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DESIGN AND CHARACTERIZATION OF BUCCOADHESIVE TABLETS OF VERAPAMIL HYDROCHLORIDE

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ABSTRACT

The aim of the study is to design and characterization of buccoadhesive tablet of verapamil hydrochloride Verapamil Hydrochloride is a calcium channel blocker and class IV antiarrhythmic agent used in the supraventricular arrhythmias, and in the management of angina pectoris, hypertension and myocardial infarction. Buccal tablets of Verapamil Hydrochloride were formulated using four mucoadhesive polymers namely, Carbopol 934 P, HPMC K4M, Hydroxy ethyl cellulose and Sodium corboxymethylcellulose carried out studies for weight variation, thickness, hardness, content uniformity, swelling index, Bioadhesive strength and in vitro drug release. The cumulative % of drug release of formulation F6 was 97.01. In-vitro releases of F6 was found to be diffusion controlled and followed zero order kinetics. The stability studies of formulation F6 showed that there was no significant change in adhesive strength, in-vitro release when stored at room temperature and 40oC, for a period of 30 days. The formulation F6 containing 45 mg Carbopol 934 P and 95 mg Hydroxyethyl cellulose are considered as a optimized formulations with respect to bioadhesive strength (26.5gm), and in vitro drug release (97.01%). The drug release pattern of this formulation was found to be non-fickian and approaching zero order kinetics. Stability study of the optimized formulation was carried out and there was no significant change with respect to adhesive strength and in vitro drug release.

KEYWORDS: Verapamil Hydrochloride, Bioadhesive strength, Buccal tablets, swelling index.

INTRODUCTION

The term ‘bioadhesive’ describes materials that bind to biological substrate, such as mucosal membranes. Adhesion of bioadhesive drug delivery devices to mucosal membranes lead to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug. In addition, bioadhesive dosage forms have been used to target local disorder at the mucosal surface (e.g. mouth ulcers) to reduce the overall dosage required and minimize side-effects that may be cpused by systemic administration of drugs. Drug absorption into the oral mucosa is mainly via passive diffusion into the lipoidal membrane.[1,2] Compounds with partition coefficient in the range 40-2000 and pK_a 2-10 are considered optimal to be absorbed through buccal mucosa. Compounds administered by buccal route include steroids, barbiturates, papain, and trypsin etc. Drugs can be absorbed from the oral cavity through the oral mucosa either by sublingual or buccal route. Absorption of therapeutic agents from these routes overcomes premature drug degradation within the gastrointestinal tract as well as active drug loss due to first-pass hepatic metabolism that may be associated with oral route of administration.[3] In general, rapid absorption from these routes is observed because of the thin mucus membrane and rich blood supply. After absorption, drug is transported through the deep lingual vein or facial vein which then drains into the general circulation via the jugular vein, bypassing the liver and thereby sparing the drug from first-pass metabolism. Since sublingual administration of drugs interferes with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration. On the other hand, the duration of buccal drug administration can be prolonged with saliva activated adhesive polymers without the problems of sublingual administration. Verapamil Hydrochloride is a calcium

channel blocker and class IV antiarrhythmic agent used in the supraventricular arrhythmias, and in the management of angina pectoris, hypertension and myocardial infarction. After oral administration, drug undergoes extensive first pass metabolism, and it shows variable absorption from GIT.[3,4] Bioavailability after oral administration is 20%. Since this drug has a short elimination half-life of 2-8 hours and is eliminated rapidly, repeated daily administration are required to maintain effective plasma levels. It has been suggested that drugs with biological half lives in the range of 2-8 hours are good candidates for sustained release formulations.

Buccal route offers several advantages such as
By passing the first pass metabolism
Rapid absorption
Ease of administration and termination of therapy
Buccal route offers several advantages for Dimenhydrinate such as
Verapamil Hydrochloride have pK_a value 8.6 are considered optimal to be absorbed through buccal mucosa.
By the buccal rout the drug Verapamil Hydrochloride has passing the first pass metabolism.
Buccal routes is beneficial in case of Verapamil Hydrochloride to overcome the problem of bioavailability
Hence, in this work, an attempt was made to formulate buccal tablets of Verapamil Hydrochloride. In order to avoid extensive first pass metabolism, and to increase bioavailability.[5,6,7]

MATERIALS AND METHODS

Analytical grades chemicals and reagents were used. Excipients used in this study are Verapamil Hydrochloride, Carbopol 934, HPMC K4M, Hydroxy ethyl cellulose, Sodium CMC, Talc, Aspartame, Potassium dihydrogen ortho phosphate, Sodium Hydroxide.

PREPARATION OF STANDARD CURVE OF VERAPAMIL HYDROCHLORIDE[1]

100 mg of Verapamil Hydrochloride was dissolved in 100 ml calibrated volumetric flask and completing to volume with phosphate buffer pH= 6.8. From this 10ml was pipetted out in 100 ml calibrated volumetric flask and dilution was made with phosphate buffer pH= 6.8. From this stock solution 10ml was pipetted out in 100ml calibrated volumetric flask and dilution was made with phosphate buffer pH= 6.8. From this solution 1 ml, 2ml, 3ml, 4ml…up to 10ml was pipetted out in different 10 ml volumetric flask and the final volume was making up with phosphate buffer pH= 6.8. The absorbance was noted at 278 nm. The absorbance values are shown in Table No.3 and Fig No.1

PREPARATION OF STANDARD CURVE OF VERAPAMIL HYDROCHLORIDE[7-16]

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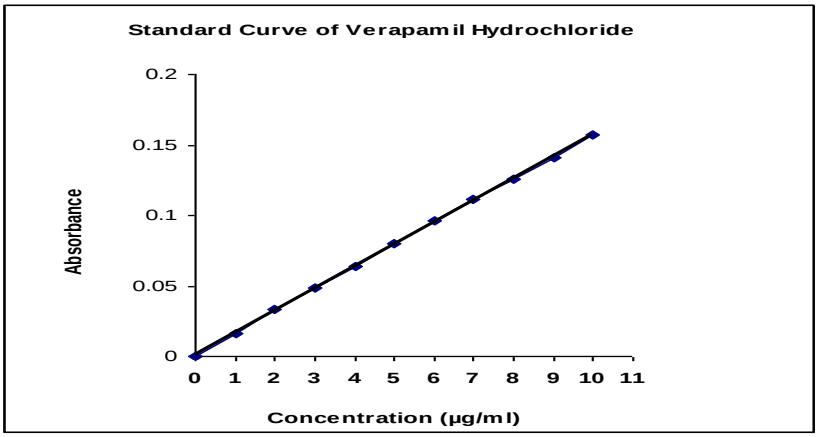

Slope:-0.0159
R^2:-0.9998

Fig. No. 1:- Standard Curve of Verapamil Hydrochloride.

FORMULATION OF BUCCOADHESIVE TABLET[17-22]

Buccoahesive tablets containing Verapamil Hydrochloride were prepared by direct compression technique using variable concentration of carbopol 934 P, HPMC K4M, Hydroxy ethyl cellulose, and Na CMC.

The entire ingredient except talc was blended uniformly. After sufficient mixing of drug as well as other components, talc was added and further mixed for additional 2-3 minutes, the tablet were compressed with 8mm punch. The weight of the tablets was kept constant for formulations F1 to F9. The formulations are shown in table No4.

EVALUATION OF BACCOADHESIVE TABLETS[22-74]

All the prepared buccoadhesive tablets were evaluated for following parameters.

Weight Variation[32,33,34]

20 tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table No.1 and none deviate by more than twice the percentage The results are shown in table no.5.

Table No. 1: Percentage deviation allowed under weight variation test.

Average weight of tablet (mg)	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

Thickness[42]

Three tablets were selected randomly from each batch and thickness was measured by using vernier caliper. The results are shown in table no.5

Friability[60]

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

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

Where, % F = friability in percentage
W_o = Initial weight of tablet
W = weight of tablets after revolution
The results are shown in table no.5

Hardness[68]

Hardness was measured using Monsanto hardness tester. For each batch two tablets were tested. The results are shown in table no.6.

Drug content[58]

Weigh and powder 20 tablets weigh accurately a quantity of the powder equivalent to 100 mg of Verapamil Hydrochloride, shake with 150ml of phosphate buffer pH 6.8 for 10 minutes, add sufficient phosphate buffer pH 6.8 to produce 200ml and filter. Dilute 10ml of filtrate to 100ml with water and measure the absorbance of the resulting solution at maximum at about 278 nm. The results are shown in table no.5

Bioadhesive Strength[71,72,73]

Bioadhesive strength of the tablet was measured on the modified physical balance. The design used for measuring the bioadhesive strength was shown in Fig. No 12. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with phosphate buffer pH 6.8, which was then placed below right side of the balance.

The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and buccoadhesive tablet was established. A preload of 10 mg was placed on the slide for 5 min (preload time) to established adhesion bonding between buccoadhesive tablet and goat buccal mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when Buccoadesive tablet was detached from the goat buccal mucosa. The weight of water required to detach buccoadhesive tablet from buccal mucosa was noted as bioadhesive strength in grams. From the bioadhesive strength following parameter was calculated.

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

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area of tablet (m}^2\text{)}}$$

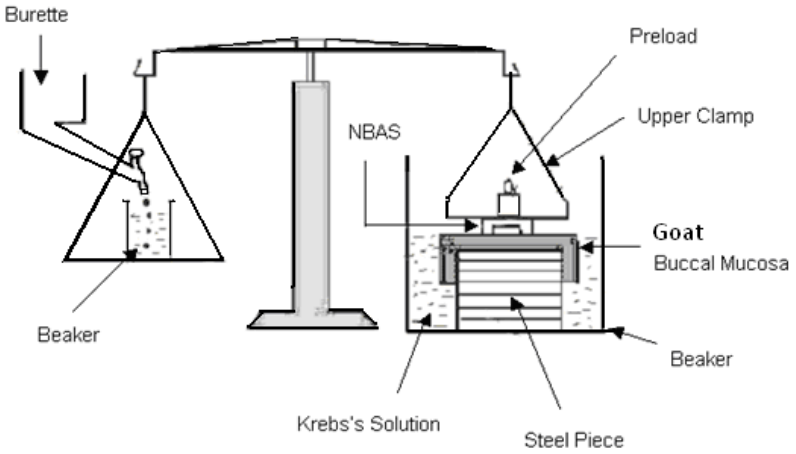

Fig. No. 2: - Physical Balance for measurement of adhesive strength.

Swelling index[47-56]

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet. The results are shown in table no.7.

Method

For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml phosphate buffer pH 6.8 media. After each interval the tablet was removed from beaker and weighed again up to 8 hours. The swelling index was calculated using following formula.

Swelling Index (S.I.) = (Wt-Wo)/Wo

Where, S.I. = Swelling index

W_t = Weight of tablet at time t

W_o = Weight of tablet before placing in the beaker

In Vitro Release Study[45,46]

Standard USP or IP dissolution apparatus have been used to study in vitro release profile using both basket and rotating paddle.

In vitro release rate study of buccoadhesive tablet of Verapamil hydrochloride was carried out using the Apparatus 2 (Basket apparatus) method. Place the tablet in a dry basket at the beginning of each test. Lower the Basket before rotation operates the apparatus immediately at 50 rpm. Medium used for release rate study was 900ml phosphate buffer pH 6.8 during the course of study whole assembly was maintained at 37±0.5 ^{o}C. Withdraw a 5 ml of sample at time interval of 1,2,3,4, ---up to 8 hr and replaced with 5 ml of fresh dissolution medium.

The withdrawn samples were dilute with dissolution medium and then filter it with whattman filter paper and assayed at 278 nm.

The % release of Verapamil HCL was calculated. The observations for different batches are shown in table no. 9 to 11. The percentage release of Verapamil HCL with respect to time for each batch, are graphically shown below in fig no.6 to 8.

Data analysis

The release data obtained from various batches were studied with respect to effect of drug: polymer ratio, diluents ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches were fitted to zero order, first-order, Higuchi, Hixon-Crowell, Korsemeyer and Peppas, and Weibull models to ascertain the kinetic modeling of drug release. The results are shown in table no.22.

RESULTS AND DISCUSSION

Buccoadhesive tablets of Verapamil Hydrochloride were prepared and evaluated to increase its local action and bioavailability.

In the present study nine formulations with variable concentration of polymer were prepared and evaluated for physicochemical parameter and in vitro dissolution studies. The formulated batches were shown in table no 4.

PREFORMULATION STUDIES

Interparticulate interactions that influence the bulk properties of powder flow. A comparison of the bulk density and tapped density can give a measure of the

relative importance of this interaction in a given powder; such a comparison is often used as an index of the ability of the powder to flow. The bulk density and tapped density was found to be 0.416 and 0.526 gm/cm^3 respectively.

A simple indication of ease with which a material can be induced to flow is given by application of a compressibility index. The value for compressibility index of Verapamil Hydrochloride was found to be 20.91 that reflect the fair passable flow property of Verapamil Hydrochloride, which was supported by the Hauser's ratio of 1.264.

The physical characterization of the Polymer was done by evaluating them for the physical characteristics such as bulk density, tapped density, compressibility index, and Hauser's ratio. All the excipients were found to have desirable physical characteristics.

a) Melting Point Determination

Melting point of Verapamil Hydrochloride was found to be in the range 131-133^{o}c, which complied with IP standards, indicating purity of the drug sample.

b) Solubility

Verapamil Hydrochloride was found to be soluble in water, phosphate buffer 6.8 pH, chloroform and water.

C) Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied.

The peaks obtained in the spectra of each samples correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation contents. The spectra for all samples were shown in Fig. No.8 to Fig. No.11.

d) Physical properties

Physical properties of Verapamil Hydrochloride and Buccoadhesive polymers like bulk density, tapped density, % compressibility and Housner ratio results shown in Table No2.

Table 2: Results of bulk and tapped density.

Parameter	Results				
	Verapamil HCL	**Carbopol 934P**	**HPMC K_4M**	**Hydroxy ethyl cellulose**	**Na CMC**
Bulk Density (gm/cm^3)	0.416	0.186	0.312	0.454	0.476
Tapped Density (gm/cm^3)	0.526	0.289	0.487	0.588	0.666
Compressibiliy Index	20.91	35.64	35.93	22.78	28.52
Hauser's Ratio	1.264	1.55	1.560	1.29	1.399

STANDARD CURVE OF VERAPAMIL HCL

Standard curve of Verapamil Hydrochloride was determined by plotting concentration v/s absorbance at 278 nm and it follows the Beer's law. The results were shown in Table No.3, the r^2 value was 0.9998 and slope was 0.0159.

Hardness test

The hardness of tablets of each batch ranged between 6.47 to 7.68 kg/cm^2 (Table No.6). This ensures good handling characteristics for all batches.

Friability Test

The values of friability test were tabulated in Table No.5. The Percentage friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight Variation Test

The percentage weight variations for all formulations were tabulated in Table No.5. All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the standard pharmacopoeia limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content Uniformity

The percentage of drug content for F1 to F9 was found to be between 98.11% and 99.74% of Verapamil Hydrochloride, it complies with official specifications. The results were shown in Table No.5

Swelling Index

Swelling index was performed for all the batches (F1 to F9) up to 6 hr. The results of swelling index were shown in Table No.7 Swelling index against time (hrs) was plotted in Fig. No.4

From the above results it was concluded that swelling increases as the time proceeds because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch F4 containing Carbopol 934P with HEC. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as adhesion capability.

The swelling values of the matrices with Carbopol 934 P and other polymers like HPMCK4M, HEC and Sodium CMC showed increase in swelling value with increase percentage of Carbopol 934 P in the formulation Table No.7.

Bioadhesive Strength

The Bioadhesive property of Verapamil Hydrochloride tablet of containing varying proportion of polymers was determined with a view to develop a good adhesiveness without any problems. The bioadhesion characteristics were affected by the type and concentration of the bioadhesive polymers (Table No.18). The highest adhesion force i.e. highest detachment force (33.1 gm) was proposed by F7 containing Carbopol 934 P and Na CMC.

In-vitro Dissolution Study

All the formulations of prepared Buccoadhesive tablets of were Verapamil Hydrochloride subjected to in vitro release studies these studies were carried out using dissolution media of Phosphate buffer 6.8 pH.

The results of in-vitro release studies were plotted in different model of data treatment as follows

Cumulative percent drug released v/s time (zero order rate kinetics)

Log cumulative percent drug retained v/s time (First Order rate Kinetics)

Cumulative percent drug released v/s square root of time (Higuchi's Classical Diffusion Equation)

Log of cumulative % release v/s log time (Peppas Exponential Equation)

(Percentage retained)$^{1/3}$ v/s time (Hixson –Crowell Erosion Equation)

In vitro release obtained for formulations F1 to F9 were tabulated in table No.19 to 21. Fig. No. 16 to 18 shows the plot of cumulative % drug released as a function of time.

The in vitro dissolution was carried out for all the batches. The release of Verapamil Hydrochloride from Buccoadhesive tablet varied according to the type and concentration of polymer. The cumulative % release of batch F1, F2 and F3 were found to be 59.09%, 67.47% and 76.86% in 8 hrs respectively. From above observation it was concluded that polymer concentration increases duration of release increases.

The cumulative % release of batch F4, F5 and F6 were found to be 69.73%, 86.15% and 97.01% in 8 hrs respectively. From the above observation it was concluded that the polymer concentration increases, the duration of release also increases.

The cumulative % release of batch F7, F8, and F9 were found to be 59.32%, 78.33% and 89.66% in 8 hrs respectively.

From the result it was concluded that the increasing polymer concentration of Carbopol 934 the release of drug might be slower.

STABILITY STUDIES

Stability studies of the optimized formulations were performed at room temperature and at 40^{o}C a period up to 30 days. The samples were withdrawn after periods of 30 days and were analyzed for its appearance, hardness, friability, drug content and in vitro release. The results are shown in table. no. 23 & 24.

Table No- 3: Preparation of Standard Curve of Verapamil Hydrochloride at 278 nm by UV Spectrometry.

S. no.	Concentration µg/ml	Absorbance
0	0	0
1	1	0.016
2	2	0.033
3	3	0.049
4	4	0.064
5	5	0.080
6	6	0.096
7	7	0.111
8	8	0.126
9	9	0.141
10	10	0.157

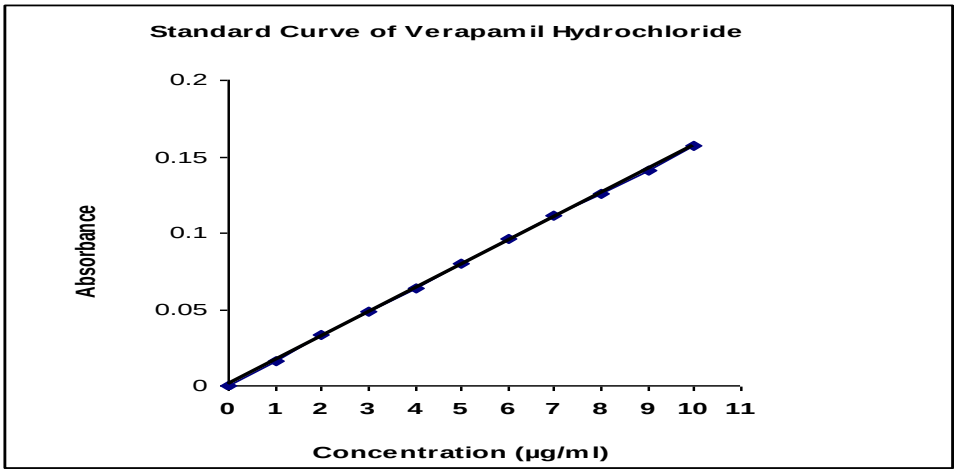

Fig no. 3: Standard Curve of Verapamil Hydrochloride.

Table No- 4: Composition of Buccoadhesive Tablets of Verapamil Hydrochloride.

Sr. no.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Verapamil HCL	50	50	50	50	50	50	50	50	50
2	Carbopol-934	75	60	45	75	60	45	75	60	45
3	HPMC-K4M	65	80	95	-	-	-	-	-	-
4	HEC	-	-	-	65	80	95	-	-	-
5	Na-CMC	-	-	-	-	-	-	65	80	95
6	Aspartame	6	6	6	6	6	6	6	6	6
7	Talc	4	4	4	4	4	4	4	4	4

*All the quantities are in mg.
Total weight of one tablet is 200 mg

Table No- 5: Physical Properties of Tablets of Batch F1 to F9.

Batch no.	Weight Variation (mg)	Thickness (mm)	Friability (%)	Drug content uniformity (mg)
F1	pass	3.06±0.057	0.49	98.36
F2	pass	3.13±0.057	0.30	98.98
F3	pass	3.1±0.10	0.39	98.56
F4	pass	3.16±0.057	0.49	98.11
F5	pass	3.13±0.11	0.49	98.98
F6	pass	3.16±0.057	0.29	99.74
F7	pass	3.23±0.057	0.39	98.48
F8	pass	3.13±0.057	0.30	99.1
F9	pass	3.06±0.057	0.39	98.74

Each reading is an average of three determinations (Avg.± S.D)

Table No- 6: Result of Hardness of Prepared Buccoadhesive tablet of Batch F1 to F9.

Batch no.	Hardness (kg/cm^2)
F1	6.87±0.035
F2	7.4±0.141
F3	7.07±0.035
F4	6.75±0.070
F5	6.47±0.035
F6	7.11±0.014
F7	6.87±0.035
F8	7.68±0.021
F9	6.55±0.070

Each reading is an average of two determinations (Avg.± S.D)

Table No- 7: Swelling Index of Tablets of Batch F1 to F9.

Batch no.	Time (hrs)						
	0	1	2	3	4	5	6
F1	0	0.112	0.346	0.595	0.848	0.917	1.117
F2	0	0.119	0.223	0.409	0.657	0.885	1.033
F3	0	0.115	0.395	0.620	0.759	0.895	0.985
F4	0	0.126	0.339	0.577	0.864	0.907	1.126
F5	0	0.129	0.248	0.425	0.679	0.918	1.114
F6	0	0.115	0.225	0.427	0.615	0.855	0.975
F7	0	0.119	0.330	0.569	0.827	0.904	1.119
F8	0	0.117	0.269	0.421	0.661	0.897	0.995
F9	0	0.119	0.368	0.655	0.818	0.866	0.971

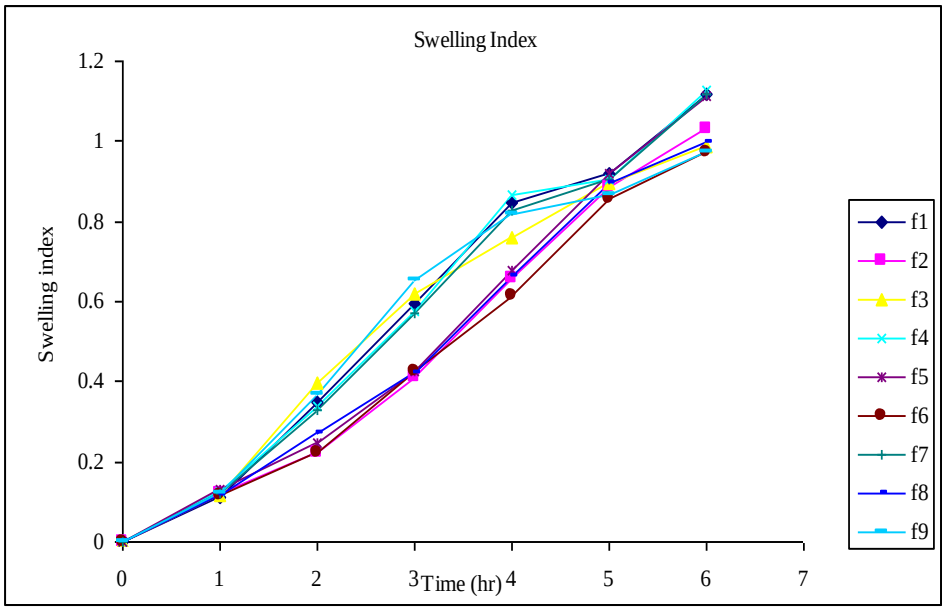

Fig. No. 4:- Graph of the Swelling index versus Time (hr).

Table No- 8: In-vitro Buccoadhesive strength of batch F1 to F9.

Batch code	Buccoadhesive strength (g)
F1	22.6
F2	19.7
F3	22.3
F4	24.1
F5	20.1
F6	26.5
F7	30.9
F8	27.1
F9	33.1

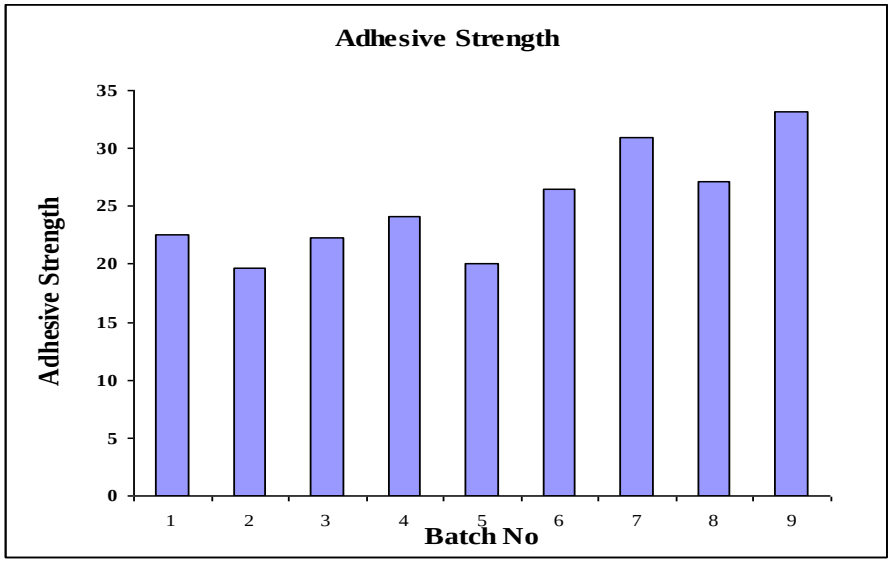

Fig. No. 5:- Column graph of the adhesive strength (gm)

Table no- 9: Dissolution profile of batch F1, F2 and F3.

Time (hrs)	Cum.% Drug release	Cum.% Drug release	Cum. % Drug release
0	0	0	0
1	11.66	12.67	13.47
2	14.49	17.77	21.28
3	23.66	29.77	34.18
4	32.26	42.00	47.20
5	41.88	51.62	56.83
6	49.24	59.77	65.20
7	54.56	60.86	73.47
8	59.09	67.47	76.86

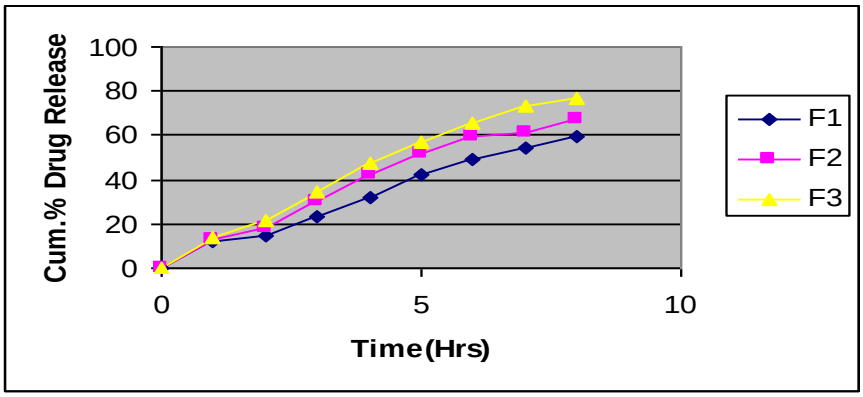

Fig. No. 6:- Graph of the Cum. % drug release versus Time (hr).

Table No- 10: Dissolution profile of batch F4, F5 and F6.

Time (hrs)	Cum.% Drug release	Cum.% Drug release	Cum. % Drug release
0	0	0	0
1	12.79	14.83	16.18
2	18.67	20.26	28.18
3	34.30	40.64	48.45
4	51.39	60.00	65.77
5	57.16	69.84	75.50
6	62.49	78.79	89.77
7	68.83	85.01	96.79
8	69.73	86.15	97.01

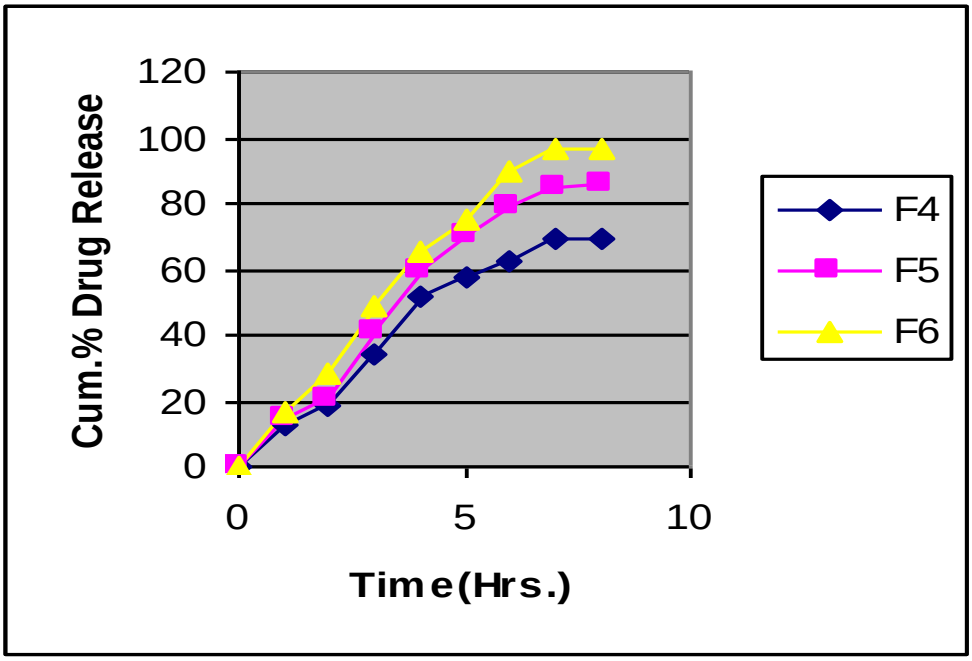

Fig. No. 7:- Graph of the Cum. % drug release versus Time (hr)

Table No- 11: Dissolution profile of batch F7, F8 and F9.

Time (hrs)	Cum.% Drug release	Cum.% Drug release	Cum. % Drug release
0	0	0	0
1	11.88	13.69	14.03
2	16.86	19.81	26.37
3	33.39	37.69	42.45
4	44.26	49.69	63.39
5	50.83	57.39	75.62
6	53.09	68.83	81.84
7	57.84	75.16	88.75
8	59.32	78.33	89.66

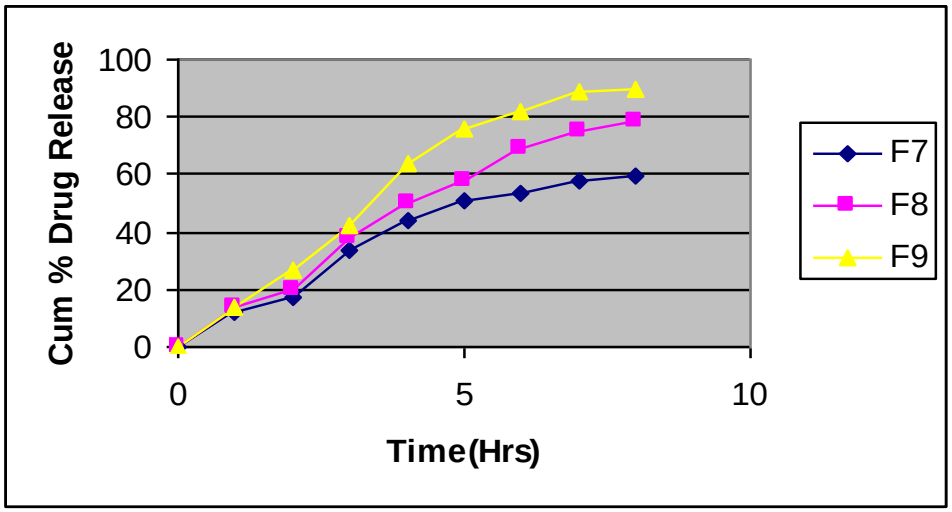

Fig. No. 8:- Graph of the Cum. % drug release versus Time (hr)

Table No-12: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F1 formulation.

Time (hr)	Root T	Log T	Cum. % drug release	Cum.% drug retained	Log Cum. % drug release	LogCum. %drug retained	(%retained)$^{1/3}$
1	1.00	0.000	11.66	88.34	1.067	1.946	4.453
2	1.4142	0.3010	14.49	85.51	1.161	1.932	4.405
3	1.7321	0.4771	23.66	76.34	1.374	1.883	4.242
4	2.00	0.6020	32.26	67.74	1.508	1.831	4.076
5	2.236	0.6989	41.88	58.12	1.622	1.764	3.873
6	2.4494	0.7781	49.24	50.76	1.692	1.706	3.703
7	2.6457	0.8450	54.56	45.44	1.737	1.658	3.568
8	2.8284	0.9030	59.09	40.91	1.772	1.612	3.445

Table No- 13: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F2 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	12.67	87.33	1.103	1.941	4.436
2	1.414	0.3010	17.77	82.23	1.250	1.915	4.348
3	1.732	0.4771	29.77	70.23	1.474	1.846	4.125
4	2.000	0.6021	42.00	58.00	1.623	1.763	3.871
5	2.236	0.6990	51.62	48.38	1.713	1.685	3.640
6	2.449	0.7782	59.77	40.23	1.776	1.605	3.426
7	2.646	0.8451	60.86	39.14	1.784	1.593	3.395
8	2.828	0.9031	67.47	32.53	1.829	1.512	3.192

Table No- 14: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F3 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	13.47	86.53	1.129	1.937	4.423
2	1.414	0.3010	21.28	78.72	1.328	1.896	4.285
3	1.732	0.4771	34.18	65.82	1.534	1.818	4.038
4	2.000	0.6021	47.20	52.8	1.674	1.723	3.752
5	2.236	0.6990	56.83	43.17	1.755	1.635	3.508
6	2.449	0.7782	65.20	34.8	1.814	1.542	3.265
7	2.646	0.8451	73.47	26.53	1.866	1.424	2.985
8	2.828	0.9031	76.86	23.14	1.886	1.364	2.850

Table No- 15: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F4 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	12.79	87.21	1.107	1.941	4.434
2	1.414	0.3010	18.67	81.33	1.271	1.910	4.332
3	1.732	0.4771	34.30	65.7	1.531	1.818	4.035
4	2.000	0.6021	51.39	48.61	1.717	1.687	3.650
5	2.236	0.6990	57.16	42.84	1.757	1.632	3.499
6	2.449	0.7782	62.49	37.51	1.796	1.574	3.347
7	2.646	0.8451	68.83	31.17	1.838	1.494	3.147
8	2.828	0.9031	69.73	30.27	1.843	1.481	3.117

Table No- 16: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F5 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	14.83	85.17	1.171	1.930	4.400
2	1.414	0.3010	20.26	79.74	1.307	1.902	4.304
3	1.732	0.4771	40.64	59.36	1.609	1.773	3.901
4	2.000	0.6021	60.00	40.00	1.778	1.602	3.420
5	2.236	0.6990	69.84	30.16	1.844	1.479	3.113
6	2.449	0.7782	78.79	21.21	1.896	1.327	2.768
7	2.646	0.8451	85.01	14.99	1.929	1.176	2.466
8	2.828	0.9031	86.15	13.85	1.935	1.141	2.402

Table No- 17: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F6 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	16.18	83.82	1.209	1.923	4.376
2	1.414	0.3010	28.18	71.82	1.450	1.856	4.157
3	1.732	0.4771	48.45	51.55	1.685	1.712	3.722
4	2.000	0.6021	65.77	34.23	1.818	1.534	3.247
5	2.236	0.6990	75.50	24.50	1.878	1.389	2.904
6	2.449	0.7782	89.77	10.23	1.953	1.010	2.171
7	2.646	0.8451	96.79	3.21	1.986	0.507	1.475
8	2.828	0.9031	97.01	2.99	1.987	0.476	1.441

Table No-18: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F7 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	11.88	88.12	1.075	1.945	4.450
2	1.414	0.3010	16.86	83.14	1.227	1.920	4.365
3	1.732	0.4771	33.39	66.61	1.524	1.824	4.054
4	2.000	0.6021	44.26	55.74	1.646	1.746	3.820
5	2.236	0.6990	50.83	49.17	1.706	1.692	3.664
6	2.449	0.7782	53.09	46.91	1.725	1.671	3.607
7	2.646	0.8451	57.84	42.16	1.762	1.625	3.480
8	2.828	0.9031	59.32	40.68	1.773	1.609	3.439

Table No- 19: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F8 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	13.69	86.31	1.136	1.936	4.419
2	1.414	0.3010	19.81	80.19	1.297	1.904	4.312
3	1.732	0.4771	37.69	62.31	1.576	1.795	3.964
4	2.000	0.6021	49.69	50.31	1.696	1.702	3.692
5	2.236	0.6990	57.39	42.61	1.759	1.630	3.493
6	2.449	0.7782	68.83	31.17	1.838	1.494	3.147
7	2.646	0.8451	75.16	24.84	1.876	1.395	2.918
8	2.828	0.9031	78.33	21.67	1.894	1.336	2.788

Table No- 20: In vitro release profile of Verapamil HCL Buccoadhesive tablets of F9 formulation.

Time (hr)	Root T	Log T	Cum.% drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum. % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	14.03	85.97	1.147	1.934	4.413
2	1.414	0.3010	26.37	73.63	1.421	1.867	4.191
3	1.732	0.4771	42.45	57.55	1.627	1.760	3.861
4	2.000	0.6021	63.39	36.61	1.802	1.564	3.320
5	2.236	0.6990	75.62	24.38	1.879	1.387	2.900
6	2.449	0.7782	81.84	18.16	1.913	1.259	2.628
7	2.646	0.8451	88.75	11.25	1.948	1.051	2.241
8	2.828	0.9031	89.66	10.34	1.953	1.015	2.179

Table no- 21: Kinetic values obtained from in-vitro released data of different Verapamil HCL Buccoadhesive tablets formulations.

	Plot of log cum. % drug retained v/s time (first order plot)			Plot of cum. % release v/s time (zero order plot)		
Formulation	Slope	First order rate constant k= -slope X 2.303	Regression coefficient	Slope	Rate constant K=-slope	Regression coefficient
F1	-0.0513	0.1181	0.9885	7.3657	-7.3657	0.987
F2	-0.0645	0.1485	0.9847	8.3175	-8.3175	0.9668
F3	-0.0868	0.1999	0.9915	9.6115	-9.6115	0.9821
F4	-0.0725	0.1669	0.9730	8.8062	-8.8062	0.9333
F5	-0.1264	0.2910	0.9832	11.277	-11.277	0.9406
F6	-0.2277	0.5244	0.9378	12.411	-12.411	0.9554
F7	-0.0517	0.1190	0.955	7.1744	-7.1744	0.9156
F8	-0.0919	0.2116	0.9899	9.8851	-9.8851	0.9711
F9	-0.1452	0.3344	0.9843	11.568	-11.568	0.9382

Table no- 22: Kinetic values obtained from in-vitro released data of different Verapamil HCL Buccoadhesive tablets formulations.

	Plot of cum. % drug released v/s time in sq. root (Higuchi matrix)		Plot of log cum. % drug released v/s log time (log T) (peppas)		Plot of (% retained)$^{1/3}$ v/s time (Hixson- Crowell)	
Formulation	Slope	Regression coefficient	Slope	Regression coefficient	Slope	Regression coefficient
F1	28.489	0.9716	0.8602	0.967	-0.1555	0.99
F2	32.601	0.9774	0.8717	0.9768	-0.1881	0.9813
F3	37.585	0.9882	0.8911	0.9903	-0.239	0.9948
F4	34.921	0.9658	0.8984	0.9618	-0.2067	0.9626
F5	44.557	0.9663	0.9486	0.9581	-0.32	0.9785
F6	49.049	0.9819	0.9188	0.983	-0.4637	0.9779
F7	28.628	0.9593	0.8452	0.9535	-0.1548	0.9431
F8	38.783	0.9836	0.9089	0.977	-0.2504	0.9906
F9	45.924	0.9730	0.9488	0.9777	-0.3513	0.9812

Table No- 23: Stability studies of formulation F6 stored at Room temperature.

Time (hr)	Cumulative % Drug Release		
	Initial	After 15 Days	After one month
0	0.00	0.00	0.00
1	16.18	15.05	15.84
2	28.18	24.79	24.90
3	48.45	45.84	44.83
4	65.77	65.09	66.11
5	75.50	80.94	79.13
6	89.77	88.07	87.96
7	96.79	96.56	96.45

8	97.01	96.90	96.79
Hardness	7.11	7.10	7.10
Friability	0.29%	0.40%	0.49%
Drug content	99.74%	99.49%	99.37%
Bioadhesive strength(gm)	26.50	26.49	26.48

Table No- 24: Stability studies of formulation F6 stored at 40ºC.

Time (hr)	Cumulative % Drug Release		
	Initial	After 15 Days	After one month
0	0.00	0.00	0.00
1	16.18	15.96	16.07
2	28.18	25.58	24.79
3	48.45	46.07	45.50
4	65.77	64.18	65.09
5	75.50	78.90	79.92
6	89.77	88.07	88.64
7	96.79	96.56	96.33
8	97.01	96.67	96.56
Hardness	7.11	7.15	7.15
Friability	0.29%	0.20%	0.29%
Drug content	99.74%	99.62%	99.49%
Bioadhesive strength(gm)	26.5	26.48	26.47

SUMMARY AND CONCLUSION

Verapamil Hydrochloride is a calcium channel blocker and class 4 antiarrhythmic agent used in the supraventricular arrhythmias, and in the management of angina pectoris, hypertension and myocardial infarction due to extensive first pass metabolism resulting in less oral bioavailability will be very less and it shows variable absorption from GIT. Buccal route offers several advantages such as rapid absorption, high plasma concentration level and ease of administration and termination of therapy. Hence in the present work Buccoadhesive tablets of Verapamil Hydrochloride were prepared with the objective of avoiding first pass metabolism and controlling the release of drug for prolonged period of time. According to the literature review controlled release formulation would increase the bioavailability and suitable for twice a daily medication. Since, the drug verapamil hydrochloride has biological half-life of 2 to 8 hrs. and undergoes extensive first pass metabolism hence, it was selected as a model drug to formulate buccoadhesive drug delivery system, which is the easiest approach for technical and logical point of view among buccal retentive drug delivery system. For the formulation of oral mucoadhesive tablet various polymers such as Carbopol 934 P, Hydroxypropyl methylcellulose K4 M, Hydroxyethyl cellulose, and Sodium CMC, used as matrix forming and mucoadhesive polymers in different concentration. Tablets were subjected to various evaluation parameters such as drug content, hardness, weight variation, friability, Bioadhesive strength, swelling index, and in vitro drug release study. It was revealed that the tablets of all batches had acceptable physical parameters. Tablets of batch F6 had good Mucoadhesion along with good swelling behavior and in vitro drug release. The formulation F6 containing 45 mg Carbopol 934 P and 95 mg Hydroxyethyl cellulose are considered as a optimized formulations with respect to bioadhesive strength (26.5gm), and in vitro drug release (97.01%). The drug release pattern of this formulation was found to be non-fickian and approaching zero order kinetics. Stability study of the optimized formulation was carried out and there was no significant change with respect to adhesive strength and in vitro drug release.

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