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FORMULATION, DESIGN AND DEVELOPMENT OF BUCCOADHESHIVE TABLETS OF VERAPAMIL HYDROCHLORIDE

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ABSTRACT: Buccoadhesive tablets have long been employed to improve the bioavailability of drugs undergoing significant first pass hepatic metabolism. Verapamil Hydrochloride is widely used in the management of Hypertension, Angina pectoris and Myocardial infraction The present investigation concerns the development of Buccoadhesive tablets of Verapamil Hydrochloride which were designed to prolong the buccal residence time after oral administration. Buccal tablets of Verapamil Hydrochloride were formulated using four mucoadhesive polymers namely, Carbopol 934 P, HPMC K_4M, 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. Formulation of F6 were formulated by using polymers Carbopol 934 P and Hydroxy ethyl cellulose provided controlled release of Verapamil Hydrochloride over period of 8 hrs. 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 40^oC, for a period of 30 days. Formulation of F6 which was formulated by using polymers Carbopol 934 P and Hydroxy ethyl cellulose was established to be the optimized formulation with optimum bioadhesive strength, swelling index & desired in-vitro drug release.
Key words- Verapamil Hydrochloride, Bioadhesive strength ,Buccal tablets, swelling index

INTRODUCTION

In recent years, significant interest has been shown in the development of novel bioadhesive dosage forms for mucosal delivery of drugs that attempt to overcome these limitations.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 used by systemic administration of drugs. Drug absorption into the oral mucosa is mainly via passive diffusion into the lipoidal membrane. 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.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.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. 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.

MATERIALS AND METHODS

Verapamil hydrochloride procured by Acron pharmaceutical ahmedabad , carbopol 934, hydroxypropyl methylcellulose, carboxymethyl cellulose sodium gifted by colorcon Mumbai, India, hydroxy ethyl cellulose Qualigens fine chemicals, mumbai, india aspartame, talc , loba chemie,cochin .

PREPARATION OF STANDARD CURVE OF VERAPAMIL HYDROCHLORIDE: [1-20]

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.

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.13 and Fig. No13. , the r^2 value was 0.9998 and slope was 0.0159.

FORMULATION OF BUCCOADHESIVE TABLET: [21-24]

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 No1.

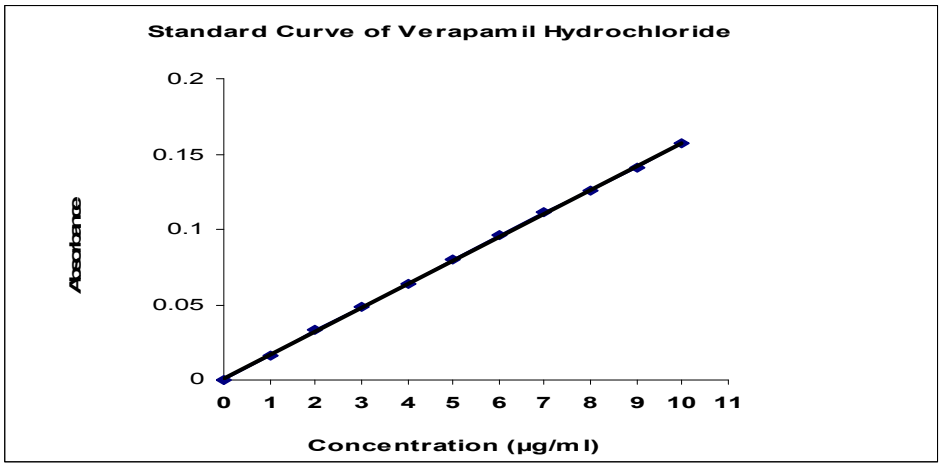

Fig No 1 :- Standard Curve of Verapamil Hydrochloride.

Table No 1: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

EVALUATION OF BACCOADHESIVE TABLETS[40-84]:-

All the prepared buccoadhesive tablets were evaluated for following parameters.

1 Weight Variation[70]:

20 tablets were randomly selected form 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 then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No.2.

Table. No. 2: 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

2. Thickness [72]:-

Three tablets were selected randomly from each batch and thickness was measured by using vernical caliper. The results are shown in table .

3. Friability[70]:

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.15

4. Hardness [69]:

Hardness was measured using Monsanto hardness tester. For each batch two tablets were tested. The results are shown in table .

5. 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 .

6 .Bioadhesive Strength

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.

Goat buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. The goat buccal mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media phosphate buffer pH 6.8. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer pH 6.8 up to the upper surface of the goat buccal mucosa to maintain buccal mucosa viability during the experiments.

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.

The results are shown in table .

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

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

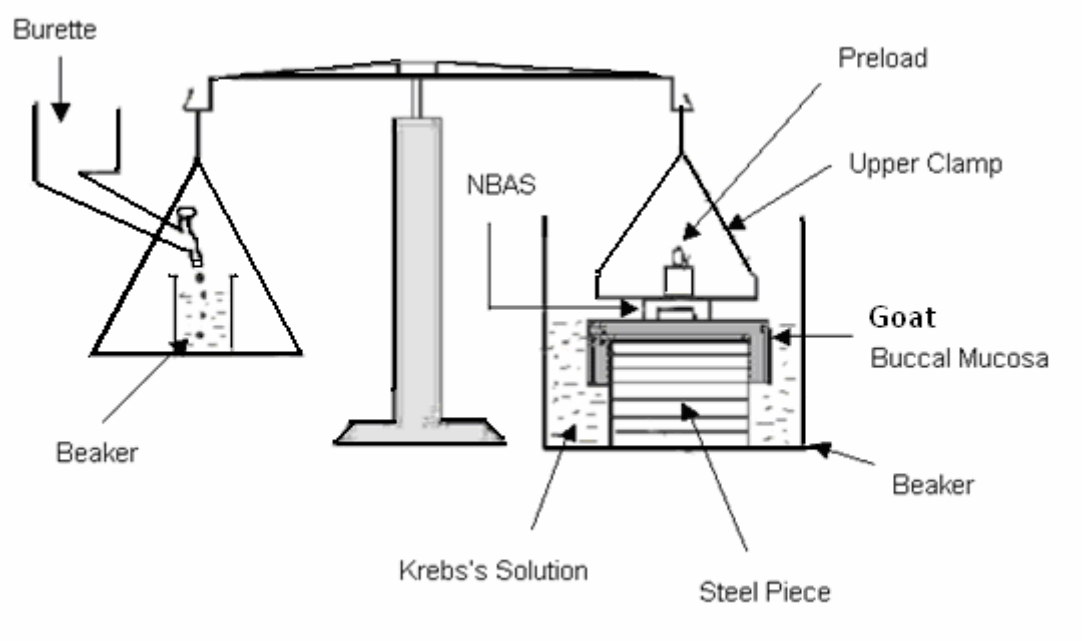

Fig No.12: - Physical Balance for measurement of adhesive strength

7. Swelling index[77, 78]:

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 .

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

8. In Vitro Release Study[79, 80]:

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. 19 to 21. The percentage release of Verapamil HCL with respect to time for each batch, are graphically shown below in fig no.16 to 18.

9 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.

***Zero Order**:

In many of the modified release dosage form particularly controlled or sustained release dosage form (those dosage forms that release the drug in planned, predictable and slower than normal manner) is zero order kinetics.

$Q = K_o t$

Where, Q is the amount of drug release at time, t and K_o is the release rate constant.

The results are shown in table no.31.

***First Order:**

Most conventional dosage form exhibits this dissolution mechanism some modified release

preparations, particularly prolonged release formulation adhere to this type of dissolution pattern.

$\text{Log } Q = K_1 t$

Where Q is the percent of drug release at time, t and K_1 is the release rate constant.The results are shown in table .

- **Higuchi Equation** [81]**:**

A Large number of modified release dosage form contain some sort of matrix system is such instances the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion control) and thus the following relation ship applies.

$Q = K_2 t^{1/2}$

Where, Q is the percentage of drug release at time t and K_2 is the diffusion rate constant.The results are shown in table.

- **Peppas Equation** [82, 83 ,84.] **:**

$Q = Ktn$

Where, Q is the percent of drug release at time, t and K is the diffusion rate constant and n is diffusional exponent. If n is equal to one the release is zero order. If n is equal to 0.5 the release is best explained by fickian diffusion and if $0.5 < n < 1$ then the release is through anomalous diffusion or case II diffusion in this model a plot of % drug released versus log time is linear.

The results are shown in table .

- **Hixson Crowell Model**

Some specialized dosage forms contain many drug particles of the same size and shape of their agglomerates that dissolve evenly in such instances the dissolution process can be expressed by the Cube–root law.

If the dissolution pattern of the drug is dictated by the actual dissolution of drug molecules, then the following relation ship applies.

$M = [(100) \times ((1/3) - k \times t)^3]$

Where k is Hixon Crowell Constant (Mass / time) $^{1/3}$

In this model the % drug unreleased versus cube root of time is linear.

The results are shown in table .

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 1.

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.

d) Physical properties:

Physical properties of Verapamil Hydrochloride and Buccoadhesive polymers like bulk density, tapped density, % compressibility and Housner ratio results shown in Table No3

Table 3: 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

Hardness test:-

The hardness of tablets of each batch ranged between 6.47 to 7.68 kg/cm^2 (Table No.5). This ensures good handling characteristics for all batches.

Friability Test:-

The values of friability test were tabulated in Table No.4. 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.4. 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.4

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.17 Swelling index against time (hrs) was plotted in Fig. No.2

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.

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

1. Cumulative percent drug released v/s time (zero order rate kinetics)
2. Log cumulative percent drug retained v/s time (First Order rate Kinetics)
3. Cumulative percent drug released v/s square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release v/s log time (Peppas Exponential Equation)
5. (Percentage retained)$^{1/3}$ v/s time (Hixson – Crowell Erosion Equation)

In vitro release obtained for formulations F1 to F9 were tabulated in Fig. No. 4 to 6 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.

Table No 4: 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 5: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: 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

Table No 6: 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

Table no 8:Kinetic values obtained from invitro 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 9: Kinetic values obtained from invitro released data of different Verapamil HCL Buccoadhesive tablets formulations

	Plot of cum. % drug released v/s time in sq. root (Higuch 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

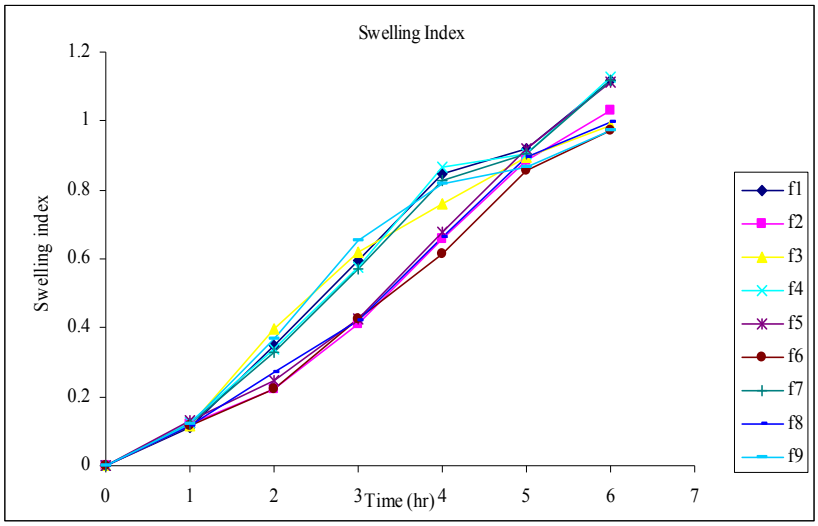

Fig. No.2 :- Graph of the Swelling index versus Time (hr).

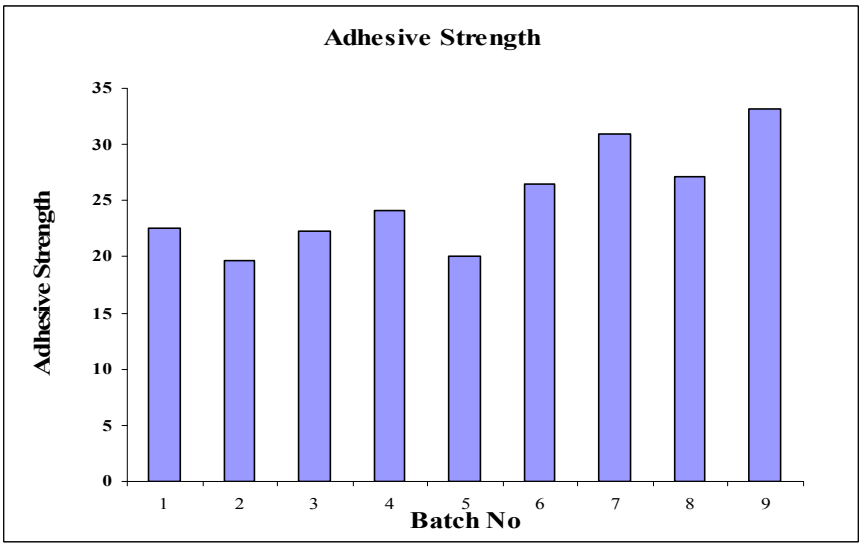

Fig. No. 3 :- Column graph of the adhesive strength (gm)

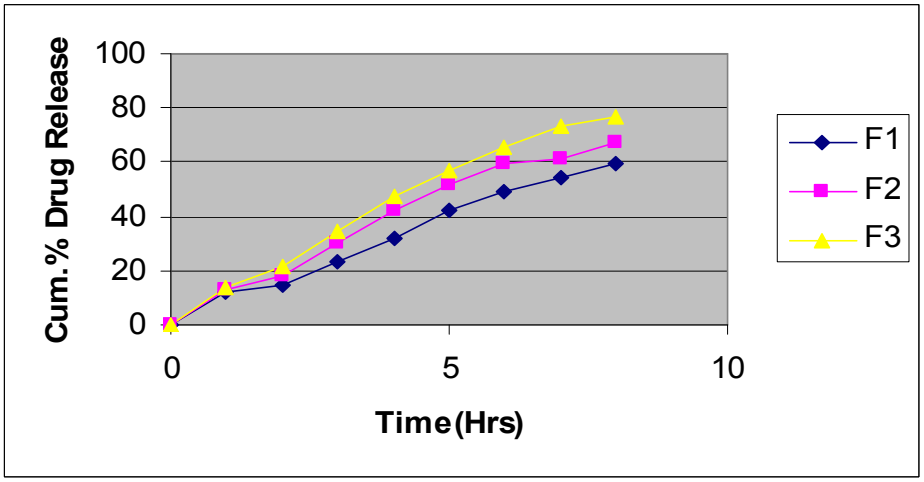

Fig. No.4 :- Graph of the Cum. % drug release versus Time (hr).

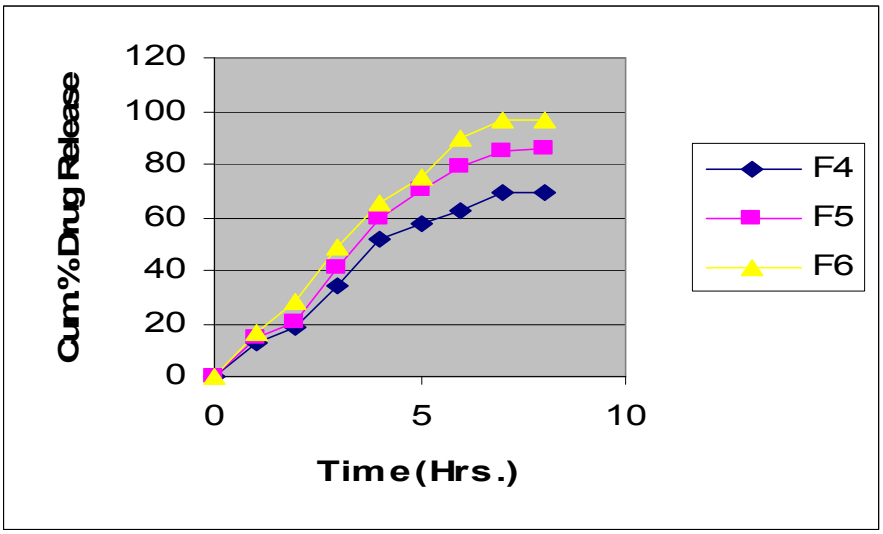

Fig. No.5 :- Graph of the Cum. % drug release versus Time (hr)

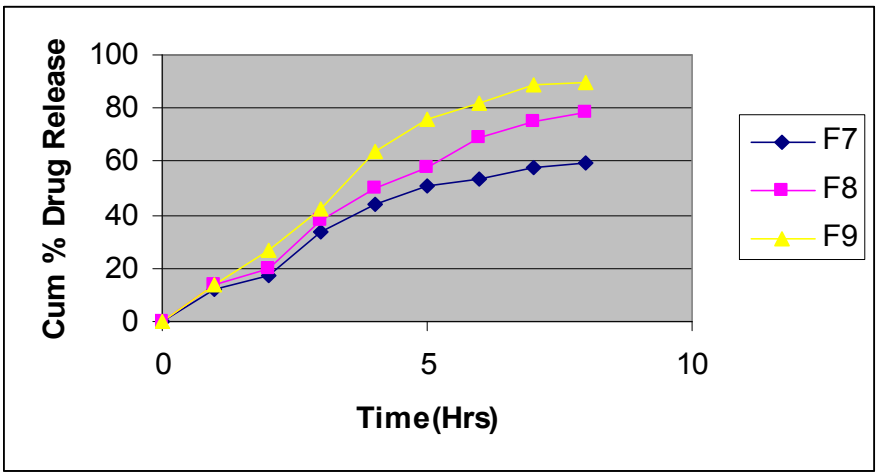

Fig. No.6 :- Graph of the Cum. % drug release versus Time (hr)

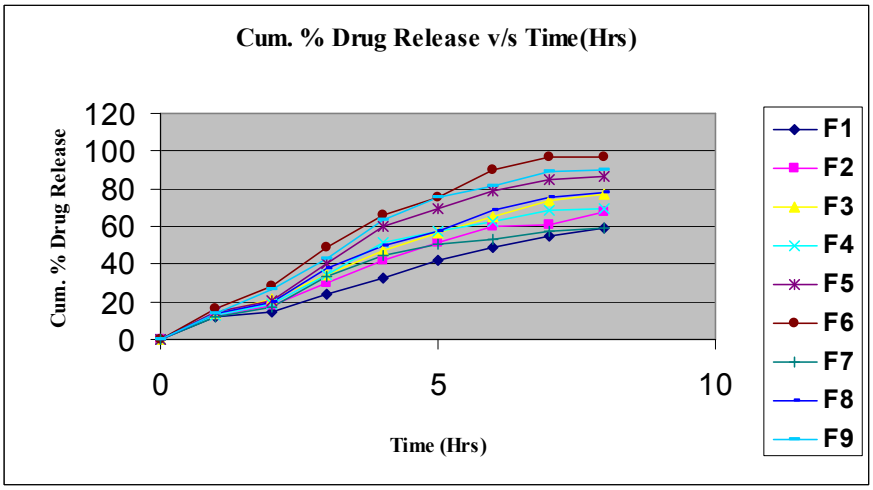

Fig. No. 7:- Invitro cumulative % drug releasd v/s time for formulation (f1 to f9) of verapamil hydrochloride[zero order rate]

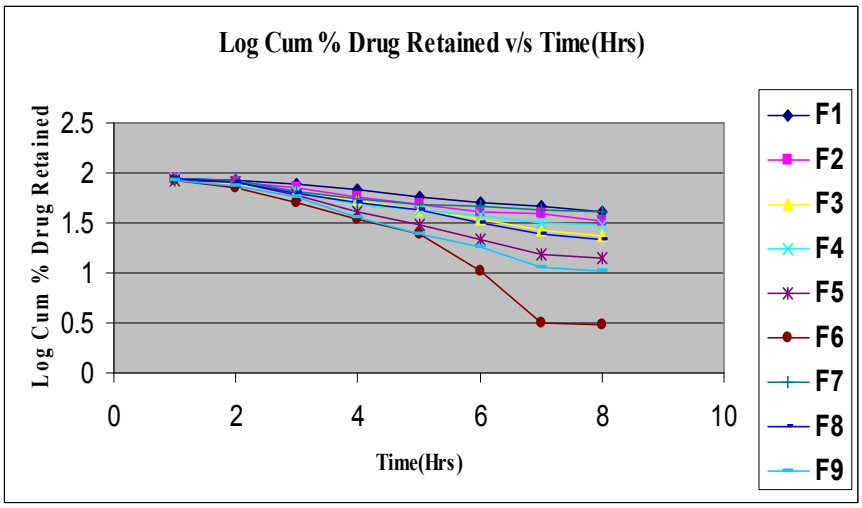

Fig. No. 8:- Log cumulative % drug retainedv/s time for formulation (f1 to f9) of verapamil hydrochloride [firstorder rate]

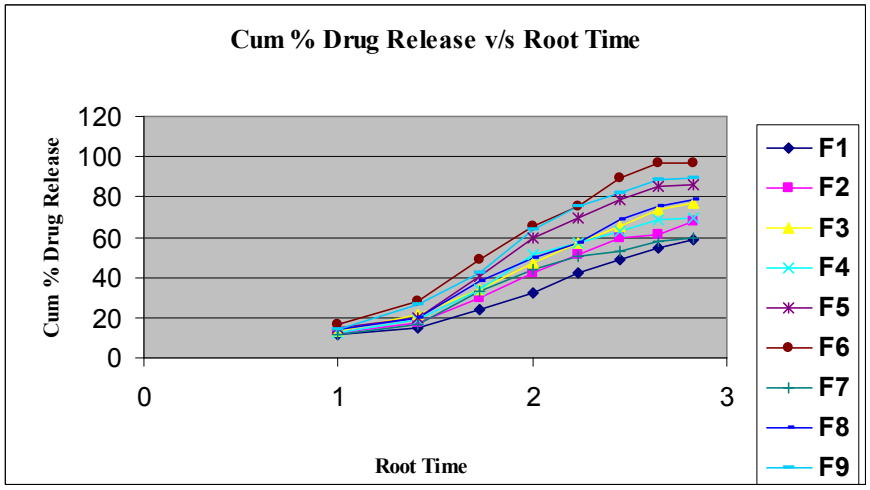

Fig. No. 9:- Cumulative % drug released v/s root time for formulation (f1 to f9) of verapamil hydrochloride [higuchi matrix]

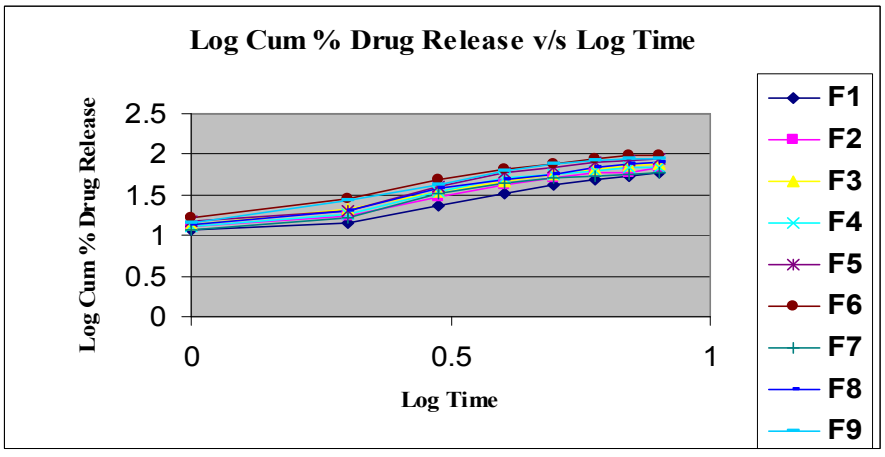

Fig. No. 10: Log cumulative % drug releasedv/s log time for formulation (f1 to f9)of verapamil hydrochloride [peppas]

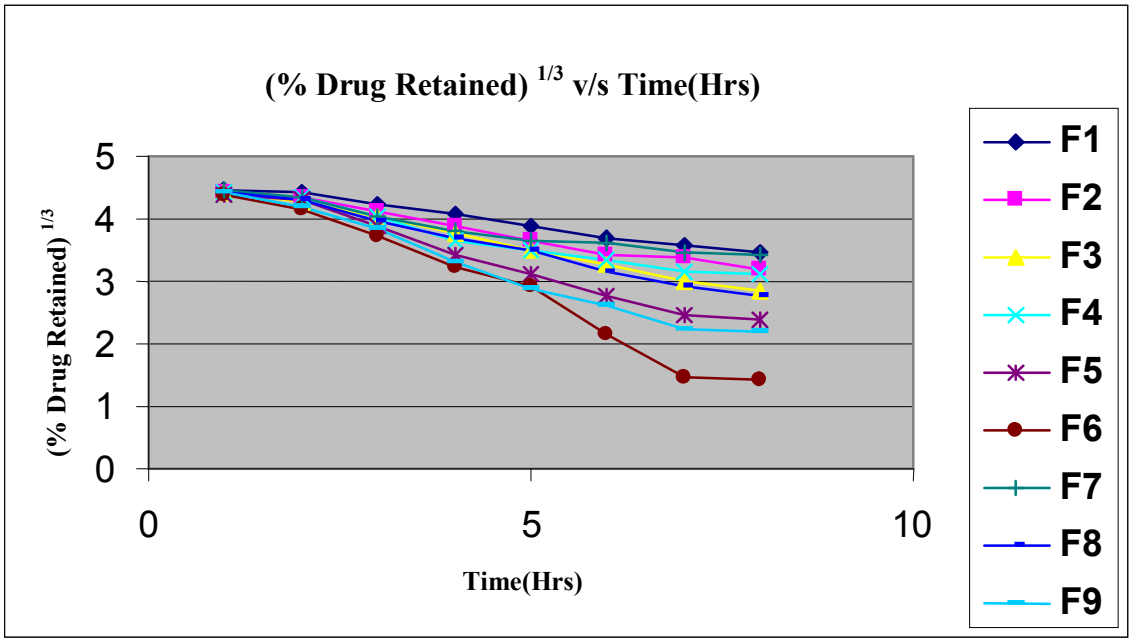

FIG. NO. 11: Cube root of % drug retained v/s time for formulation (f1 to f9) of verapamil hydrochloride [hixson-crowell]

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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