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Research Article

Formulation and Evaluation of Mucoadhesive Bilayered Buccal Tablet of Ziprasidone Hydrochloride

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Abstract

The present project was carried out to formulate and evaluate the mucoadhesive bilayered buccal tablet of Ziprasidone Hcl. Ziprasidone HCl is an antipsychotic agent with half-life of about 2hrs and shows extensive metabolism i.e the drug concentration is < 5% after elimination in the body. The formulations (F1 to F6) were developed which comprises of polymers such as Hydroxypropyl methyl cellulose (HPMC K-15), Polyvinyl pyrollidine (PVP K-30) in various concentrations along with carbopol to achieve the desired characteristics. Mucoadhesive bilayered buccal tablets were fabricated with the aid of direct compression technique and the prepared formulation was evaluated for its physicochemical parameters along with evalauation test. The results from different evaluation test demonstrated that the formulation F1 containing HPMC (25 mg) and CP (10 mg) was selected as optimised formulation and result values of precompression parameters were within the limits and post compression results showed the mucoadhesive strength of F1 formulation was 25.27gm, the drug release at 8th hr was 85.7 % and the formulation was stable throughout the stability studies. Hence mucoadhesive bilayered buccal tablets of Ziprasidone HCl can be prepared. Based on the above results it can be stated that mucoadhesive bilayered buccal tablets can be successfully developed. Formulation described that the nature of tablet depends not only on the se lected polymer excipient but also on the concentration of polymers selected.

Keywords: Ziprasidone HCl, Bilayered Buccal Tablet, Mucoadhesion.

INTRODUCTION

Mucoadhesive dosage forms are specially designed to adhere to the mucosal surface, thus intensifying retention of the drug at the site of application, while providing a controlled rate of drug release for better therapeutic outcome[1]. The mucosal site which has a high extent of vascularization and permits direct drain of blood flow into the jugular vein and which also aid to avoid the possible metabolism of drugs by the liver and gastrointestinal route is the buccal mucosa [2].

Ziprasidon Hcl is a latest addition to the class of anti-psychotic drugs, with good anti-psychotic property along with other activities such as monotherapy for psychoses, most commonly used for the treatment of psychoses. It is characterized as a biopharmaceutical classification system (BCS) class II drug. It is highly protein-bound and possesses a short biological half-life of 2hrs. The usual dose of ziprasidone hydrochloride is 20 mg twice daily. The conventional dosage form of ziprasidone Hcl leads to a lot of inconvenience and fluctuations in therapy, with some adverse effects like etc. Thus, devising sustained-release medication is a good alternative for reducing its dosing frequency, for prolonged effect with improved bioavailability, while also improving safety and efficacy of the medication [3].

MATERIALS AND METHODS

Drug and chemicals

Ziprasidone HCl Reddy's laboratories, HPMC K15 Research lab fine chem., PVP K30 Biochemika Reagents, Carbopol 934, Microcrystalline cellulose, Magnesium stearate, Mannitol, Ethyl cellulose S.D. Fine Chem. Ltd. All the chemicals and reagents used were of analytical grade.

Methods

Preparation of Mucoadhesive Bilayer Buccal Tablets

All the ingredients including drug, polymer, and excipients were weighed accurately according to the batch formula. Then all the ingredients except ethyl cellulose were screened through sieve and were mixed in the order of ascending weights. The prepared blend (150 mg) of each formulation was pre-compressed, on tablet punching machine to form single layered flat-faced tablet of 9 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done to get bilayer buccal tablet.[4-5]

Table 1: Formulation of bilayered buccal tablet

S.no	Ingredients (mg)	F1	F2	F3	F4	F5	F6
1	Ziprasidone HCl	20	20	20	20	20	20
2	HPMC K-15	25	35	45	-	-	-
3.	PVP K-30	-	-	-	25	35	45
4.	Carbopol 934	10	20	30	10	20	30
5.	Microcrystalline cellulose	80	60	40	80	60	40
6.	Mannitol	10	10	10	10	10	10
7.	Magnesium stearate	5	5	5	5	5	5
8.	Ethyl cellulose	50	50	50	50	50	50
	Total weight(mg)	200	200	200	200	200	200

PREFORMULATION STUDIES

Bulk Density

It was determined by pouring pre-sieved drug excipients blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/mL and is given by,

$$Db = M / VO$$

Where, M is the mass of powder and VO is the Bulk volume of the powder.

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipients blend, on mechanical tapping apparatus.

$$DT = M / VT$$

Where, M is the mass of powder and VT is the tapped volume of the powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL.

Powder flow properties

Angle of repose

This is the Maximum angle possible between the surface of the pile or powder and horizontal plane. Angle of repose was determined by using funnel method. The frictional forces in the lose powder can be measured by Angle of repose. The tangent of Angle of repose is equal to the coefficient friction between the particles.

$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose, h is the height in cm and r is the radius in cm

Compressibility index

It is an important measure that can be obtained from the bulk and tapped densities. A material having values less than 20 to 30% is defined as the free-flowing material, based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$I = DT - Db / DT \times 100$$

Where, I is the Compressibility index, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density

$$H = Dt / Db$$

Where, H is the Hausner's ratio Dt is the tapped density of the powder and Db is the bulk density of the powder. [6-7]

POST COMPRESSION EVALUATION

Thickness

The thickness of each tablet was measured by using vernier caliper and the average thickness was calculated. It is expressed in mm.[8]

Hardness

The hardness of tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. [9]

Friability

The Roche friability test apparatus was used to determine the friability of the Tablets. Ten preweighed Tablets were placed in the apparatus and operated for 100 revolutions and then the Tablets were reweighed. The percentage friability was calculated according to the following formula.[9]

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Weight variation

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

% Weight Variation= Average Weight- Individual Weight /Average Weight x 100

Drug Content

To determine the amount of drug present in each tablet, six tablets from each prepared formulations were taken. To 100ml of pH 6.8 phosphate buffer solution powder drug which is equivalent to wt of one tablet was taken and added in it which is then followed 10 minutes stirring. By using 0.45µ membrane filter the solution was filtered, and it was suitably diluted and with help of UV-Visible spectrophotometer using pH 6.8 phosphate buffer as blank resulting solution absorbance was measured.[10]

Surface pH study

In order to investigate the possibility of any side effects *in vivo* of the buccal tablets prepared, surface pH values of tablets was determined. Buccal mucosa irritation is observed at acidic or alkaline pH, to keep the surface pH as close to neutral as possible it was carried out. Phosphate buffer (pH 6.8) 15 ml is taken in petri dish and tablet was placed in it and was allowed to swell without disturbing for 2 hr at room temperature. By equilibrating the electrode with surface of tablet for 1 minute the surface pH was calculated.[11]

Mucoadhesion test: Mucoadhesive forces of the tablets were determined utilizing modified balance using strips of the sheep buccal mucosa washed with tyrode solution. The mucoadhesive forces of the tablets were determined by the modified pan balance as shown in Figure.

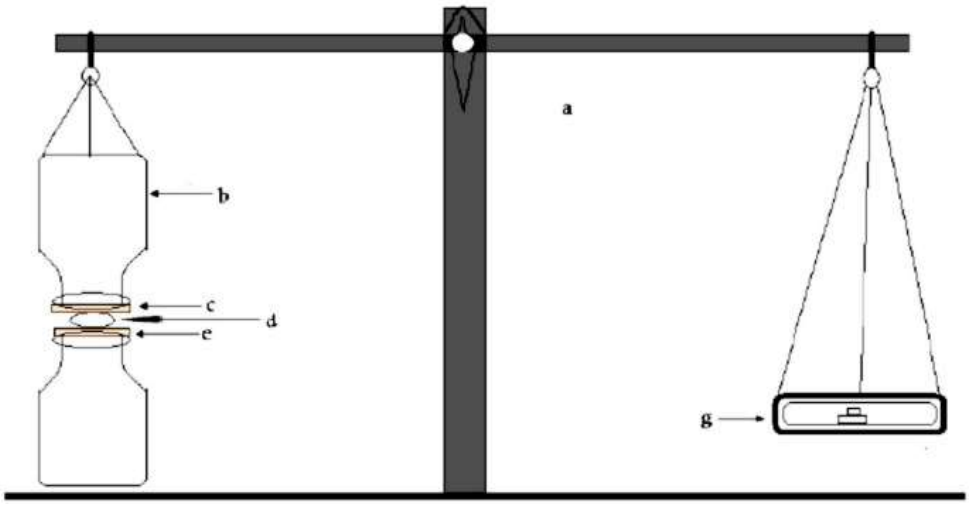

Figure 1: Modified physical balance

The sheep buccal mucosa was cut into the appropriate size pieces and washed with tyrode solution. During the test, a section of buccal mucosa (c) was fitted on the upper glass vial (b) using a rubber band. The exposed mucosa had a diameter of 1 cm. The vial with buccal mucosa (b) was stored in the tyrode solution for 10 min at room 37 C. Then, the vial with buccal mucosa (b) and another vial (e) were fixed on adjusted height which was equal to the thickness of the tablet. To the lower vial, the tablet was placed with the help of bilayered adhesive tape. The position of both vials was adjusted so that the adhesive tape and the buccal mucosa get attached. A constant force was applied to the upper vial to get the tablets attached to buccal mucosa uniformly for 2 min, and then the upper vial was connected to the balance.[12]

Swelling index

15 mL of phosphate buffer (pH 6.8) solution were taken in petri dish and the formulated tablets were taken. The formulated buccal tablets were individually weighed before At regular intervals (1, 2, 3, 4, 5, 6 hr), the buccal tablets were taken out from petri dishes and excess water from the surface was removed with the help of filter paper. The swollen tablets were then reweighed (W2).This experiment was performed. The swelling index (water uptake) is calculated using eq.[13-14]

$$\text{Swelling Index (S.I)} = [(W2-W1)/W1] \times 100$$

Where, W1- initial weight of Tablet, W2- weight of disks at time t

***In Vitro* Release Dissolution**

The in vitro dissolution tests were performed using the USP TYPE II apparatus. With the aid of a dissolution apparatus rotating at 100 rpm. The dissolution medium was 900 ml phosphate buffer (pH 6.8) and the temperature maintained was at 37 ± 1 0C. Samples of the dissolution solution were withdrawn at definite time intervals. The dissolution media was then replaced by fresh dissolution fluid to maintain a constant volume. The solution was filtered to remove any un dissolved solid particles. Then the concentration of TS in solution was measured with an Ultraviolet-Visible spectrophotometer, at a wavelength of 280 nm.[15-16]

Release kinetic studies

In order to determine the release mechanism of the optimised formulation, the data obtained was fitted into the zero, first, higuchi and peppas model and its release mechanism was studied

RESULTS AND DISCUSSION

Evaluation of precompression blend

The precompression blend was characterised with the following such as angle of repose whose values were between 25 to 27 indicating good flowability, carr's index values were in the range of 11 to 14 showing good to free flowing nature and hausner' ratio were less than 1.2 indicating free flowing property.

Table 2: Precompression Blend Evaluation

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's Index (%)	Hausner's ratio
F1	26.56 ±1.4	0.47 ±0.8	0.53 ±0.2	11.32 ±1.8	1.12 ±0.5
F2	25.64 ±0.9	0.41 ±1.2	0.48 ±0.6	14.58 ±0.5	1.17 ±0.6
F3	26.10 ±0.3	0.44 ±0.9	0.51 ±0.1	13.72 ±0.7	1.15 ±0.2
F4	25.17 ±1.2	0.42 ±1.0	0.49 ±1.2	14.28 ±0.1	1.16 ±0.6
F5	27.02 ±0.6	0.46 ±0.2	0.52 ±0.9	11.53 ±1.3	1.13 ±0.3
F6	27.42 ±1.1	0.47 ±0.6	0.54 ±0.7	12.96 ±1.2	1.14 ±0.5

Physicochemical evaluation

The prepared mucoadhesive bilayered buccal tablets were evaluated for its physicochemical parameters such as thickness, hardness, friability, weight variation and drug content whose values were presented in the following table.

Table 3: Physicochemical Evaluation Parameters

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug Content (%)
F1	200.1±1.63	4.74±0.24	5.5±0.58	0.47±0.02	99.2±0.52
F2	202.3±0.54	4.76±0.72	5.3±0.32	0.61±0.10	98.4±0.37
F3	200.2±0.37	4.73±0.43	5.6±0.26	0.49±0.34	99.3±0.41
F4	200.4±1.32	4.75±0.40	5.9±0.21	0.46±0.31	99.6±0.34
F5	199.2±0.61	4.78±1.64	6.1±0.42	0.63±0.06	98.2±0.22
F6	201.3±0.41	4.8±1.39	6.2±0.13	0.62±0.22	98.7±0.91

Surface pH:

The surface pH values for the prepared tablets are shown in the given table. The values were found to be near to that of buccal pH (6.8) hence it can be stated that the prepared tablets does not show any irritation in oral cavity.

Table 4: Data for Surface pH Studies.

S.no	Formulation code	Value
1.	F1	6.84±0.45
2.	F2	6.93±1.05
3.	F3	7.18±1.09
4.	F4	6.89±0.35
5.	F5	5.92±0.49
6.	F6	5.87±0.18

Mucoadhesive strength: The optimised formulation was selected and mucoadhesive test was carried out and the result indicates that 25.27 gm of strength was required for its detachment from the surface.

Swelling index:

The mucoadhesive bilayered buccal tablets which were prepared using polymers such as hydroxypropyl methyl cellulose and PVP in combination with carbopol demonstrated the following data for swelling studies. The tablets containing HPMC and Carbopol showed faster swelling behaviour when compared to tablets containing PVP and Carbopol.

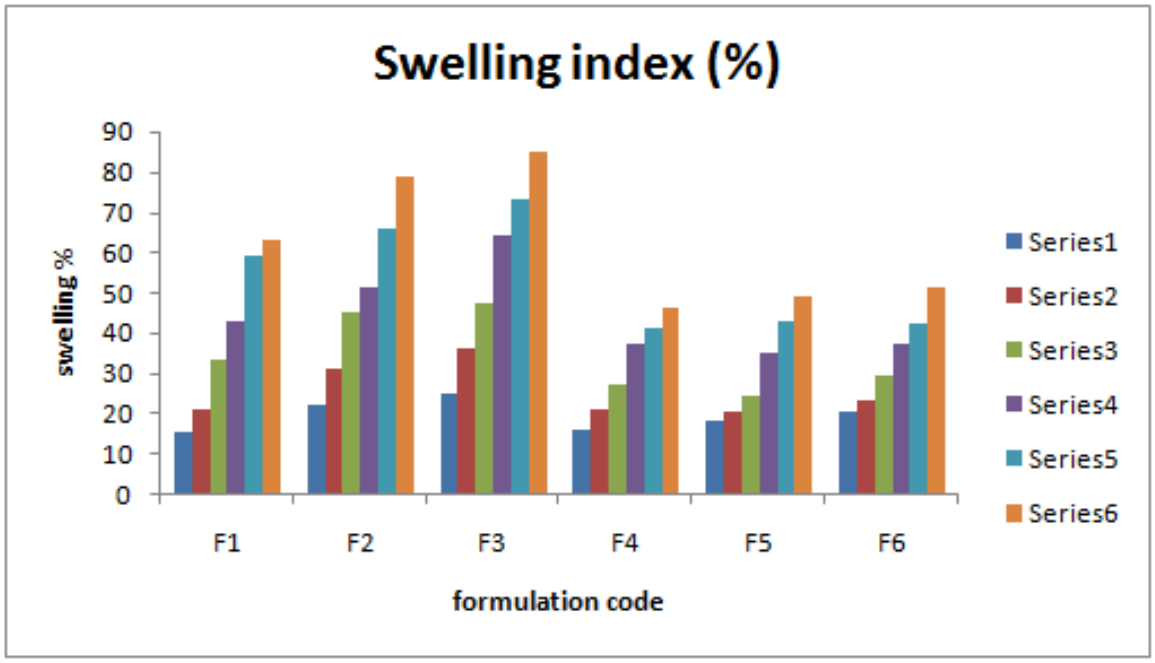

Figure 2: Comparitive Swelling behaviour of formulations (F1 to F6)

CUMULATIVE % DRUG RELEASE:

Invitro dissolution test was performed for the prepared mucoadhesive bilayered buccal tablets containing HPMC, PVP and Carbopol in different concentrations. The tablets containing HPMC and carbopol (F1 to F3) showed better drug release compared to tablets containing PVP and Carbopol (F4 to F6). Drug release in PVP and carbopol containing tablets was incomplete and time taking with respect to HPMC and Carbopol containing tablets.

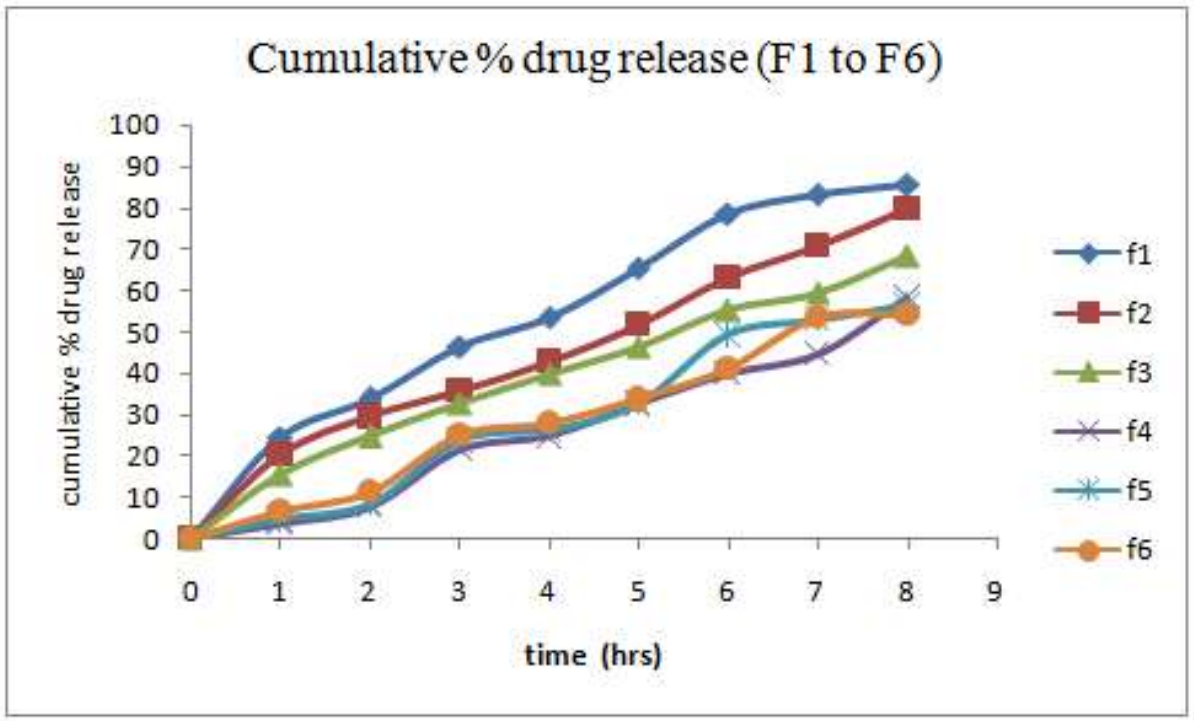

Figure 3: Comparitive Dissolution data for *invitro* release (F1to F6)

Release kinetics

The release kinetics of the optimised formulation demonstrated that it follows the first and higuchi model of the release mechanism.

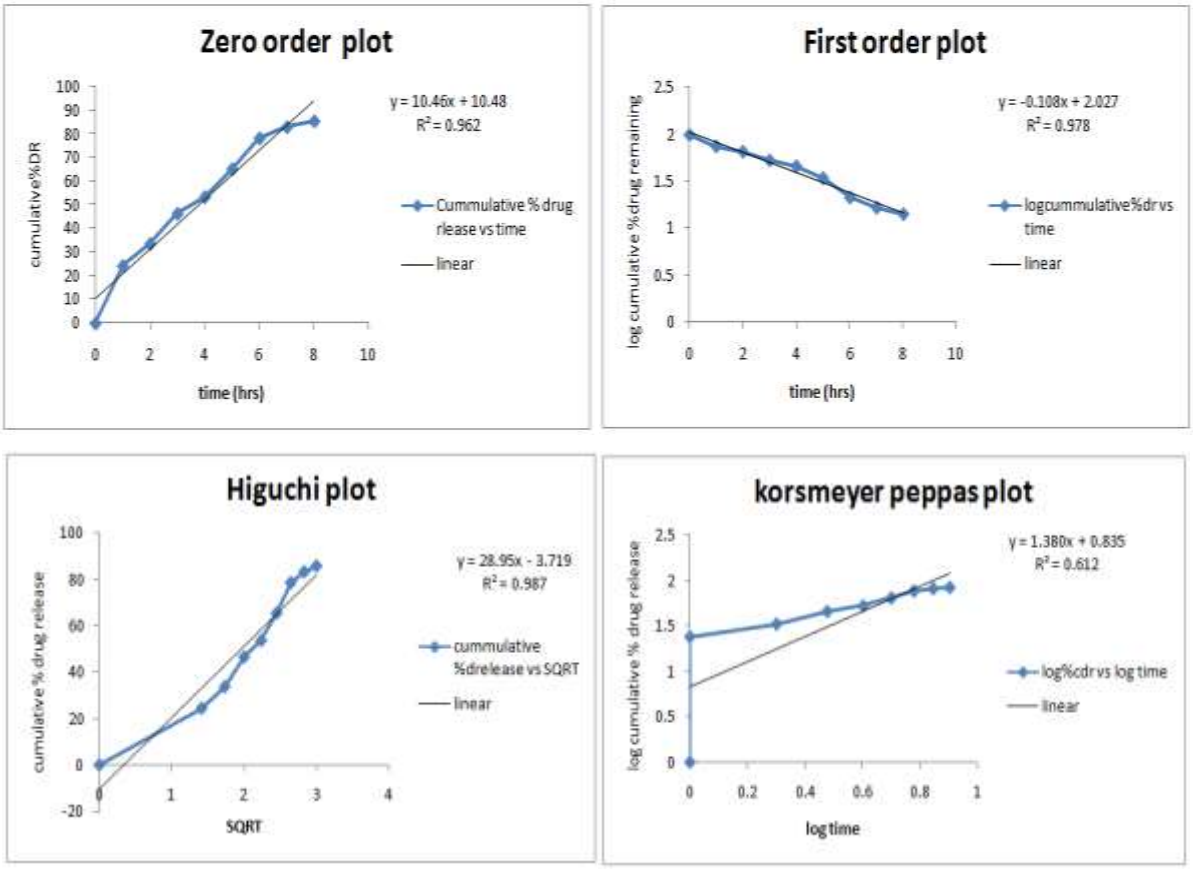

Figure 4: kinetic analysis studies

STABILITY STUDIES:

Stability studies were carried out for optimised formulation selected and was characterised for % drug release, drug content and physical appearance which indicated that no significant changes were observed in the formulation during the storage conditions.

CONCLUSION

The study was carried out to develop Mucoadhesive Buccal bilayered tablets which were formulated using polymers such as hydroxypropyl methyl cellulose (HPMC), Polyvinyl pyrollidone (PVP), carbopol in different concentrations (F1 to F6). Ziprasidone HCL was used in treatment of psychoses. The formulation F1 prepared using HPMC (25 mg) and CP (10 mg) was selected as the optimised formulation based on the comparitive results obtained from the prepared formulations which showed pre evaluation results to be within the acceptable limits. The mucoadhesive strength of F1 was observed as 25.27gm, *invitro* results of F1 showed 85.7 % drug release and stability studies showed it was stable throughout the shelf life of the product and revealed it follows first order kinetics and follows higuchi order kinetics. Hence it showed that mucoadhesive bilayered buccal tablets can be developed with good drug release property.

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