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Design and *In- Vitro* Evaluation of Mucoadhesive Buccal Tablets of Terbutaline Sulphate

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ABSTRACT: Mucoadhesive buccal tablets of terbutaline sulphate were prepared by direct compression method. Carbapol 934P, chitosan, HPMC K_4M and HPMC $K_{15}M$ were used as a polymers. Tablets were then evaluated for various physicochemical parameters such as drug content (100 ±0.28%), hardness (7.09 ±0.55 kg/cm^2), weight uniformity (100 ±0.35 gm), thickness (3.04 ±0.10 mm), and friability (0.31%). Prepared formulations were evaluated for the release of drug in phosphate buffer pH 6.8 using USP type-II dissolution apparatus. Optimum formulation consisted of terbutaline sulphate (5mg), carbapol 934P (40mg), HPMC K_4M (40mg), mannitol (13mg), magnesium stearate (1mg) and talc (1mg) showed a maximum drug release after 10 hrs. Mannitol was used to accelerate the release of drug from polymer matrices. Maximum swelling was attained in 5 hrs. The highest bioadhesive strength i.e. 0.277N was possessed by optimum formulation. Decreasing the content of carbapol 934P resulted in decreased in adhesion force. The surface pH of tablets of all batches was between 5 and 7. Good correlation was observed between *in-vitro* drug release and drug permeation with a correlation coefficient of 0.9928. Results indicate that the release rate from optimum formulation best fitted zero order rate kinetics. In conclusion, *in-vitro* release profile and mathematical models indicate that this novel delivery system is useful formulation, which can by-pass the first pass metabolism and enhance the release of drug for extended period of time.
Keywords: Mucoadhesive buccal tablet, Terbutaline sulphate, Swelling index, Bioadhesive strength

INTRODUCTION: Terbutaline sulphate [2-(tert-butylamino)-1-(3,5- dihydroxyphenyl) ethanol sulphate] is a selective β_2- adrenergic agent, widely used in the treatment of bronchiole asthma, chronic bronchitis and emphysema[1]. The oral bioavailability of drug is only 14.8% and half-life is 3 to 4 hrs[2]. This is because of undergoing of drug to first pass metabolism in liver and gut wall[3].

Buccal mucosa is an attractive route for systemic delivery of many drugs since it is relatively permeable with a rich blood supply[4]. The mucoadhesive buccal drug delivery system offers several advantages as compare to traditional methods of systemic drug administration[5]. In addition to this, drug can be easily applied and localized to the application site, and can be removed from there if necessary (See Fig. 1). Furthermore, mucoadhesive delivery system via buccal mucosa can by-pass the disadvantages of oral route. Therefore, mucoadhesive delivery system has been considered to be an ideal route for administration of terbutaline sulphate.

In earlier research, attempts have made to develop various mucoadhesive formulations of terbutaline sulphate[6-7]. Nevertheless, there was no report of mucoadhesive buccal tablets of terbutaline sulphate. In this research, we have tried to design novel mucoadhesive buccal tablets of terbutaline sulphate which will reduce the first pass metabolism and frequency of dosage.

Firstly, polymers such as carbapol 934P, chitosan, HPMC K_4M, HPMC $K_{15}M$, sodium CMC, mannitol, and magnesium stearate were used in different ratio to examine their effect on the retardation of drug release from tablet matrix. Hydroxypropyl methylcellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems[8]. The transport phenomena involved in the drug release from hydrophilic

matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the fluid, HPMC swells and finally dissolves slowly[9]. The rate of polymer swelling and dissolution as well as corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC[10].

MATERIALS AND METHODS

Materials

Terbutaline sulphate was a generous gift sample from Glenmark Research Center, Sinnar, Nashik. Carbapol 934P, HPMC K_4M and HPMC $K_{15}M$ were obtained from Colorcon Asia Pvt. Ltd., Goa. Chitosan was obtained from Central Institute of Fisheries and Technology, Cochin, India. Mannitol was procured from Merck Ltd. Mumbai. All other reagents and chemicals used were of analytical reagent grade.

Preparation of Tablets

Polymers like carbapol 934P, chitosan, HPMC K_4M, HPMC $K_{15}M$, sodium CMC, mannitol, magnesium stearate and other ingredients in different ratios were tried to select optimum formulation. The amount of drug was established according to its clinical use and doses usually contained in some brand drug products. Finally, formulation given in Table No. 1 was selected as optimum formulation. Different components in each formula were mixed by trituration in glass pestle and mortar for 30 min. The mixture was then compressed using 6 mm flat-faced punch using a single stroke-punching machine.

Evaluation of Mucoadhesive buccal Tablets[11]

All the prepared mucoadhesive buccal tablets were evaluated for following official and unofficial parameters.

Drug Content

Three tablets from each batch were taken in separate 100 mL volumetric flaks containing 100 mL of pH 6.8 phosphate buffer and were kept for 24 hrs under constant stirring. The solutions were then filtered, diluted suitably and analyzed at 276 nm using UV- spectrophotometer. The average of three tablets was taken as the content of drug in one tablet unit.

Hardness

The resistance of tablets to shipping or breaking under the condition of storage, transportation, and handling before the uses depends on its hardness. The hardness of tablets of each batch was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Weight uniformity, Thickness and Friability

The average weights of the formulated tablets were determined using electronic balance. Thickness was measured using screw gauge at different places and average was calculated. The friability of tablets was determined by using Roche friabilator.

In-Vitro Release[12]

The United state pharmacopoeia (USP) type II dissolution apparatus was used to study the release of drug from buccal tablets. The dissolution medium consisted of 900 mL of phosphate buffer pH 6.8. The release was performed at 37 ±0.5°C, at a rotation speed of 50 rpm. One side of buccal tablet was attached to a glass disk with instant adhesive. The disk was put in the bottom of dissolution vessel, so that the patch remained on the upper side of the disk. Samples (5 mL, at each time) were withdrawn at pre-determined time intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper no. 41 with appropriate dilutions with phosphate buffer pH 6.8 and were assayed spectrophotometrically at 276 nm against phosphate buffer pH 6.8 as blank.

Swelling Study[13]

Swelling study was performed on 1% agar gel plates. Twenty tablets were weighed and average weight of each four tablets was calculated. The tablets were placed on the gel surface in five Petri dishes (each containing four tablets), which were placed in an incubator at 37°C. Four tablets were removed at time intervals of 1, 2, 4 and 6 hrs, excess water from the surface was carefully soaked using filter paper, and swollen tablets were weighed. The swelling index was calculated by using formula,

$$\text{Swelling index} = \frac{\text{wet weight - dry weight}}{\text{wet weight}} \text{ X } 100$$

Surface pH[14]

Mucoadhesive buccal tablets were subjected to swell on the surface of agar plate for 2 hrs. The surface pH was measured by using pH paper placed on the surface of the swollen tablets. The mean of two readings was recorded.

***In-Vitro* Bioadhesive Strength[12]**

The term bioadhesion implies attachment of a drug carrier system to a specific biological location. *In–vitro* bioadhesive strength of tablets was measured using modified physical balance. Porcine buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. Bioadhesive studies were performed in triplicate and average bioadhesive strength was determined. From the mucoadhesive strength, force of adhesion was calculated, Force of adhesion (N) = (Bioadhesive strength/100)× 9.81

Drug-Excipient Interactions[15]

There is always possibility of drug-excipient interaction in any batch due to their intimate contact. The drug-excipient interaction study was carried out for optimum formulation by using IR-spectroscopic technique, which is one of the most powerful analytical technique that offers possibility of chemical identification. IR-spectra of terbutaline sulphate, HPMC K_4M, chitosan and tablets of optimum batch were obtained by KBr disc method.

Short term stability[16]

Tablets of optimum batch were selected for short-term stability study. It was carried out at accelerated condition of 40 ±2°C for a period of three months. For this, ten tablets were individually wrapped using aluminum foil and packed in amber color screw cap bottle and put at above specified condition in incubator for 3 months. After each month tablet sample was analyzed for physical characteristics, mucoadhesive properties, duration of mucoadhesion and *in- vitro* drug release study and drug content.

Drug Release Kinetics[17]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained was fitted into a) Zero order kinetics; b) First order kinetics; c) Higuchi's square root model and d) Korsemeyer and Peppas model. The data obtained from stability study was also subjected to statistical analysis (student's t-test) in order to find out any significant difference in the drug content of optimum formulation.

RESULTS AND DISCUSSION

An ideal pharmaceutical dosage form for buccal affection treatments would be able to (1) release drug immediately to produce a prompt pharmacological action, (2) remain in oral cavity, and (3) provide a sustained release of enough drug over an extended period of time. Taking into account such requirements, mucoadhesive buccal tablets of terbutaline sulphate were prepared, and were evaluated for various physicochemical parameters.

The percent drug content for all the formulations was found to be 100.00 ±0.28% w/w. Hardness of the tablets was found to be 7.09 ±0.55 kg/cm^2. Hardness increases with increasing carbapol proportion in the formulation. The average weight of the tablets was found to be 100.00 ±0.35 mg, and the percent deviation was within a specified limit. Hence, all formulations complied with the test for weight uniformity.

All the tablets were circular with no visible cracks, and smooth in appearance with average thickness of 3.04 ±0.10 mm. Further, to strengthen these values, friability test values are also considered. The weight loss less than 1% in friability test is considered as an acceptable value for conventional tablets. It indicates that the tablets can withstand the mechanical shocks reasonably well during their handling. Thus, all the tablets complied with IP standard.

From *in-vitro* release study of all batches, formulation (F7) containing terbutaline sulphate (5mg), carbapol 934P (40mg), HPMC K_4M (40mg), mannitol (13mg), magnesium stearate (1mg) and talc (1mg) was selected as optimum formulation for further study as it had maximum drug release after 10 hrs. The release of drug was decreased with increasing the concentration of HPMC K_4M and HPMC $K_{15}M$ as shown in formulation F8 to F14. The drug release was decreased in formulation F3, F4, F5, and F6 containing carbapol 934P in combination with chitosan. It indicates that increase in viscosity of chitosan results in slight decrease in rate of drug. Mannitol was used to accelerate the release of drug from polymer matrices (See Table No. 2, Fig. 2-4).

The swelling properties of all the formulations were studied, and its results indicate that all the formulations possess good swelling indices. The optimum formulation showed maximum swelling index. Maximum swelling

was attained in 5 hrs after which polymers started eroding slowly in the swelling medium. The swelling index of formulations containing carbapol 934P and chitosan was increased with increasing the amount of chitosan (See Table No. 3).

The surface pH of all the formulations was found to be between 5 and 7. Therefore, it reveals that all formulations provide an acceptable pH in the range of salivary pH (5.5-7.0) and they cannot produce any risk of mucosal damage or irritation.

Different kinetic equations were applied to interpret the release rate of drug from mucoadhesive tablets of optimum batch. Results indicate that the release rate from tablets of optimum batch best fitted zero order rate kinetics (See Fig. 5, Table No. 4).

The bioadhesion characteristics were affected by the types and ratios of bioadhesive polymers. The highest bioadhesive force i.e. 0.277N was possessed by optimum formulation. This is because of polymer carbapol 934P, which swells and becomes adhesive upon hydration (See Fig. 6-7).

In the IR spectral study of optimum formulation, prominent peaks of terbutaline sulphate were appeared without interference or the shifting of peaks; it reflects that there is no drug-excipient interaction in optimum formulation.

The stability study was carried out on optimum formulation, and its results reflect that there is no significant change in dissolution profile, drug content and mucoadhesive strength of the formulation. Hence, it concludes that the tablets from this formulation are stable for the period 3 months at 40 ±2°C (See Table No. 5).

CONCLUSION

Mucoadhesive buccal tablets of terbutaline sulphate were prepared by direct compression method. Different polymers and ingredients in different ratios were tried to select optimum formulation. They were selected on the basis of their effect on the retardation of release of drug from tablet matrix. The formulation consist of terbutaline sulphate (5mg), carbapol 934P (40mg), HPMC K_4M (40mg), mannitol (13mg), magnesium stearate (1mg) and talc (1mg) was selected as optimum formulation. Various physicochemical parameters tested for this formulation showed good results (See Table No. 6). From the release study and mathematical models, it conclude that this novel formulation can by-pass the first pass metabolism and enhance the release of drug for extended period of time.

Table No. 1- Composition of Mucoadhesive Buccal Tablet Formulations (mg/tab)

Ingredients	Batch																
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**
Terbutaline sulphate	5	5	5	5	5	5	5	5	5	20	20	20	20	20	20	20	20
Carbapol 934P	80	80	40	26.7	20	16	40	26.7	20	16	40	26.7	20	16	40	40	40
Chitosan	--	--	40	53.3	60	64	--	--	--	--	--	--	--	--	40	--	--
HPMC K_4M	--	--	--	--	--	--	40	53	60	64	--	--	--	--	--	40	--
HPMC $K_{15}M$	--	--	--	--	--	--	--	--	--	--	40	53.	60	64	--	--	40
Mannitol	13	--	13	13	13	13	13	13	13	13	13	13	13	13	--	--	--
Spray dried Lactose	--	13	--	--	--	--	--	--	--	--	--	--	--	--	13	13	13
Magnesium Stearate(%)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc (%)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Table No. 2- In-Vitro Drug Release of Mucoadhesive Buccal Tablet Formulations

Batch	Release exponent (n)	Kinetic constant (k)	Determination coefficient (R^2)
F1	0.6696	1.15	0.9856
F2	0.657	1.13	0.9889
F3	0.6635	1.15	0.9821
F4	0.6126	1.36	0.9229
F5	0.6058	1.53	0.879
F6	0.5468	1.59	0.7728
F7	0.7024	1.11	0.9928
F8	0.6898	1.91	0.9869
F9	0.6504	1.25	0.9662
F10	0.6455	1.34	0.9381
F11	0.7165	1.24	0.979
F12	0.6909	1.02	0.9941
F13	0.6721	1.31	0.9527
F14	0.648	1.40	0.9357
F15	0.7167	1.28	0.9695
F16	0.694	1.20	0.9779
F17	0.6858	1.81	0.8492

Table No. 3- Swelling Index of Mucoadhesive Buccal Tablet

Batch	% Swelling index				
	Time (h)				
	0.5	1	2	4	6
F1	21.12 ±0.044	61.78 ±1.01	103.06 ±0.58	138.42 ±1.04	193.2 ±1.66
F2	25.00 ±0.25	33.42 ±0.46	42.31 ±1.16	103.06 ±0.58	141.56 ±0.48
F3	40.12 ±0.23	70.05 ±0.90	135.90 ±1.570	200.00 ±0.20	253.00 ±0.56
F4	35.40 ±0.12	85.09 ±0.050	150.08 ±0.90	190.00 ±0.090	254.00 ±0.72
F5	61.51 ±0.11	108.11 ±1.29	141.56 ±0.30	226.09 ±0.18	291.00 ±1.97
F6	60.12 ±0.25	110.03 ±1.44	225.17 ±0.37	283.00 ±0.72	295.99 ±2.74
F7	36.79 ±0.35	77.00 ±1.01	135.00 ±0.54	180.07 ±1.11	210.00 ±0.83
F8	31.77 ±0.44	39.22 ±0.40	102.21 ±0.38	150.27 ±0.22	205.00 ±0.96
F9	28.35 ±0.15	64.52 ±0.98	92.00 ±1.47	135.96 ±1.33	219.00 ±0.78
F10	33.27 ±0.15	58.33 ±0.32	123.18 ±2.58	200.03 ±2.76	218.31 ±3.05
F11	22.40 ±0.47	56.13 ±0.12	83.45 ±1.74	169.00 ±3.04	204.95 ±2.25
F12	33.07 ±0.41	60.61 ±0.25	102.09 ±0.26	156.11 ±2.27	185.58 ±1.01
F13	50.01 ±0.70	79.75 ±2.06	111.07 ±0.24	146.27 ±2.48	223.82 ±0.99
F14	42.10 ±0.20	63.12 ±0.088	98.91 ±0.52	158.70 ±0.37	201.00 ±0.67
F15	26.92 ±0.10	58.64 ±0.74	119.00 ±0.48	149.27 ±0.05	193.66 ±1.34
F16	19.73 ±0.25	50.00 ±0.21	89.33 ±0.79	151.19 ±2.76	171.33 ±0.95
F17	45.31 ±0.24	76.01 ±0.19	105.01 ±1.22	185.01 ±1.04	239.01 ±0.55

**Each values represents mean ± S.D (n = 3)*

Table No. 4 - Kinetic values for optimum formulation

Equation	**r^2**
Zero order	1.0000
First order	0.9967
Square root t kinetics	0.9421

Table No. 5 – Stability study of optimum formulation

Time (Hrs)	**%Cumulative drug release***			
	0 Month	**1 Month**	**2 Month**	**3 Month**
0	0.00	0.00	0.00	0.00
1	15.00 ±0.45	15.01±0.32	13.01±0.71	13.09±0.32
2	22.00 ±0.35	20.00±0.17	20.01±0.45	20.00±0.45
3	30.29 ±0.24	30.25±0.59	29.29±0.67	27.29±0.20
4	39.21 ±0.52	39.20±0.22	38.21±0.26	36.01±0.21
5	48.8 ±0.34	48.8±0.18	48.7±0.22	46.7±0.12
6	54.70 ±0.10	53.70±0.25	53.70±0.84	52.07±0.96
7	64.49 ±0.46	64.49±0.21	62.49±0.75	61.98±0.77
8	75.39 ±0.17	75.19±0.24	74.09±0.77	73.09±0.84
9	85.29 ±0.41	85.28±0.11	84.29±0.98	83.27±0.54
10	94.77 ±0.33	94.77±0.53	93.86±0.17	92.76±0.15

**Each values represents mean ± S.D (n = 3)*

Table No. 6- Physical characterization of optimum formulation

Physical characteristics	**Time (months)**			
	0	**1**	**2**	**3**
Uniformity of Weight	99.36±0.24	99.96±0.54	99.99±0.24	100.02±0.46
Drug content* (%)	100.86± 0.15	99.89±0.14	99.83±0.23	97.89±0.15
Friability (%)	0.37	0.39	0.35	0.32
Hardness* (Kg/cm^2)	7.7±0.23	7.5±0.18	7.3±0.34	7.0±0.84
Thickness* (mm)	3.21±0.053	3.21±0.05	3.21±0.07	3.21±0.95

**Each values represents mean ± S.D (n = 3)*

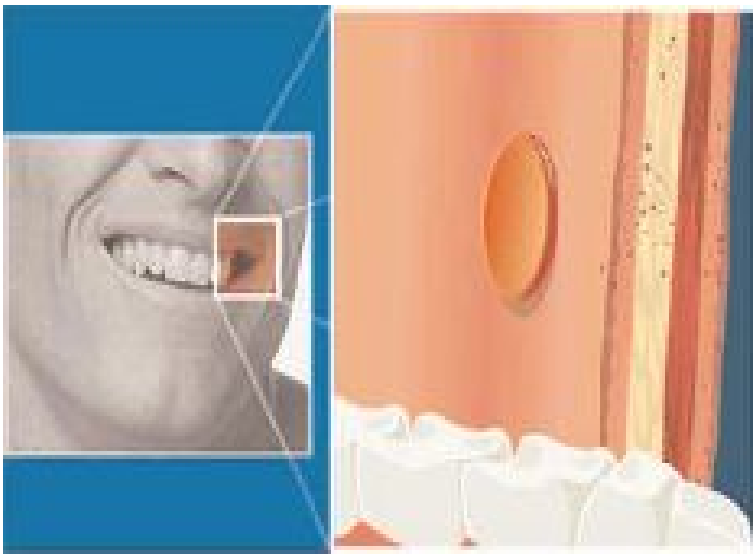

Fig. 1- Overview of attachment site of mucoadhesive tablet

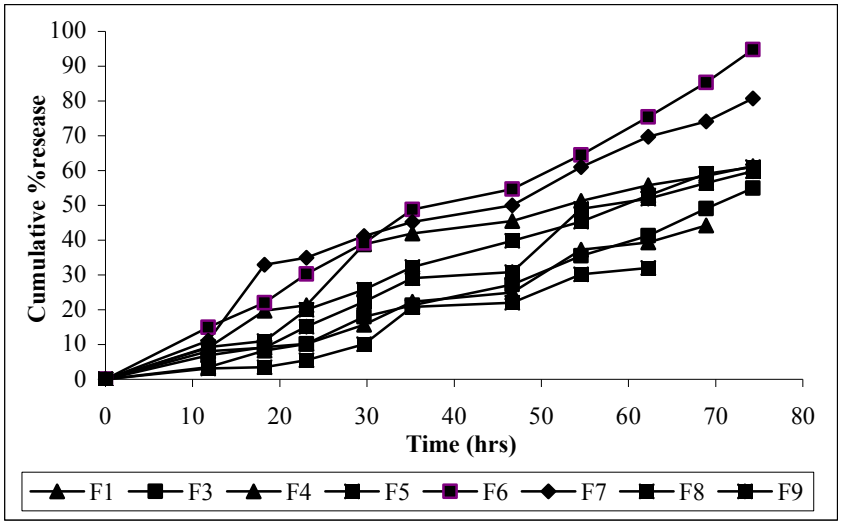

Fig. 2- In-Vitro release profile of tablets, F1, F2-F10

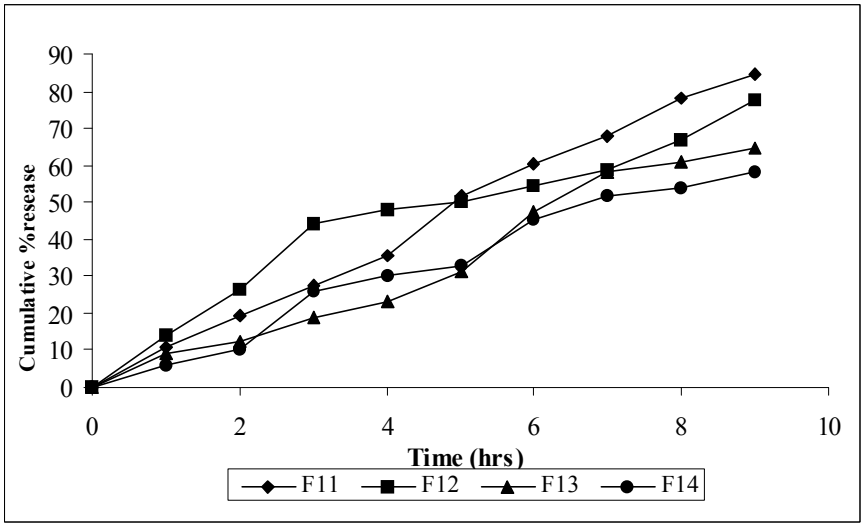

Fig. 3- In-Vitro release profile of tablets, F11 - F14

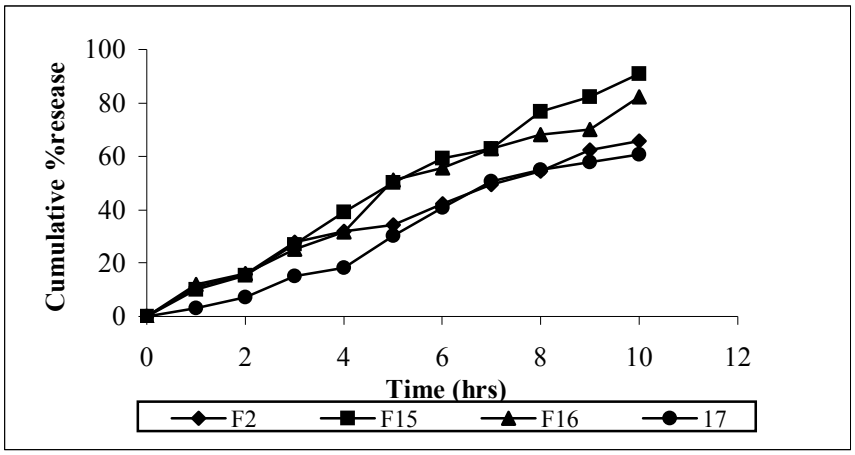

Fig. 4- In-Vitro release profile of tablets, F2, F15, F16, F17

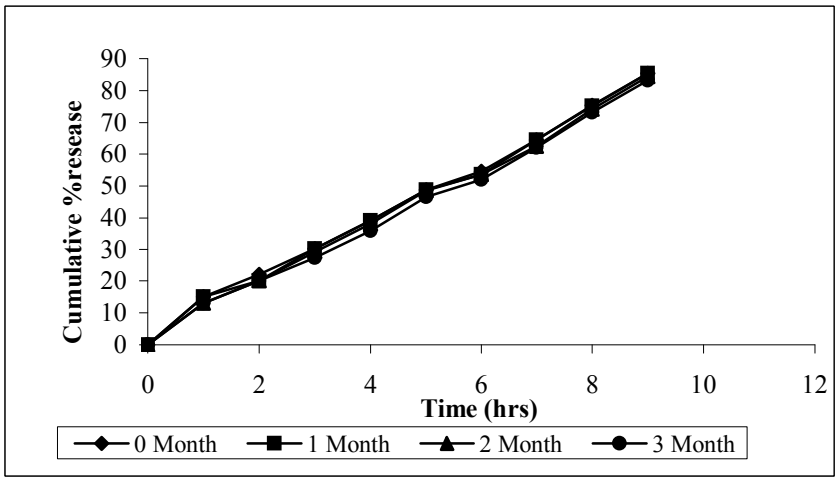

Fig. 5: In- vitro release profile of optimum formulation, F7

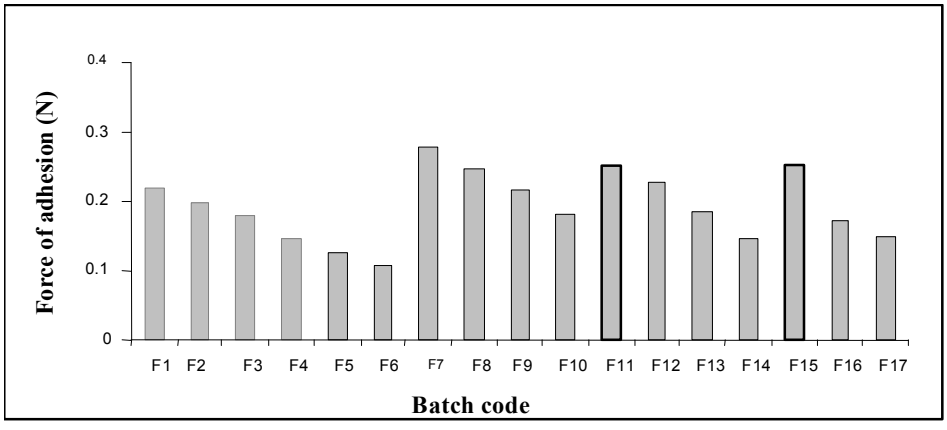

Fig. 6- In- vitro bioadhesion strength of various formulations

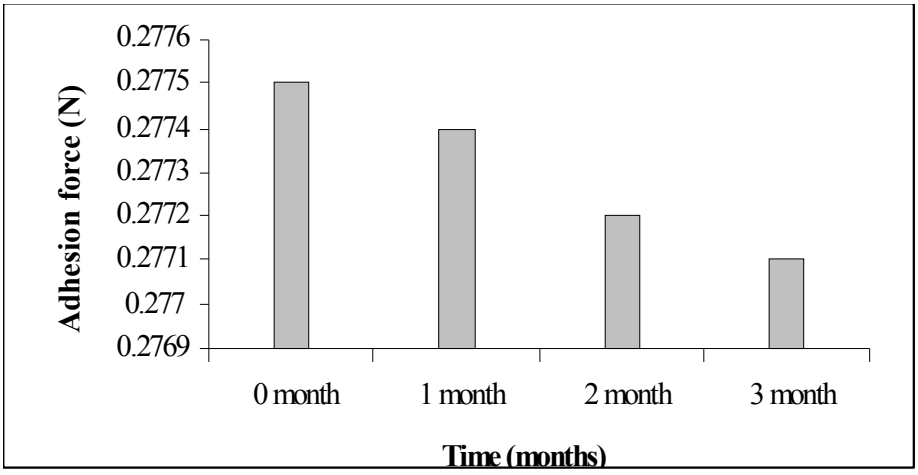

Fig. 7- Mucoadhesive measurement of optimum formulation

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