepared by direct compression method as follows:

1. Diltiazem hydrochloride tablets were prepared by direct compression techniques.

2. Drugs and the excipients were homogeneously blended. 70 mg of the powder blend was pre-compressed on 6 station tablet punching machine at a pressure of 0.5 ton to form single-layered flat beveled tablets of 3 mm diameter.

3. Further, 30 mg of ethylcellulose powder was added and the final compression was done at a pressure of 3.5 tons to get a bilayer tablet.

4. Each tablet contained a total weight of 100 mg. The prepared formulation was evaluated for parameters like weight variation test, tablet hardness, friability, tablet thickness, in vitro dissolution study, in vitro bioadhesion force study, swelling index, in situ diffusion study.

Table No. 1: Composition of buccoadhesive tablets of Diltiazem HCl

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Diltiazem HCL(mg)	30	30	30	30	30	30	30	30
Xanthan gum(mg)	7.5	7.5	7.5	7.5	12.5	12.5	12.5	12.5
HPMCK10 (mg)	7.5	7.5	12.5	12.5	7.5	7.5	12.5	12.5
Carbopol 930(mg)	7.5	12.5	7.5	12.5	7.5	12.5	7.5	12.5
Mg Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose(mg)	15	10	10	5	10	5	5	-
Ethylcellulose (mg)	30	30	30	30	30	30	30	30
Total(mg)	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION

Pre-compression parameters of Diltiazem HCl powder blend

Table No. 2: Pre-compression parameters of Diltiazem HCl powder blend

Formulation	Bulk Density gm/cm^3	Tapped Density gm/cm^3	Angle of Repose (degrees)	Carr's Index %	Hausner Ratio
F1	0.265±0.01	0.332±0.02	22.45±0.01	10.2	1.12
F2	0.286±0.01	0.367±0.01	25.08±0.02	13.5	1.16
F3	0.274±0.02	o.345±0.02	22.94±0.01	13.6	1.16
F4	0.288±0.03	0.326±0.03	18.46±0.02	23.5	1.17
F5	0.269±0.0.2	0.353±0.02	25.40±0.0.3	14.3	1.38
F6	0.285±0.01	0.344±0.01	21.35±0.01	13.4	1.26
F7	0.305±0.02	0.361±0.02	22.66±0.03	15.3	1.23
F8	0.292±0.01	0.358±0.01	23.28±0.01	18.8	1.33

All values are expressed as average ± S.D. (n=3)

Compatibility studies

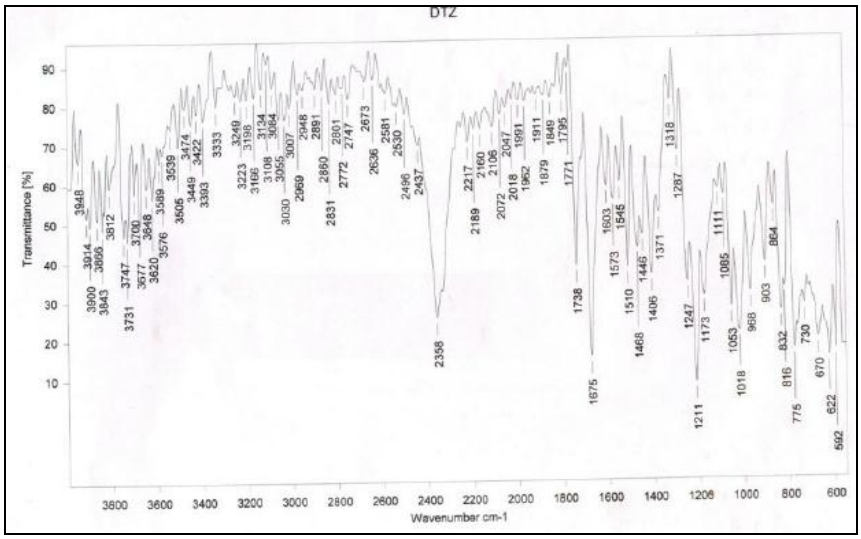

Figure No. 1: IR Spectra of Diltiazem HCl

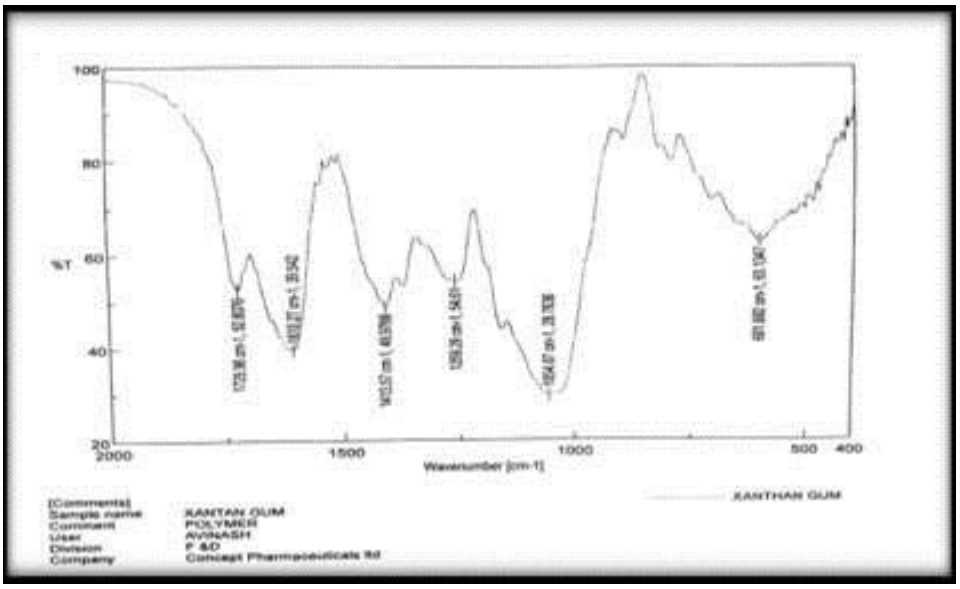

Figure No. 2: IR Spectra of Xanthan gum

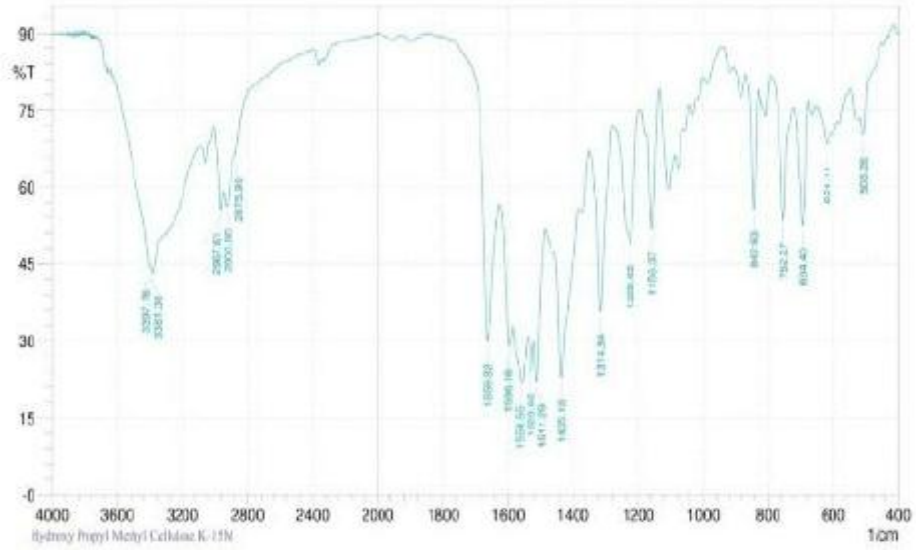

Figure No. 3: IR Spectra of Carbopol 940

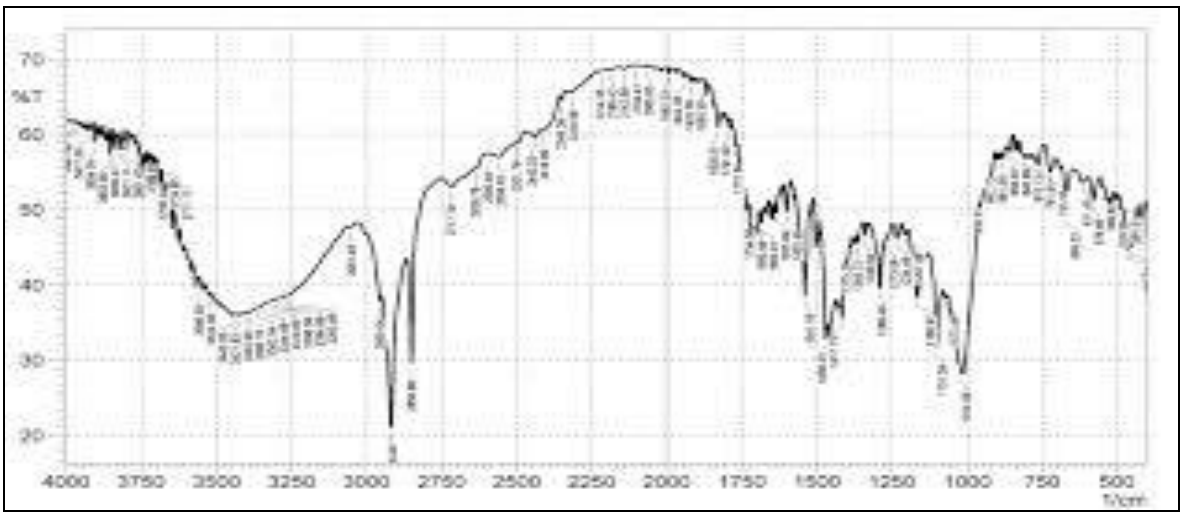

Figure No. 4: IR spectra of drug and excipients

Evaluation of Diltiazem Hydrochloride Tablets:

Table No. 3: Standard physical test for Buccoadhesive Bilayer Tablets

Formulations	Thickness (mm)±S.D	Hardness (kg/cm2)± S.D	Friability (%)±S.D	Weight Variation (gm) ±S.D	Drug content (%w/w)±S.D	Surface pH± S.D
F1	1.61±0.39	5.5±0.49	0.48±1.08	101.0 ±4.97	96.24±0.64	6.46±0.1
F2	2.10±0.43	5.2±0.14	0.52±1.11	101.38± 1.09	99.68±0.68	6.53±0.3
F3	1.99±0.37	4.9±0.19	0.54±1.17	101.44± 1.04	99.93±0.85	6.47±0.2
F4	2.35±0.33	5.1±0.10	0.55±1.23	100.48± 0.96	93.66±0.71	6.70±0.3
F5	2.02±0.49	5.2±0.46	0.50±1.19	101.56± 1.04	93.73±0.88	6.91±0.1
F6	2.22±0.47	5.4±0.12	0.52±1.24	99.98± 1.71	94.82±0.75	7.07±0.3
F7	2.20±0.50	4.8±0.34	0.56±1.30	101.88±1.59	97.76±0.65	6.25±0.2
F8	2.45±0.20	5.6±0.42	0.38±1.40	100.85±1.24	95.45±0.84	6.55±0.3

All the values represent mean ± standard deviation (n=3)

Tablets of all formulations F1 to F8 were evaluated for different parameters such as thickness, hardness, weight variation, friability, and results shown in the table.

Table No. 4: Swelling index of all formulations:

% Swelling Index						
Formulation	**1hr**	**2hr**	**3hr**	**4hr**	**5hr**	**6hr**
F1	17.74±0.259	25.41±0.341	33.47±0.356	37.43±0.289	42.11±0.386	45.42±0.593
F2	19.25±0.211	27.55±0.236	35.8±0.179	40.2±0.349	45.19±0.451	48.33±0.209
F3	25.00±0.282	29.76±0.412	39.56±0.439	44.76±0.103	57.14±0.198	60.61±0.543
F4	35.56±0.542	40.42±0.459	48.86±0.389	54.39±0.208	60.65±0.395	65.53±0.502
F5	35.96±0.305	42.11±0.412	46.78±0.403	50.83±0.573	54.52±0.406	58.33±0.325
F6	37.65±0.197	41.32±0.365	50.76±0.428	56.98±0.438	62.02±0.311	63.76±0.543
F7	40.45±0.231	43.12±0.103	54.73±0.569	70.29±0.183	85.43±0.234	93.00±0.475
F8	48.40±0.138	55.17±0.209	68.14±0.497	76.39±0.282	88.31±0.259	96.87±0.35

All the values represent mean ± standard deviation

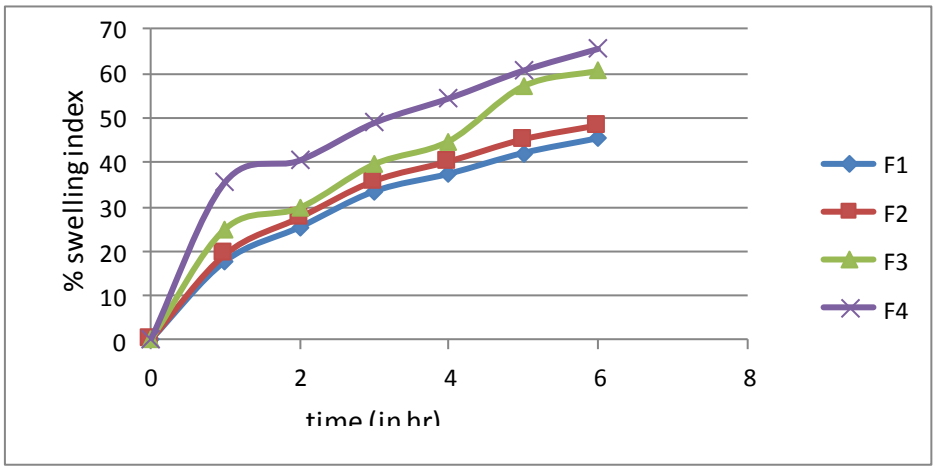

Figure No. 5: Swelling index of F1 to F4 formulations

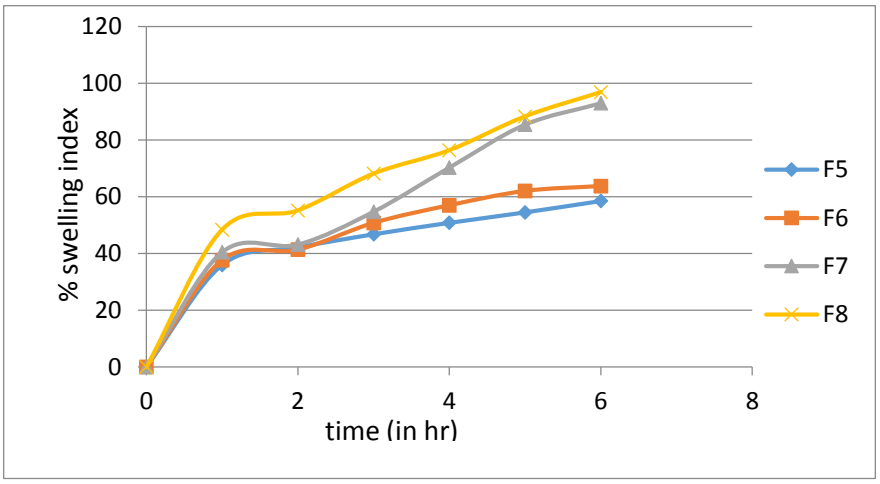

Figure No. 6: Swelling index of F5 to F8 formulations

Mucoadhesive strength values of buccoadhesive bilayer tablets of Diltiazem HCl

Table No. 5: Mucoadhesive strength values of buccoadhesive bilayer tablets of Diltiazem HCl

Formulation	Bioadhesive strength (gm) (mean ± S.D.)	Force of Adhesion (N)
F1	15.486±0.170	1.41
F2	19.58±0.128	1.98
F3	16.45±0.134	1.59
F4	30.54±0.145	2.7
F5	15.98±0.231	1.51
F6	20.64±0.138	2.2
F7	22.45±0.225	2.5
F8	35.76±0.145	2.9

All the values represent mean ± standard deviation.

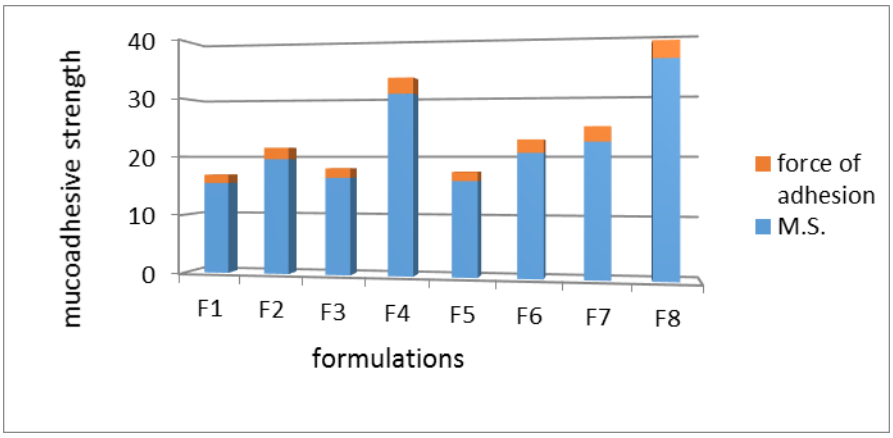

Figure No. 7: Bioadhesion strength of all formulations

By observing the results from batches F1-F8, it was concluded that as the concentration of Carbopol increased the mucoadhesive strength increases. Very strong bioadhesion could damage the epithelial linings of the buccal mucosa.

***In-vitro* Drug release studies:**

Table No. 6: *In-vitro* Dissolution Data of F1, F2, F3, F4 Formulation

Time (min)	Cumulative percent Drug release %			
	F1	F2	F3	F4
60	35.30	19.53	28.61	24.92
120	47.06	29.67	38.82	33.03
180	54.32	38.73	47.01	41.04
240	60.43	47.24	57.64	48.76
300	65.90	55.99	65.21	54.13
360	73.86	63.96	69.49	59.03
420	76.17	69.17	72.95	62.95
480	81.32	76.32	73.60	65.74
540	93.18	83.67	80.17	72.29
600	99.41	87.89	81.84	74.23
660	108.55	93.56	91.15	79.91
720	112.85	98.56	98.90	85.46

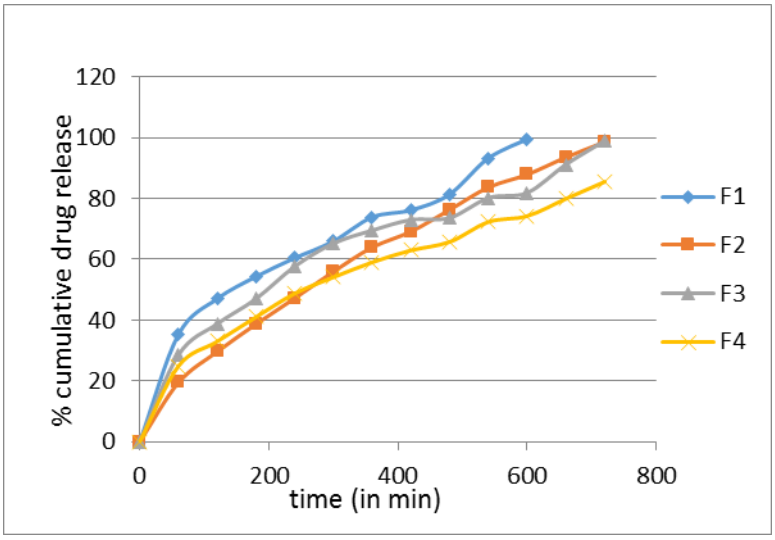

Figure No. 8: *In-vitro* Dissolution Data of F1, F2, F3, F4 Formulation

Table No. 7: *In-vitro* dissolution data of F5 to F8 formulations

Time (min)	Cumulative percent Drug release %			
	F5	F6	F7	F8
60	29.20	21.45	26.29	25.75
120	39.12	28.06	36.21	29.19
180	46.68	35.12	44.80	35.16
240	55.55	42.76	55.51	44.52
300	62.20	50.53	60.94	52.14
360	72.10	56.97	67.17	54.82
420	76.13	64.68	72.80	61.70
480	77.48	68.95	77.60	65.20
540	81.52	69.81	79.79	67.46
600	86.88	72.85	85.67	72.90
660	92.01	73.53	91.40	73.53
720	97.64	79.37	91.63	84.43

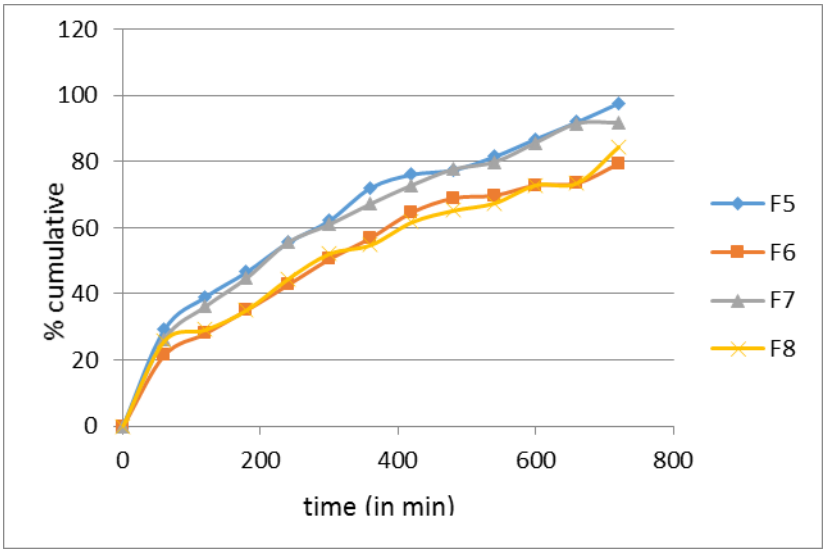

Figure No. 9: *In-vitro* dissolution data of F5 to F8 formulations

Release kinetics:

Table No. 8: Release kinetics

Formulation Code	Zero Order	First-order	Hixon Crowell	Peppas Model	Higuchi Model
F1	0.93	0.46	0.70	0.75	0.98
F2	0.97	0.57	0.80	0.44	0.98
F3	0.90	0.46	0.68	0.65	0.99
F4	0.92	0.48	0.70	0.51	0.99
F5	0.91	0.47	0.69	0.62	0.99
F6	0.92	**0.52**	0.73	0.40	0.98
F7	0.91	**0.48**	0.71	0.45	0.99
F8	0.93	**0.50**	0.72	0.42	0.99

The model fitting for percent cumulative release was done using PCP dissolution software to find the best fits kinetic equation for the dissolution profile. As observed from table no 21, the values of correlation coefficients (r^2) for all formulations were enough to evaluate the drug dissolution behavior. The values of the release of exponent (n) were found to be a function of retardant polymer used and the Physico-chemical nature of the drug. The values of release exponent (n), the kinetic rate constant (k), and correlation coefficient (r^2) as calculated.

Higuchi Plot

The graph was plotted between cumulative percent release and the square root of time. The regression values for drug release profiles of formulations F2 was found to be 0.98. This indicates that diffusion is the mechanism of drug release from the system.

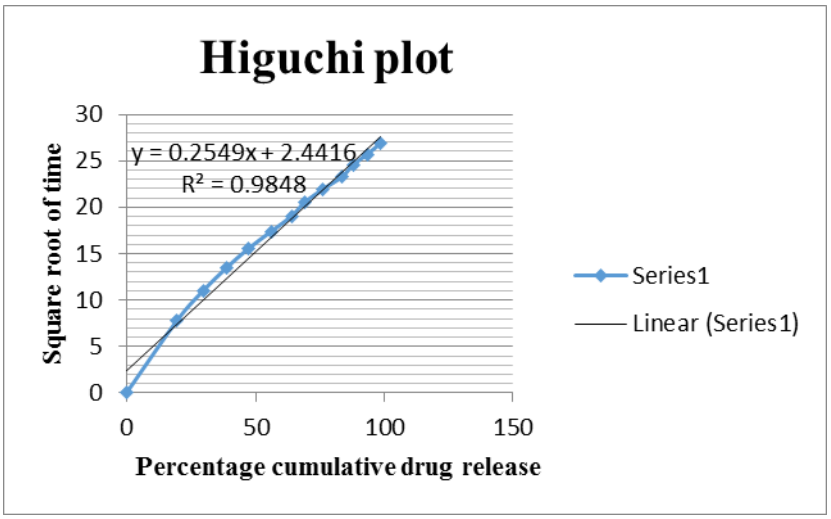

Figure No. 10: Higuchi plot of optimum batch F2

Evaluation Parameter of Optimized Formulation after stability study

Table No. 9: Evaluation Parameter of Optimized Formulation after stability study

Sr. No.	Parameter	Observation	
		Before stability	After stability
1	Hardness	5.2±0.14kg/cm^3	5.3±0.14kg/cm^3
2	Friability	0.50±1.11%	0.52±1.11%
3	Thickness	2.13±0.43mm	2.10±0.43mm
4	Drug contents	99.73±0.68%	98.68±0.68%
5	Weight Variation test	102.38±1.09	101.33±1.09
6	Bioadhesive strength	0.264±0.001	0.243±0.001
7	Surface pH	6.53±0.3	6.22±0.3

Table No. 10: Cumulative percent drug release of optimized formulation F2, before and after stability

	Observation	
Time (min)	**Before stability study (%)**	**After stability study (%)**
60	19.53	19.52
120	29.67	29.60
180	38.73	38.68
240	47.24	47.20
300	55.99	55.90
360	63.96	63.90
420	69.17	69.10
480	76.32	76.28
540	83.67	83.60
600	87.89	87.85
660	93.56	93.50
720	98.56	98.52

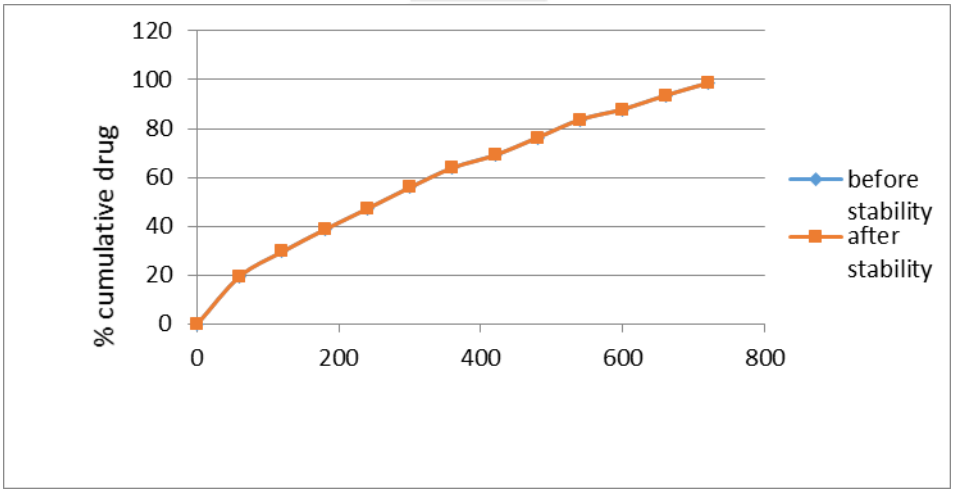

Figure No. 11: Cumulative percent drug release of optimized formulation F2, before and after stability

Dissolution profile of formulation F2 before and after stability

The UV spectrum of Diltiazem HCL in water showed maximum absorption at 235 nm. Hence, Drug used in the formulation was found to be pure. The bulk densities of dry powder

blends of all formulations were found to be in the range of 0.265-0.305gm/cm^3 and tapped densities were found to be in the range of 0.326-0.367gm/cm$^{3.}$ This indicates a good packing capacity of powder blends. Thus it can be concluded that powder of all batches possessed good flow characteristics. In all formulations, Hausner's ratios were found between 1.12 to 1.33 that indicates good flow, and the formulation having Hausner's ratios more than 1.25 requires adding glidant to improve flow properties. The values of Carr's index below 16 usually show good flow characteristics, but reading above 23 indicates poor flow ability. Carr's indexes of all the formulations were found between 10.2 to 23.5 that indicates excellent to passable flow properties. Formulation F4 having Carr's index more 23.5 which indicates poor flow properties and the presence of more fine particles. Values of the angle of repose≤25 generally indicate the free-flowing material and angle of ≥40 suggest a poor flowing material. The angle of repose is indicative of the flowability of the material. The angle of repose of all formulations fell within the range of 18.46 to 25.40 *i.e.* dry powder blends were of good properties. Tablets of all formulations were evaluated for different parameters such as thickness. Hardness. Weight variation. Drug content and friability and results are shown in the table.

Tablet hardness was determined by using Monsanto hardness tester. The hardness of three tablets of each tablet was determined. Hardness values of the formulation ranged from 4.8 to 5.6 kg/cm^2, which indicates good strength of the tablet. Tablet friability was determined by Roche friabilator and weight loss was calculated and represented in the terms of percent friability. Friability values of all the formulation were less than 1%, indicating good strength of tablet. In the weight variation test, the pharmacopoeial limit for percent of deviation for tablets weighing less than 130 is not more than 10%. The average percent deviation of all tablets was found to be within the limit and hence all formulation passes the weight variation test. The thickness of the tablets was determined using Vernier caliper. The thickness of tablets ranged from 1.61 to 2.45 mm. The swelling of a polymer depends upon the degree of hydration of polymer i.e. water uptake. As time increases, the swelling index was increased, because weight gain by tablet was proportional to the rate of hydration up to 6 hrs. Moisture absorption was increased as time increases. The increasing moisture absorption may be due to an increased concentration of polymer mixture from F1-F8. The highest adhesion force i.e. the highest strength of mucoadhesive bonds (2.197N) was proposed by batch F8 i.e. the formulation containing Xanthan gum, Carbopol, HPMC and the force of adhesion was proposed by batch F-1 i.e. the formulation containing least amount of xanthan gum, HPMC,

Carbopol. By observing the results from batches F1-F8, it was concluded that as the concentration of Carbopol increased the mucoadhesive strength increases. Very strong bioadhesion could damage the epithelial linings of the buccal mucosa.

The *in-vitro* drug release of all formulations was also compared and evaluated. All the eight formulations prepared were subjected to *in-vitro* release studies and results are shown in table. The cumulative percentage Drug release of F1 at the end of 9 hrs was found to be 99.41%. The release was faster in F1 than all the formulations. The cumulative percentage drug release of F2 at the end of 12 hours is 98.56%, F3 is 98.90%, F4 is 85.46%, F5 is 92.01%,F6 is 73.53%,F7 is 91.40%,F8 is 73.53% . F1 batch shows 99.41 % of drug release in 9 hours this is not a suitable pattern of drug release as the formulation is sustained release. F4, F5, F6, F7 and F8 batches show less drug release than other F1, F2, and F3 batches. F3 batch shows the 98.90 % drug release but it has less bioadhesion and more swelling index. Batch F2 shows 98.56% of drug release with optimum bioadhesion and swelling index. Batch F2 is an optimized batch. Hence, by the determination of the in-vitro release Data, it can be concluded that the drug release was faster in the case of F1 with fewer polymers. The formulations containing xanthan gum, HPMC K100, Carbopol 940 in more quantity showed slower release rates when compared to fewer amounts of polymers. The use of xanthan gum (7.5mg), HPMC K100(7.5mg), Carbopol 940(12.5) polymers showed proper sustained release of the drug. The stability studies were carried out on optimized formulation f2. The formulation was stored at 40^{o}C/ 75^{o} % relative humidity for 90 days. After 90 days, samples were withdrawn and evaluated for thickness, hardness, drug release.

There were no considerable changes in physical parameters of tablets such as thickness, the hardness of formulation f2 after accelerated stability study.

CONCLUSION

In the present study, the attempt has been made to develop the novel buccoadhesive drug delivery system in the form of bilayer tablets of Diltiazem HCL to achieve the prolonged therapeutic effect by continuously releasing the medicament over an extended period. It can be concluded that this study has demonstrated direct compression technique was suitable for producing bilayered buccal tablets. Diltiazem HCL can be successfully penetrated through the buccal membrane. The formulated Diltiazem HCL buccal tablets showed a significant

increase in oral bioavailability. Higher bioavailability would be due to the avoidance of first-pass hepatic metabolism by intestinal lymphatic transport, which circumvents the liver.

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