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DESIGN AND *IN VITRO* EVALUATION OF BILAYERED BUCCAL TABLETS OF TERBUTALINE SULPHATE

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ABSTRACT

The aim of this work was to develop a tablet for the buccal delivery of the poorly water-soluble drug Terbutaline sulphate which is a selective beta-2 adrenergic agonist used as a bronchodilator and tocolytic. Useful in treatment of fast acting bronchodilator (often used as a short-term asthma treatment) and as a tocolytic to delay premature labor for that an attempt was made to solubilizing Terbutaline sulphate in buccal and then delivery via buccal mucosa. HPMC K100 and carbopol were selected as mucoadhesive polymers while Ethyl cellulose, as backing material. The complexation was studied by solubility method which indicates the formation of complex with in stoichiometry. The complexation was further characterized and studied by FTIR. Modification of the release for a poorly water-soluble drug, Terbutaline sulphate from. The buccoadhesive tablets for the delivery of Terbutaline sulphate were prepared by factorial designs by direct compression of HPMC K100 and Carbopol. The tablets were evaluated for their dissolution, surface pH, swelling study and mucoadhesive properties. The Surface pH of all formulations was found to be within ±1 units of neutral pH hence these formulations should not cause any irritation in buccal cavity. CP showed superior bioadhesion properties compared to HPMC. The in vitro release results demonstrated that drug is released by non-Fickian diffusion mechanism with first order kinetics. From the drug release data, it is evident that formulation F5 has shown highly satisfactory values forcorrlation coefficient percentage in vitro release 0.994. swelling index = 78.4±1.04after 6 hours) best formulation with correlation coefficient of 0.994 Hence, formulation F5 may be considered as the optimized buccal tablet containing Terbutaline sulphate improved bioavailability.

KEY WORDS

Terbutaline sulphate CP 934, PVP K30, SCMC, HPMCK100; Buccal delivery.

INTRODUCTION

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes.

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). Buccal and sublingual sectors are the most appropriate for drug delivery and they may be used for the treatment of local or systemic diseases [(1)]. The sublingual mucosa is more permeable and thinner than the buccal mucosa and, because of the considerable surface area and high blood flow; it is a

feasible site when a rapid onset is desired. The sublingual route is generally used for drug delivery in the treatment of acute disorders, but it is not always useful because its surface is constantly washed by saliva, and tongue activity makes it difficult to keep the dosage form in contact with the mucosa for an extended period of time. Unlike the sublingual mucosa, the buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of a retentive sustained or controlled release system, well accepted by patients. The buccal mucosa is relatively permeable, robust and, in comparison with other mucosal tissues, is more tolerant to potential allergens and has a reduced tendency to irreversible irritation or damage. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies.

In addition, the buccal mucosa is a well vascularized tissue and is easily accessible for both application and removal of a delivery device [(2)]. It's having facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions.

MATERIALS AND METHODS

Terbutaline sulphate, Spectrum labs Hyderabad; Hydroxy propyl methyl cellulose K100M, Poly vinyl pyrrolidine k 30, Carbopol 934, Drugs India, Hyderabad; Sodium carboxy methyl cellulose, Sd fine Chem.Ltd. Mumbai; Ethyl cellulose, Sd fine Chem.Ltd. Mumbai Lactose, Sd Fine Chem.Ltd. Mumbai Mannitol, Sd fine Chem.Ltd. Mumbai; Magnesium stearate, Sd fine Chem.Ltd. Mumbai; Potassium Dihydrogen phosphate, Hi Pure fine chem. Industries, Chennai; Sodium hydroxide, Qualigens fine chemicals, Mumbai; Dimethyl sulfoxide, Sd fine Chem.Ltd. Mumbai

CONSTRUCTION OF CALIBRATION CURVE

100 mg of the drug (Terbutaline sulphate) was dissolved in 7.2 pH Phosphate buffer and made up to 100 ml with the same to give a concentration of 1000 µg/ml. From this stock solution, 10 ml was taken and diluted to 100 ml with the same buffer to give the concentration of 100 µg/ml, from this 0.2, 0.4, 0.6…2ml of the solution was transferred to 10 ml volumetric flasks and made up to the volume with 7.2 phosphate buffer to give the concentrations of 2, 4, 6, ……20 µg/ml. Then the absorbance was measured at 2723 nm against a blank using UV Spectrophotometer. Using these absorbance values the standard graph was plotted by taking concentration on X-axis and absorbance onY-axis.

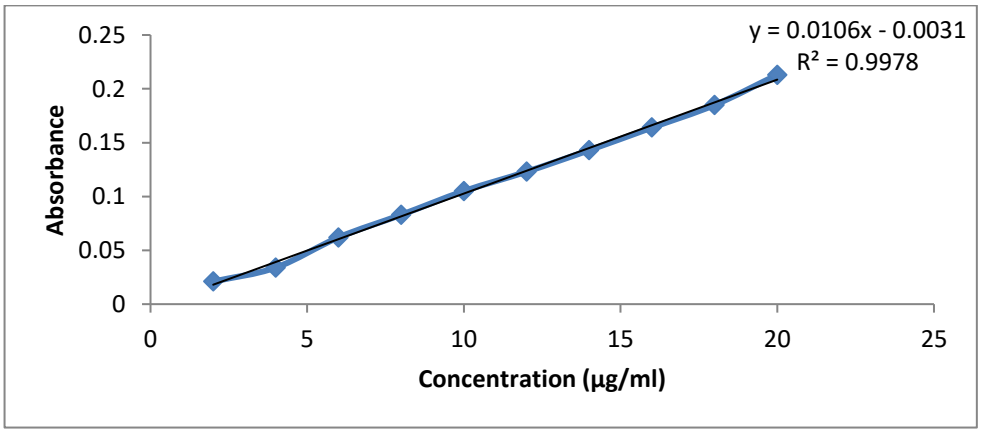


Figure No 1: Calibration curve of Terbutaline sulphate

Preparation of Buccoadhesive bilayer tablets

Bilayer buccoadhesive tablets containing Terbutaline sulphate were prepared by direct compression method4-7. Various batches were prepared by changing the ratio of HPMC K 100, SCMC and PVP K 30 to identify the most effective formulation. The drug and polymer mixture was prepared by homogeneously mixing the drug with HPMC K 100, SCMC, PVP K-30, CP-934 (mucoadhesive polymers), Mannitol and lactose (diluents) in a glass mortar for 15 minutes. Before direct compression, the powder were screened through a 60 µm sieve and thoroughly blended. The blend was lubricated with magnesium stearate for 3-5 min. The mixture (100 mg) was then compressed using

an 8 mm diameter die in a 9-station rotary punching machine (Ahmadabad, India). The upper punch was raised, and the backing layer of EC was placed on the above compact; the two layers were then compressed into a mucoadhesive bilayer tablet. Each tablet weighed 150 mg and the compositions of Terbutaline sulphate bilayer buccal tablets were given in Table No:1

Table No: 1 Formulation of bilayer buccal tablets

Formulation ode	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Terbutaline sulphate	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
HPMC K	25	-	12.5	12.5	25	-	6.25	25	6.25	37.5	-	-	12.5	12.5	12.5
SCMC	12.5	25	-	25	-	12.5	6.25	6.25	25	-	37.5	-	12.5	12.5	12.5
PVP K 30	-	12.5	25	-	12.5	25	25	6.25	6.25	-	-	37.5	12.5	12.5	12.5
CP 934	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose	18	18	18	18	18	18	18	18	18	18	18	18	18	32.5	-
Mannitol	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	-	32.5
EC	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Total Wt	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

DRUG –POLYMER COMPATIBILITY STUDIES BY FTIR

Drug polymer compatibility studies were performed by FT-IR (Fourier transform infrared spectroscopy). Infrared (IR) spectra were obtained on a Perkin Elmer 2000 IR system (Perkin Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm-1 and the resolution was 1 cm-1. FTIR absorption spectra of pure drug and all the polymers used like HPMC, SCMC, CP, PVP, EC and the combination of drug and polymers were shows no significant interaction between drug and polymers. The spectra obtained were shown in the Figure 2.

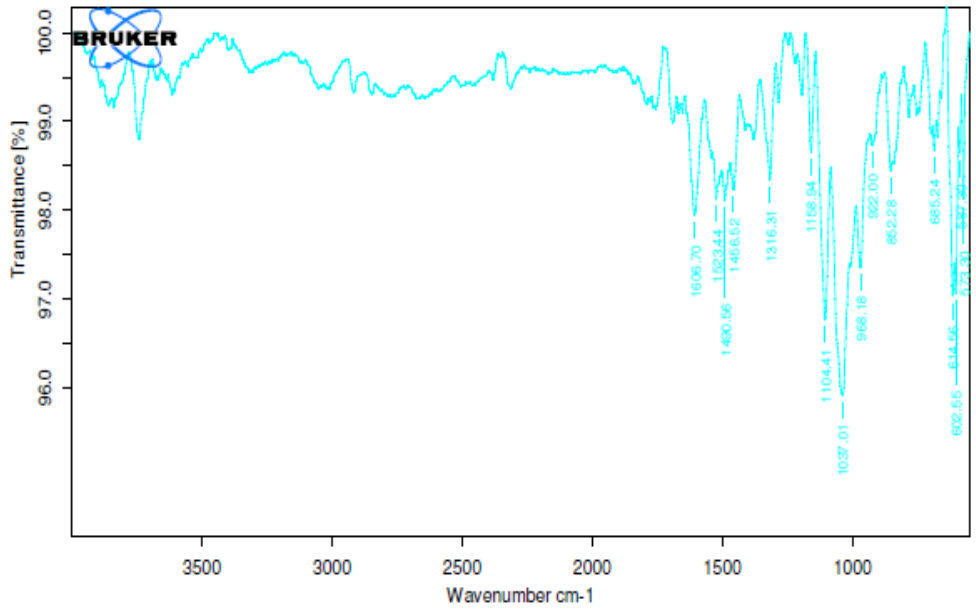


Figure.2 FTIR Spectra of Terbutaline sulphate

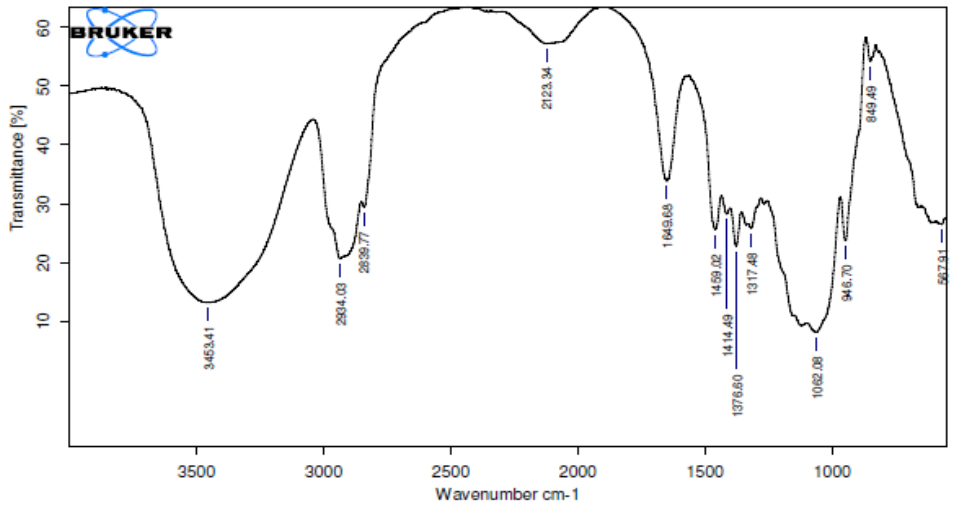


Figure.3 FTIR Spectras of HPMC K100

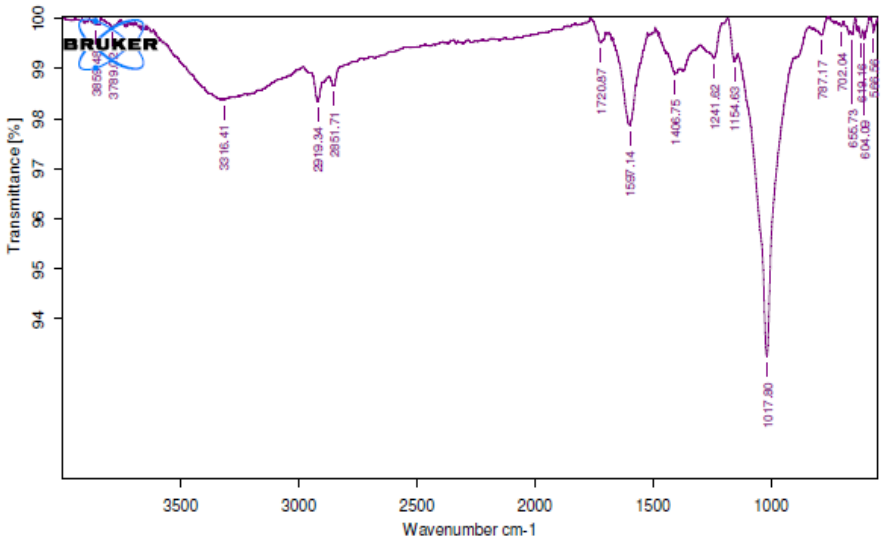


Figure.4 FTIR Spectra of Sodium Carboxyl Methyl Cellulose

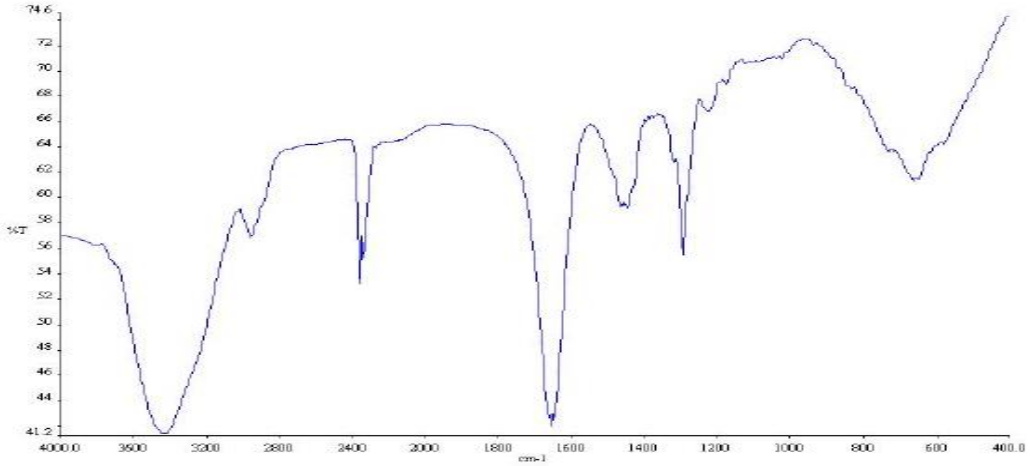


Figure.5 FTIR Spectra of PVP K30

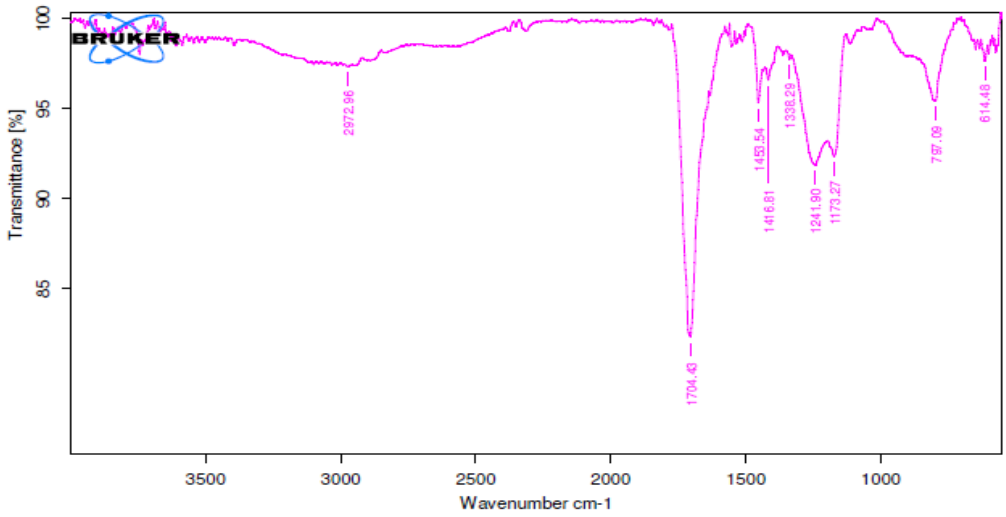


Figure.6 FTIR Spectra of Carbopol 934

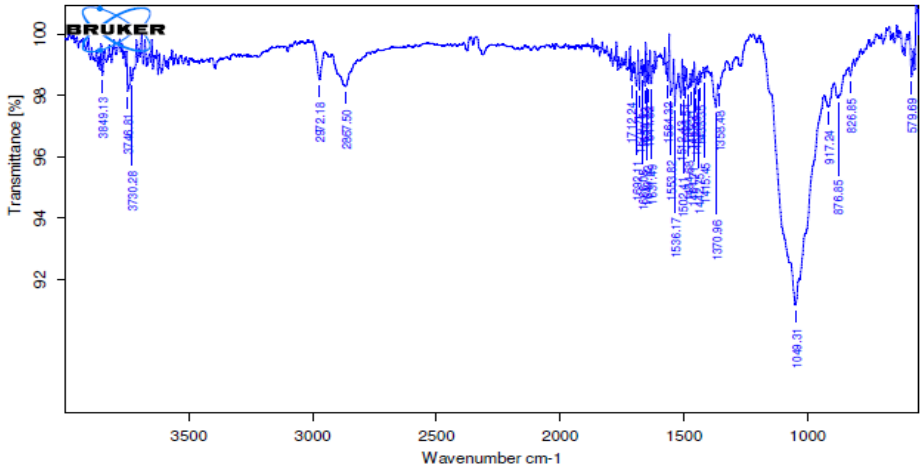


Figure.7 FTIR Spectra of Ethyl Cellulose

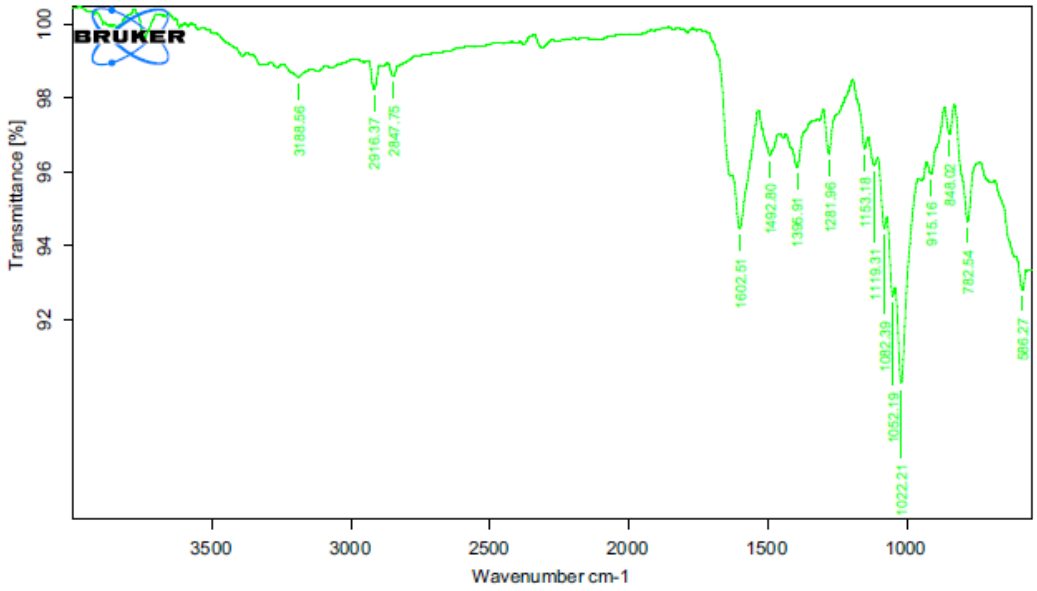


Figure.8 FTIR Spectra of optimized formulation

PREFORMULATION STUDIES[9,10]

Before formulation of drug substances into a dosage form, it is essential that drug polymer should be chemically and physically characterized. Preformulation studies gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the manufacture of a dosage form.

Derived properties

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,

$$Db = M / V_O$$

Where, M is the mass of powder and V_O 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.

$$DT = M / V_T$$

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.

$$I = DT - D_b / D_T \times 100$$

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

$$H = D_t / D_b$$

Where, H is the Hausner's ratio Dt is the tapped density of the powder and Db is the bulk density of the powder.

Table No: 2 Limits for flow properties of powder

S.NO	Type of flow	Angle of repose	Carr's index	Hausner's ratio
1	Excellent	25-30	10	1-1.11
2	Good	31-35s	11-15	1.12-1.18
3	Fair	36-40(aid not needed)	16-20	1.19-1.25
4	Passable	41-45(may hang up)	21-25	1.26-1.34
5	Poor	46-55(must agitate)	26-31	1.35-1.45
6	Very poor	56-65	2-37	1.46-1.54
7	Very very poor	>66	>38	>1.60

Table No: 3 Results for Derived and Flow properties

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
C1	0.434±0.01	0.492±0.015	26.45±0.30	11.47±1.97	1.128±0.02
C2	0.449±0.015	0.505±0.02	27.26±0.39	11.21±1.96	1.128±0.03

C3	0.490±0.015	0.57±0.01	24.94±0.68	11.87±3.97	1.138±0.05
C4	0.479±0.015	0.527±0.015	23.22±0.96	9.45±1.81	1.109±0.02
C5	0.432±0.02	0.498±0.03	25.95±0.73	12.65±2.25	1.145±0.03
C6	0.45±0.01	0.466±0.006	24.24±0.36	9.32±3.16	1.107±0.04
C7	0.452±0.025	0.532±0.025	28.26±0.29	15.56±1.19	1.185±0.02
C8	0.44±0.01	0.55±0.017	23.82±0.40	11.65±3.61	1.127±0.05
C9	0.45±0.01	0.457±0.025	25.14±0.34	10.84±2.84	1.116±0.04
C10	0.443±0.015	0.516±0.032	26.75±0.63	14.23±1.11	1.164±0.01
C11	0.405±0.02	0.48±0.01	23.96±0.46	13.48±2.48	1.156±0.03
C12	0.416±0.02	0.476±0.015	28.24±0.27	14.22±3.22	1.158±0.02
C13	0.454±0.015	0.514±0.02	22.86±0.39	12.24±1.75	1.142±0.02
C14	0.45±0.017	0.485±0.02	26.95±0.54	13.05±4.32	1.156±0.08
C15	0.458±0.015	0.8±0.02	25.84±0.28	9.29±2.71	1.105±0.03

PHYSICO-CHEMICAL EVALUATION

Thickness[11]

The thickness of each tablet was measured by using vernier caliper and the average thickness was calculated.

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

Hardness [12]

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

Friability [13]

The Roche friability test apparatus was used to determine the friability of the Tablets. Twenty pre-weighed 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.

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

Drug Content [14]

Drug content uniformity was determined as triplicate by dissolving the tablets in DMSO (Dimethyl sulfoxide) and filtering with Whatman filter paper (0.45 µm, Whatman, Maidstone, UK). The filtrate was evaporated, and the drug residue dissolved in 100 ml of phosphate buffer (pH 7.2). The 5 ml solution was then diluted with phosphate buffer up to 20 ml, filtered through Whatman filter paper and analyzed at 272 nm using a UV spectrophotometer.

Surface pH study [15]

The surface pH of the buccal Tablets was determined in order to investigate the possibility of any side effects in *vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible, the tablet was allowed to swell by keeping it in contact with 5 ml of phosphate buffer containing agar medium (pH 7.2±0.01) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the Tablet and allowing it to equilibrate for 1 minute.

Swelling index [16,17]

The swelling index of tablets was determined by gravimetry. The swelling rate of the bioadhesive tablet was evaluated by using 1 % agar gel plate. The average weight of the tablet was calculated (W_1). The tablets were placed on gel surface in a petri dish placed in an incubator at 37±1°C. Tablets was removed at different time intervals (1, 2, 3, 4, 5 and 6 h), wiped with filter paper and reweighed (W_2). The swelling index was calculated by the formula.

$$\text{Swelling Index (S.I)} = [(W_2 - W_1)/W_1] \times 100$$

Where, W_1- initial weight of Tablet, W_2- weight of disks at time t

***In Vitro* Release Dissolution**

The in vitro dissolution tests were performed using the basket method of USP 24. With the aid of a dissolution apparatus (TDT 08L Dissolution Tester Electro Lab) rotating at 100 rpm. The dissolution medium was 900 ml phosphate buffer (pH 7.2) and the temperature maintained was at 37 ± 1 ^{0}C. 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 272 nm. The test was carried out in triplicate

Kinetic Fitting of Data

Data of *in-vitro* release were fit into different equations and kinetic models to explain the release kinetics of Terbutaline sulphate from the buccal tablet. The kinetic models used were a zero-order equation, higuchi's model and peppa's models. The obtained results in these formulations were plotted in various model treatment are as follows. I.e. Cumulative percentage release of drug Vs Square root of time (Higuchi's) and Log cumulative percentage release Vs Log time (Peppas). To know the mechanism of drug release of Terbutaline sulphate from the buccal tablet the drug release data was fit into higuchi's models.

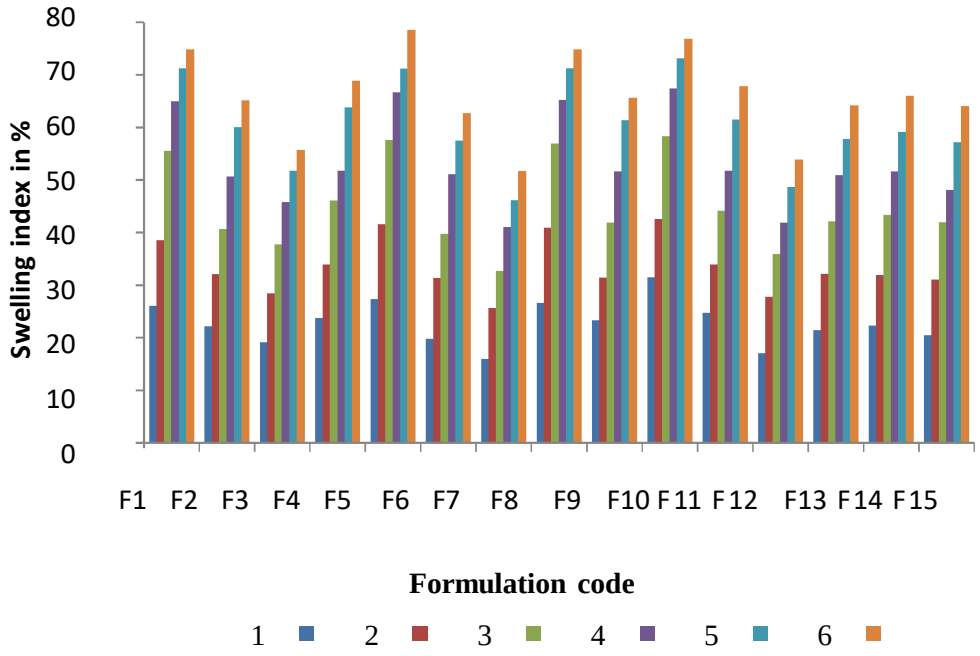
Table No: 4 Physicochemical evaluation of bilayer buccal Tablets of Terbutaline sulphate

Formulation Code	Thickness (mm) ± SD	Weight variation mg ± SD	Hardness (Kg/cm^2) ±SD	Friability (%) ± SD	Drug content mg ± SD	Surface pH ± SD
F1	2.14±0.03	148±1.55	4.5±0.15	0.46±0.025	12.58±0.41	6.42±0.061
F2	2.19±0.02	145±0.94	4.6±0.25	0.55±0.03	12.86±0.19	6.71±0.03
F3	2.12±0.03	147±0.81	4.2±0.31	0.62±0.042	12.32±0.48	6.62±0.026
F4	2.15±0.05	145±0.72	3.5±0.21	0.47±0.036	15.29±0.41	6.75±0.040
F5	2.18±0.03	149±0.19	4.6±0.2	0.45±0.01	15.45±0.15	7.55±0.065
F6	2.16±0.04	148±0.84	4.4±0.26	0.53±0.02	12.16±0.01	6.72±0.066
F7	2.14±0.07	152±0.38	4.2±0.31	0.64±0.038	15.23±0.03	7.77±0.061
F8	2.19±0.02	145±0.52	4.6±0.25	0.57±0.025	15.15±0.65	7.52±0.066
F9	2.13±0.02	146±0.76	4.2±0.45	0.45±0.01	12.74±0.31	6.75±0.045
F10	2.15±0.02	149±0.41	4.5±0.41	0.48±0.026	12.46±0.15	6.72±0.04
F11	2.22±0.03	153±0.82	4.6±0.21	0.47±0.03	15.07±0.44	7.63±0.045
F12	2.17±0.03	145±0.48	4.3±0.15	0.68±0.025	15.35±0.61	7.65±0.077
F13	2.18±0.02	148±0.65	4.4±0.31	0.46±0.015	12.91±0.45	6.73±0.049
F14	2.17±0.01	146±0.23	4.2±0.41	0.44±0.036	15.16±0.35	7.65±0.056
F 15	2.19±0.02	148±0.57	3.9±0.15	0.52±0.041	12.65±0.28	6.76±0.080

Table No: 5 Swelling index data for all formulations

Formulation code	Swelling index ± S. D					
	Time in h					
	1	2	3	4	5	6
F1	24.15±0.76	37.55±1.08	53.55±0.80	62.97±0.70	72.25±0.76	73.85±0.27
F2	23.26±0.72	33.19±0.91	42.72±0.46	52.72±0.54	61.05±0.61	62.22±0.53
F3	20.25±0.64	26.45±0.63	39.81±0.67	43.85±0.68	52.2±0.66	57.72±0.51
F4	21.74±1.08	34.96±0.48	48.14±0.93	54.84±0.69	62.84±0.28	69.91±0.93
F5	24.48±1.03	42.64±0.90	55.65±0.53	62.65±0.75	72.25±0.61	78.6±1.04
F6	21.88±0.67	33.48±0.98	38.81±0.67	52.15±0.62	59.55±1.08	64.73±0.43
F7	18.06±0.84	26.64±0.75	34.77±0.54	43.17±0.88	48.44±0.87	53.72±0.64
F8	22.65±0.72	39.95±0.79	58.96±0.86	63.36±0.97	72.32±0.30	71.85±0.60
F9	21.32±1.12	33.46±0.64	43.94±0.93	53.61±0.57	63.45±0.63	62.67±0.64
F10	30.47±0.93	41.62±0.77	55.45±0.79	63.45±0.96	75.14±0.61	77.88±0.65
F11	23.75±0.38	31.91±0.81	46.14±0.91	53.82±0.67	62.56±1.06	64.84±0.51
F12	18.13±0.55	29.75±0.61	37.96±0.86	43.95±0.88	46.72±0.65	51.92±0.75
F13	22.45±0.94	31.23±0.82	44.18±0.37	49.91±0.82	59.81±0.99	62.26±0.78
F14	19.14±0.65	33.91±0.49	45.39±0.48	54.65±0.49	58.19±0.70	68.05±0.83
F15	21.41±0.76	34.17±0.75	43.05±0.86	47.19±0.62	59.2±0.40	65.04±0.63

Figure.9 Swelling index after 6 h for formulation F5



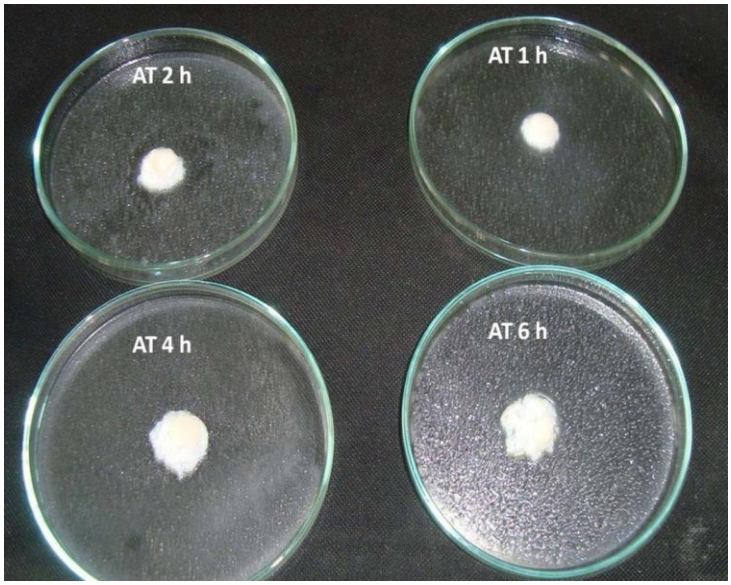


Figure.10Swelling index after 6 h for formulation F5

***IN-VITRO* DRUG RELEASE STUDY**

The USP type II rotating paddle method was used to study the drug release from the bilayer Tablet. The dissolution medium consisted of 900 ml of phosphate buffer pH 7.2. The release study was performed at 37 ± 0.5° C, with a rotation speed of 50 rpm. The backing layer of the buccal Tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, with appropriate dilutions with phosphate buffer pH 7.2 and were analyzed spectrophotometrically at 272 nm.

Table No:6 *In-vitro* drug release data for bi layer buccal tablet F5

***In-vitro* drug release data**		**Higuchi's data**		**Peppa's data**	
Time in h	**Cumulative % Release**	**SQRT of time**	**Cumulative % release**	**Log time**	**Log cumulative % release**
0	0	0	0		1.10723
1	12.4	1	12.4	0	1.2836
2	19.1	1.414216	19.1	0.30105	1.45935
3	28.2	1.732053	28.2	0.477123	1.55872
4	36.7	2	36.7	0.60208	1.63748
5	43.6	2.236066	43.6	0.69899	1.70419
6	50.5	2.44947	50.5	0.778153	1.78677
7	61.6	2.645753	61.6	0.845096	1.84265
8	69.7	2.828425	69.7	0.90311	1.89326
9	78.8	3	78.8	0.954245	1.93652
10	86.5	3.162276	86.5	1	1.96757
11	92.7	3.316627	92.7	1.041395	1.99388
12	98.9	3.464104	98.9	1.079183	1.10726

Figure no. 11 *In-vitro* drug release data for formulation F5

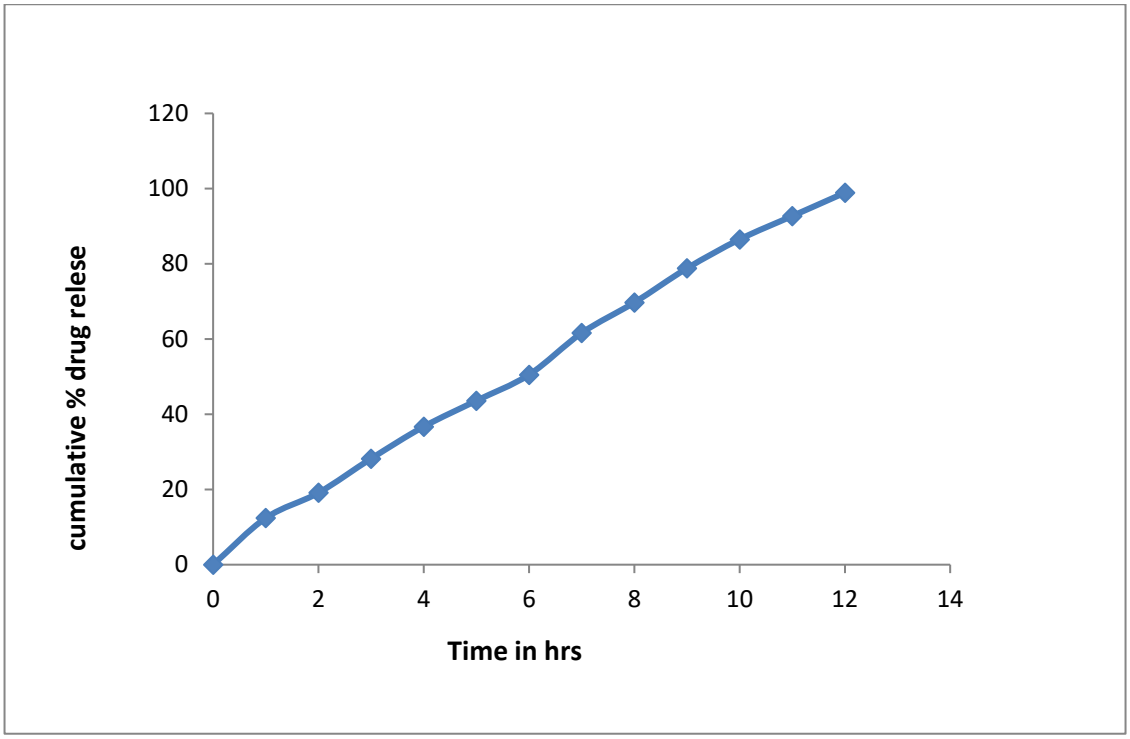


Figure no. 12 Higuchi's plot for formulation F5

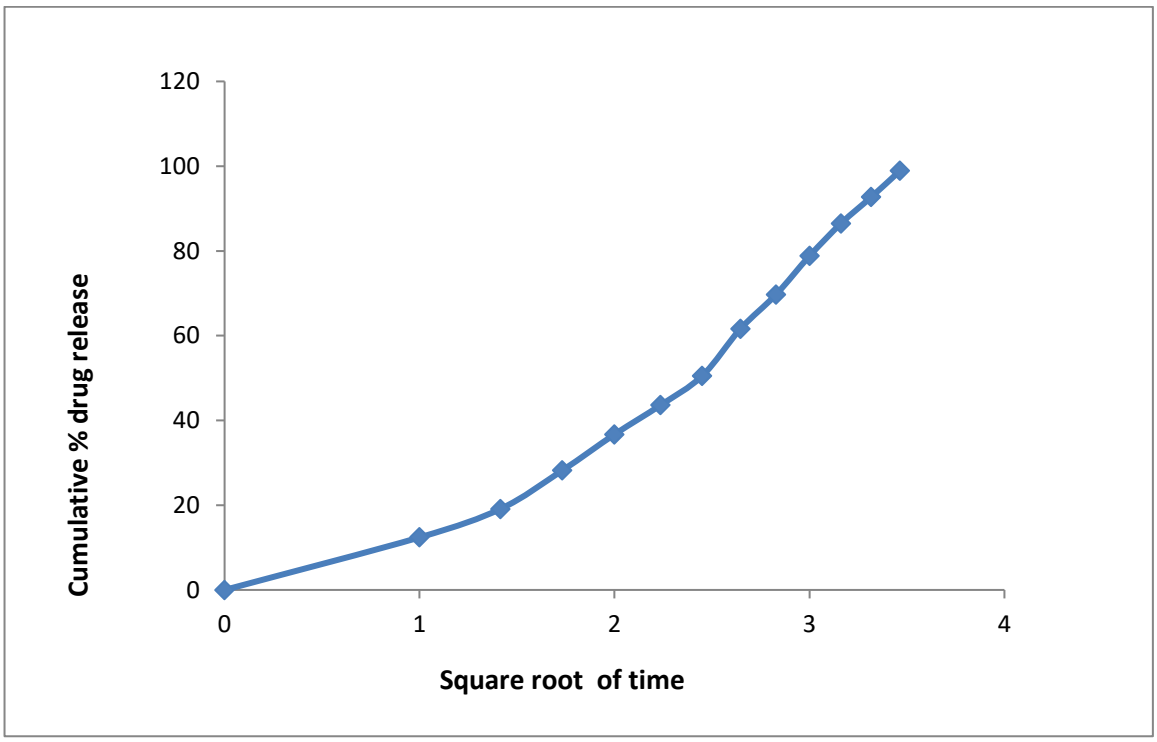
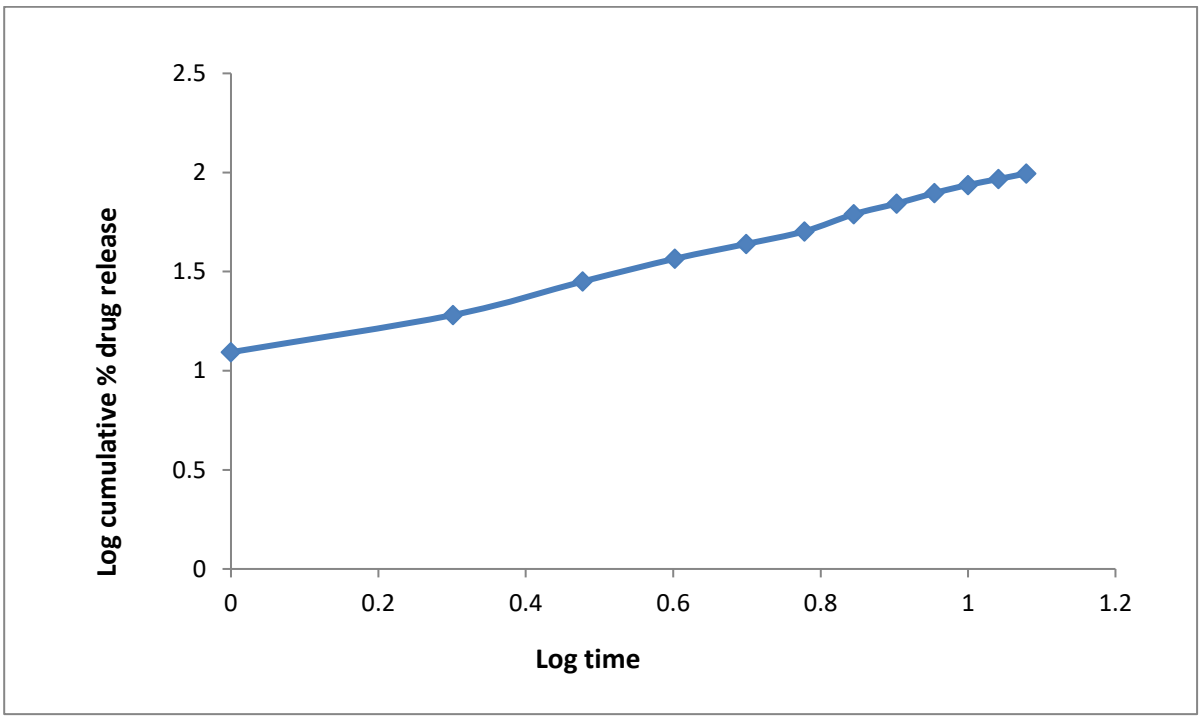


Figure no. 13 Peppa's plot for formulation F5



Stability study

The formulation F5 was selected and the stability studies were carried out at accelerated condition of 40±2°C, 75±5 % RH conditions, stored in desiccators, the tablets were packed in amber colour screw cap container and kept in above said condition for period of three months. The tablets were analyzed periodically for their physical appearance, buccoadhesive strength and *in-vitro* drug release. Results were analyzed by One-way ANOVA followed by Tukey's test. Differences were considered statistically significant at $p<0.05$.

Table No: 6 Stability studies of best formulation (F5)

Parameters	1st month	2nd month	3rd month	p value
Physical appearance	No Change	No Change	No Change	-
Buccoadhesive strength	34.86±1.09ns	35.4±1.09ns	37±0.34ns	0.1538
In-vitro drug release	98.08±0.55ns	98.15±0.32ns	98.28±0.5ns	0.8706

All values are expressed as Mean±SD ns = non-significant

Distinguishable difference was observed in the release of Terbutaline sulphate in all formulations. The results and data of in vitro studies are shown in the Table No: 2 to 7 and the individual graphs were shown in 4-48, The comparative in-vitro drug release, Higuchi's and peppa's models were shown in the Graph No: 11-16. Formulations F1, F2, F3, F4, F5 and F6 containing Combination of HPMC, SCMC, PVP and carbopol gave a reasonable Terbutaline sulphate release up to 12 hr. The formulations F1, F2, F3, F4, F5 and F6 has shown release 98.5 %, 97.3%, 97.4 %, 98.4 %, 98.9 % and 97.8 % respectively. The in-vitro drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). The diffusion exponent (n) obtained by peppas plot showing 0.93067, 0.85066, 0.89323, 0.85197, 0.85956, 0.89929 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations F2, F4 and F5 and Super case II transport type in of case of formulations F1, F3 and F6.

Formulations F7, F8, F9, F10 and F11 containing HPMC, SCMC alone and Combination of HPMC, SCMC, PVP and Carbopol gave a reasonable Terbutaline sulphate release up to 12 hr.

The formulations F7, F8, F9, F10 and F11 has shown release 97.7%, 98.2% 98.2 %, 98.2 %, and 97.4 % respectively. The in-vitro drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value

(R). Peppa's plot was drawn which has shown slope value of 0.8421, 0.94699, 0.83522, 0.91332 and 0.83572 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations F7, F9, F11and Super case II transport type in of case of formulations F8 and F10.

Formulations F12, F13, F14 and F15 containing PVP alone and Combination of HPMC, SCMC, PVP and CP gave a reasonable Terbutaline sulphate release up to 10 h.Formulations F12, F13, F14 and F15 has shown release 96.2% , 96.9%, 97.4% and 96.7% respectively

The in-vitro drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). Peppa's plot was drawn which has shown slope value of 0.82907, 0.83835, 0.82543, 0.88105 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations F12, F13, F14 and F15.

The incorporation of HPMC, SCMC, PVP and Carbopol bilayer buccal tablets, the drug release was found to maximum at the end of 12th hr.

Figure no-14 In-*vitro* drug release data for formulation F1 – F5

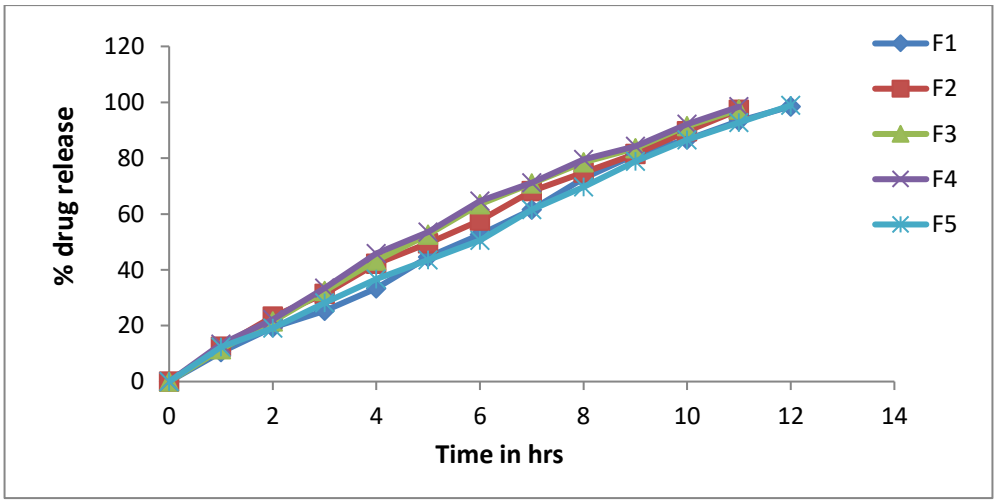


Figure no-15 In-*vitro* drug release data for formulation F6 – F10

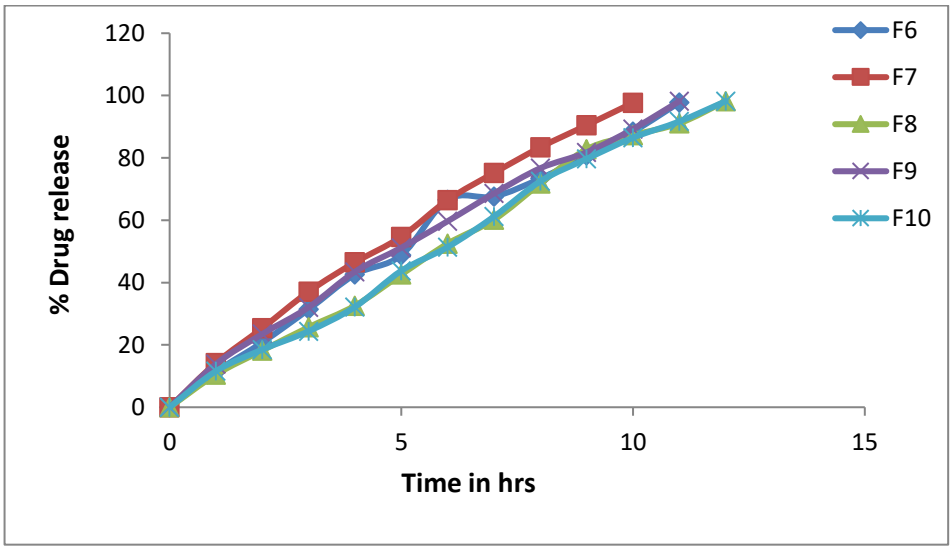
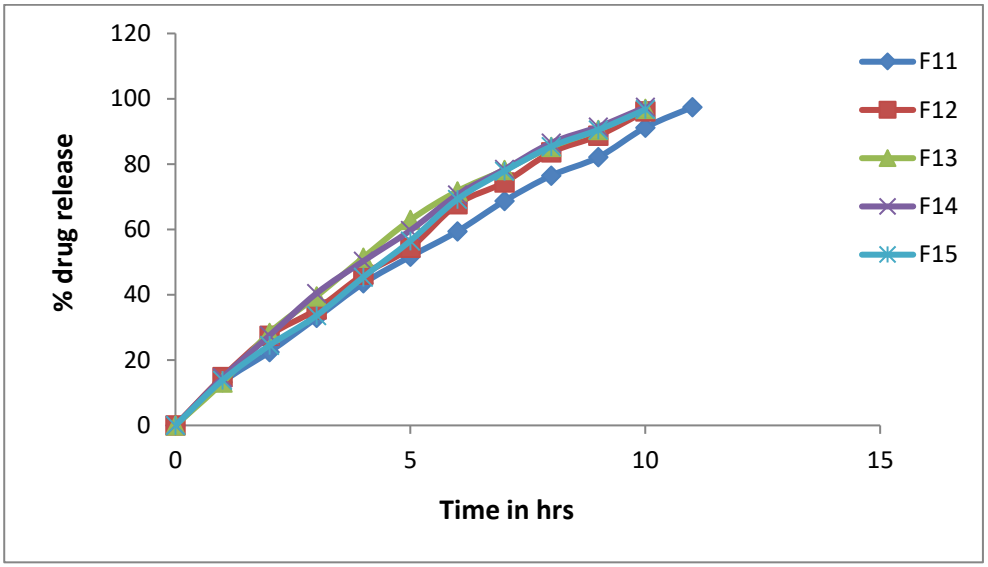


Figure no-16 *In-vitro* drug release data for formulation F10 – F15



To find out the mechanism of drug release from hydrophilic matrices, the *in- vitro dissolution* data of each formulation with different kinetic drug release equations[76]. Namely Zero order: Q=K0t; Higuchi's square rate at time: $Q=KHt_{1/2}$ and Peppas: $F=K_m t^n$, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K0 is zero order kinetic drug release constant, KH is Higuchi's square root of time kinetic drug release constant, Km is constant incorporating geometric and structural characteristic of the films and n is the diffusion exponent indicative of the release mechanism. The correlation coefficient values (r^2) indicate the kinetic of drug release was zero order. (Table No: 8). The mechanism of drug release was by peppas model indicates the non fickian release and super case II transport evidenced with diffusion exponent values (n) (Table No: 8 and 9)

Table No: 8 Diffusion characteristics of Terbutaline sulphate buccal tablet formulations

Formulation code	Correlation coefficient values (r^2)		Diffusion exponent value (n) in Peppa's model
	Zero order	Higuchi's model	
F1	0.996	0.929	0.930671
F2	0.994	0.952	0.85066
F3	0.989	0.954	0.89323
F4	0.988	0.958	0.851974
F5	0.997	0.935	0.859561
F6	0.995	0.947	0.899291
F7	0.992	0.956	0.8421
F8	0.995	0.926	0.946998
F9	0.993	0.956	0.835221
F10	0.995	0.927	0.913316
F11	0.993	0.999	0.83572
F12	0.989	0.997	0.829072
F13	0.974	0.993	0.838346
F14	0.981	0.995	0.82543
F15	0.987	0.993	0.881046

Table No: 9 Diffusion exponent drug release mechanism

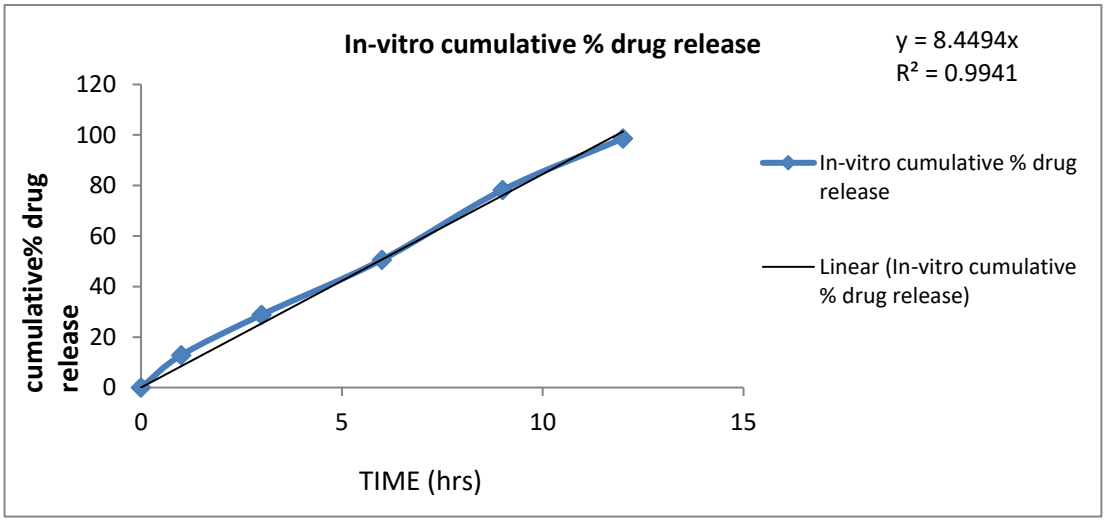
S. No.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.45	Fickian release
2	0.45 to 0.89	Non fickian release
3	0.89	Case II transport
4	> 0.89	Super case II transport

In-vitro were performed for the therapeutic efficacy of Terbutaline sulphate buccal tablets the factors related *in-vitro* characteristics of the drug. The obtained data of best formulation were shown in the Table No:10 A graph was plotted by taking cumulative % *in-vitro* release on x-axis and Time in y-axis for the same period of time and the release rate followed zero order with correlation coefficient value to be 0.994 shown in Graph No. 16.

Table No: 10 *In-vitro* correlation data for formulation F5

Time in h	*In-vitro* cumulative % drug
1	12.8
3	28.8
6	50.6
9	78.4
12	98.8

Figure no. 17 i*n-vitro* correlation plot



CONCLUSION

The Terbutaline sulphate bilayered buccal tablets were prepared by direct compression method using different polymers such as hydroxy propyl methyl cellulose 100K cps (HPMC), sodium carboxy methyl cellulose (SCMC), poly vinyl pyrrolidone K 30 (PVP) and carbopol 934 (CP) along with ethyl cellulose (EC) as an impermeable backing layer.

Drug polymer compatibility studies by FTIR indicates there is no possible interaction between the drug and polymer and prepared tablets were characterized on their physico-chemical characteristics like surface pH, swelling percentage, thickness, weight variation, hardness, friability and drug content are lies within the limit of pharmacopoeia in all formulations. Amongst all formulation, the formulation F5 contains HPMC 25 mg, CP 12.5mg, and PVP 12.5 mg was the best one in all the aspects. Good correlation was observed between *in-vitro* drug release profile of best formulation with correlation coefficient of 0.994, The formulation was stable and non-significant from p value obtained by one-way ANOVA. Terbutaline sulphate buccoadhesive

bilayer tablets could be promising one as they, increase bioavailability, minimize the dose, reduces the side effects and improves patient compliance hence, Terbutaline sulphate might be a right and suitable candidate for oral controlled drug delivery via buccoadhesive bilayer tablets for the therapeutic use.

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