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Research Article

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Design and development of Buccal tablet of Terbutaline Sulphate

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ABSTRACT

Bioadhesive polymers and other excipients were used to develop buccal tablet of terbutaline sulphate. In this research, the effect of bioadhesive polymers HPMC $K_{100}M$, ethyl Cellulose, carbopol and sodium carboxy methyl cellulose were studied. Direct compression method was followed for the formulation and characterized by various evaluation parameters, some of which are hardness, thickness, drug content, friability, hardness, weight variation, thickness in-vitro bioadhesion, in-vitro swelling index and in-vitro drug release etc. In-vitro drug release was performed on USP type II dissolution apparatus at 50 rpm in 900ml of dissolution media (simulated salivary fluid pH 6.75) for 8 hrs. Carbopol was very helpful and important polymer for current study. Carbopol promote the bioadhesion and swelling index although controls the drug release.

Keywords: Bio-adhesion, Swelling index, Drug release, Terbutaline sulphate, Simulated salivary fluid.

INTRODUCTION

Oral route perhaps the most preferred by patients and clinicians among various routes of drug delivery. However, per oral administration of drugs have such disadvantages: hepatic first-pass metabolism or enzymatic degradation within the gastrointestinal (GI) tract that prohibits oral administration of certain classes of drugs mostly peptides and proteins. Thus, other absorptive mucosa is considered as potential sites for drug administration. Transmucosal routes of drug delivery (the mucosal linings of the nasal, rectal, oral, vaginal & ocular cavities) offer distinct advantages over oral administration for systemic effect. These advantages include bypass of first-pass effects and avoidance of presystemic elimination within the GI tract.[1]

Buccal route in the oral cavity is an attractive target to deliver molecules like protein and peptide due to acid hydrolysis and hepatic first pass effect. The mucosal lining of the oral cavity offers some distinct advantages like high vascularization and accessibility for the administration and removal of a dosage form, in addition to high patient accessibility compared to other non-oral route of drug administration and there is rapid cellular recovery.[1,2]

EXPERIMENTAL SECTION

1.1 Materials:

Terbutaline sulphate obtained as a free gift sample from Themis Laboratories PVT LTD, Mumbai (India). The polymers (HPMC $K_{100}M$, Ethyl cellulose, Carbopol 934-P and Na-CMC) and excipients (magnesium stearate and lactose monohydrate) were purchased from CDH distributors. All other excipients and reagents were of pharmaceutical grade.

1.2 Methods:

A. Preparation of buccal tablets of terbutaline sulphate

Buccal tablets were formulated by different concentrations of polymers and excipients including drug, composition are given in table no. 1. First, all the polymers according to their formula or concentration were weighed accurately and triturate well, then lactose monohydrate was added into the mixture and triturate for 2 min. Lactose was used as binder. After proper mixing, magnesium stearate as a lubricant was added into the mixture and again triturate. Direct compression method was followed for the preparation of tablets, through it the mixture was compressed by rotary compression machine with a constant compression force and maintain same environment for all formulations. Total weight of per tablet was 150 mg including drug.

Table 1: Compositions of buccal tablet of terbutaline sulphate (5mg)

Formulation code	HPMC K100M (mg)	Ethyl cellulose (mg)	Carbopol (mg)	Sodium carboxy methyl cellulose (mg)	Magnesium Stearate (mg)	Lactose (mg) (q.s.)
F1	80	--	--	--	3	62
F2	--	80	--	--	3	62
F3	--	--	80	--	3	62
F4	--	--	--	80	3	62
F5	40	--	40	--	3	62
F6	27	--	53	--	3	62
F7	53	--	27	--	3	62
F8	20	--	60	--	3	62
F9	60	--	20	--	3	62
F10	--	40	40	--	3	62
F11	--	27	53	--	3	62
F12	--	53	27	--	3	62
F13	--	20	60	--	3	62
F14	--	60	20	--	3	62
F15	--	--	40	40	3	62
F16	--	--	53	27	3	62
F17	--	--	27	53	3	62
F18	--	--	60	20	3	62
F19	--	--	20	60	3	62

Preformulation study:

Fourier transforms infra red spectroscopy (FTIR):[3,4]

The primary objective of this investigation was to identify the drug in solid state. The FTIR spectrum of terbutaline sulphate is given in fig. 1.

Differential scanning calorimetry (DSC):[5,6]

DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a reference and sample are measured as a function of temperature. The sample and reference are maintained at nearly the same temperature throughout the study. Mainly, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The DSC analysis of terbutaline sulphate was given in fig. 2.

B. Post Compression Parameters:

Thickness:[7]

The thickness and diameter of the tablets of all formulations were determined with vernier caliper.

Tablet weight variation:[8]

Every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. Weight control is based on a sample of 20 tablets. Twenty tablets were randomly selected and accurately weighed using an electronic balance. The results are expressed as mean values of 20 determinations.

Hardness:[9]

The hardness of the tablets was determined using a hardness testing apparatus (Monsanto type). A tablet hardness of about 4-6 kg/cm^2 is considered adequate for mechanical stability.

Friability:[10]

The friability of the tablets was measured with a roche friabilator. Tablets of a known weight (W0) or a sample of 10 tablets were deducted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 % w/w.

% Friability = (W0 −W)/W0 ×100

***In-vitro* bioadhesion study:[11-15]**

The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance[22] using bovine cheek pouch as model mucosal membrane. (The buccal mucosa was collected from the local slaughterhouse).

A double beam physical balance was taken; the left pan was removed. To left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass stopper with uniform surface was tied. A clean glass mortar was placed below hanging glass stopper. In this mortar, a clean 500-ml glass beaker was placed, within which was placed another glass beaker of 50 ml capacity in inverted position and weighted with 50 g to prevent floating. The temperature control system involves placing thermometer in 500-ml beaker and intermittently adding hot water in outer mortar filled with water. The balance was so adjusted that right hand-side was exactly 5 g heavier than the left.

METHOD

The balance adjusted as described above was used for the study. The bovine cheek pouch was excised, washed, and then tied tightly with mucosal side upward using thread over the base of inverted 50-ml glass beaker. This beaker suitably weighted was lowered into 500-ml beaker, which was then filled with simulated salivary fluid (pH 6.75) kept at 37°C such that the fluid reaches the surface of mucosal membrane and keeps it moist. This was then kept below left hand side of balance. The buccal tablet was then stuck to glass stopper using a cyanoacrylete adhesive (feviquick). The 5 g on right hand side is removed; this causes application of 5 g of pressure on buccal tablet overlying moist mucosa. The balance was kept in this position for 3 min and then slowly weights were increased on the right pan, till tablet separates from mucosal membrane. The total weight on right pan minus 5 g gives the force required to separate tablet from mucosa. This gives bioadhesive strength in grams. The mean value of three trials was taken for each set of formulations.

Force of adhesion (N) = (Bioadhesive strength/1000) × 9.81

***In-vitro* swelling index:[16-18]**

The degree of swelling of bio-adhesive polymers is an important factor affecting adhesive. For conducting the study, a tablet was weighed and placed in a petri-dish containing 5 ml of simulated salivary fluid (pH 6.75) for a time interval (1,2,4,6 hrs), the tablets were taken out from the petri-dish and excess fluid was removed carefully by using filter paper. Reweighed it and swelling index was calculated using the following formula:

Swelling Index (SI) + (Wt-Wo)/Wo ×100

Where:
SI= Swelling index.
Wt = Weight of tablets after time at 't'.
Wo = Weight of tablet before placing in the beaker.

***In-vitro* drug release characteristics:[19,20]**

Drug release from the buccal tablets was assessed by dissolution test using USP type II dissolution apparatus (paddles) at 37^{o}C ±0.5^{o}C with 50 rpm. The test was performed using 900 ml of simulated salivary fluid (pH 6.75) as dissolution media. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of samples were withdrawn at regular time intervals, filtered and assayed spectro-photometrically at 280.40 nm.

Drug release kinetics:[20,21]

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.

RESULTS AND DISSCUSSION

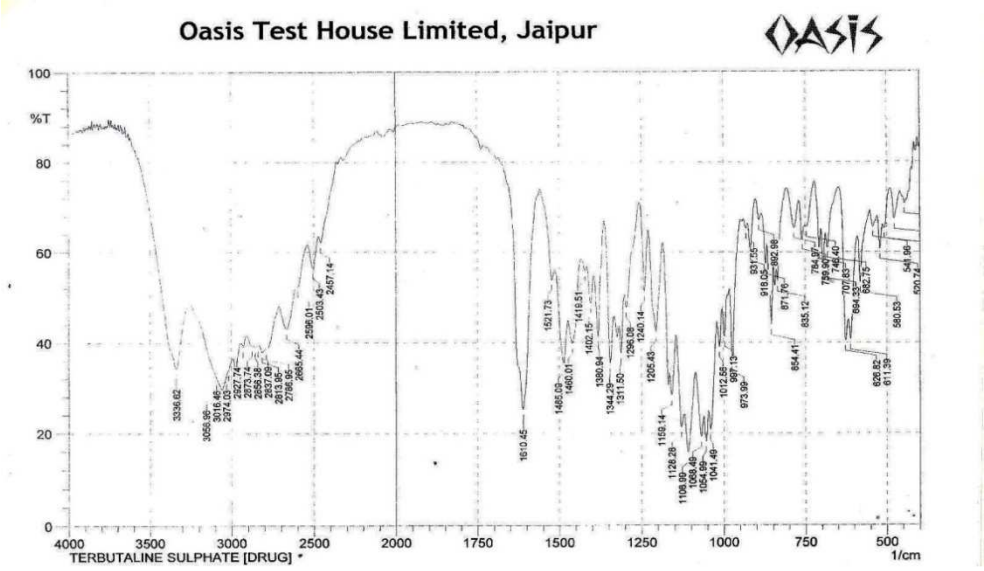

Fig. 1: IR spectra of terbutaline sulphate

Fig. 2: DSC study of terbutaline sulphate

On the basis of DSC analysis the melting point of terbutaline sulphate was found to be 268.22^{0}C.

1.3 Post compression characterization

All batches of formulation were evaluated for various physical parameters and display in table 3. The hardness of tablets was found in the range of 3.08 to 5.69 kg/cm^2 but formulation (F1-F4, F14-F17, and F19) is out of range according to pharmacopoeia. The average weight of all formulation was within the range 147.23-149.89 mg and according to IP the weight variation of each formulation was found in range. Friability was found in 0.15 to 1.09 % ranges except F4. Thickness of all formulations was found in uniform size.

Table No. 2: Data of hardness, weight variation, friability, thickness

Formulation code	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Thickness (mm)
F1.	3.98±0.011	148.37±1.218	0.94±0.137	3.30±0.028
F2.	3.97±0.011	148.09±0.439	0.99±0.037	3.55±0.098
F3.	5.69±0.020	149.89±0.470	0.15±0.050	3.38±0.098
F4.	3.08±0.023	147.42±1.145	1.09±0.065	3.22±0.030
F5.	4.10±0.020	148.69±0.897	0.57±0.030	3.38±0.046
F6.	4.23±0.011	148.91±0.660	0.52±0.025	3.38±0.046
F7.	4.04±0.011	148.18±1.006	0.66±0.030	3.30±0.028
F8.	4.72±0.020	149.69±0.212	0.45±0.026	3.38±0.046
F9.	4.01±0.010	147.93±0.165	0.89±0.025	3.30±0.000
F10.	4.06±0.020	148.40±0.513	0.69±0.369	3.55±0.098
F11.	4.18±0.011	148.12±0.544	0.47±0.052	3.38±0.046
F12.	4.02±0.000	147.23±0.321	0.78±0.030	3.55±0.098
F13.	4.20±0.011	149.32±0.371	0.42±0.041	3.38±0.046
F14.	3.99±0.011	148.14±0.416	0.85±0.040	3.55±0.098
F15.	3.81±0.011	147.25±0.927	0.78±0.025	3.25±0.028
F16.	3.89±0.011	147.81±0.170	0.62±0.020	3.30±0.046
F17.	3.48±0.011	148.15±0.510	0.93±0.092	3.22±0.017
F18.	4.15±0.011	148.01±0.662	0.52±0.047	3.30±0.046
F19.	3.22±0.011	147.31±0.268	0.97±0.036	3.22±0.017

**Each value represents Mean±Standard Deviation (n=3)*

Table No. 3: Data of adhesion force, swelling index and %CDR

Formulation code	Force of adhesion (N)	Swelling index (6hr.)	%Cumulative drug release (8hr.)
F1	0.32±0.015	84.04±0.187	84.78±1.718 (6hr)
F2	0.28±0.025	83.30±0.395	96.93±1.011
F3	0.59±0.015	93.60±0.015	79.00±0.931
F4	0.33±0.010	90.57±0.138	93.69±0.952 (6hr)
F5	0.44±0.010	90.49±0.746	96.88±0.125
F6	0.49±0.005	93.24±0.197	94.03±0.978
F7	0.43±0.015	93.20±0.233	97.01±0.023
F8	0.54±0.010	93.28±0.105	91.06±1.213
F9	0.36±0.005	90.55±0.108	97.01±1.119
F10	0.43±0.010	89.70±0.531	88.01±0.276
F11	0.48±0.010	90.70±0.476	85.15±0.123
F12	0.39±0.010	90.76±0.141	93.99±1.011
F13	0.53±0.005	91.53±0.785	81.72±1.212
F14	0.35±0.005	84.40±0.560	93.95±0.786
F15	0.46±0.005	90.30±0.616	97.06±0.679
F16	0.52±0.005	91.52±1.331	94.02±0.117
F17	0.41±0.005	90.76±0.502	97.13±1.232
F18	0.57±0.020	93.41±0.180	90.99±1.109
F19	0.37±0.005	90.07±0.738	90.67±0.87 (6hr)

**Each value represents Mean±Standard Deviation (n=3)*

A. *In-vitro* bioadhesion study:

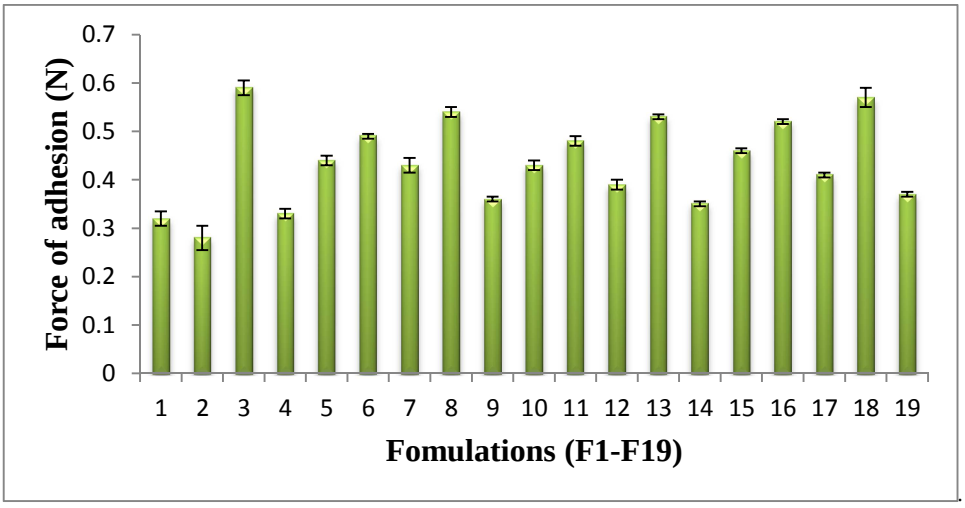

Figure 3: *In-vitro* adhesion force of formulations F1-F19

For this study, apparatus was assembled in laboratory and simulated salivary fluid (pH 6.75) was used for the bioadhesion study. The results are mention in the above table, which ranges in 0.28-0.59 N.

The adhesion results are varying according to polymer and their ratio. For buccal drug delivery, the formulation should have good adhesion force. According to results, ethyl cellulose shows the lowest adhesion force and carbopol shows highest adhesion force. The adhesion force is increased by increasing concentration of carbopol and on decreasing ethyl cellulose concentration the adhesion force was decreased. From the study, carbopol exhibit best bioadhesive agent in comparison to HPMC, ethyl cellulose, Na-CMC.

B. *In-vitro* swelling study:

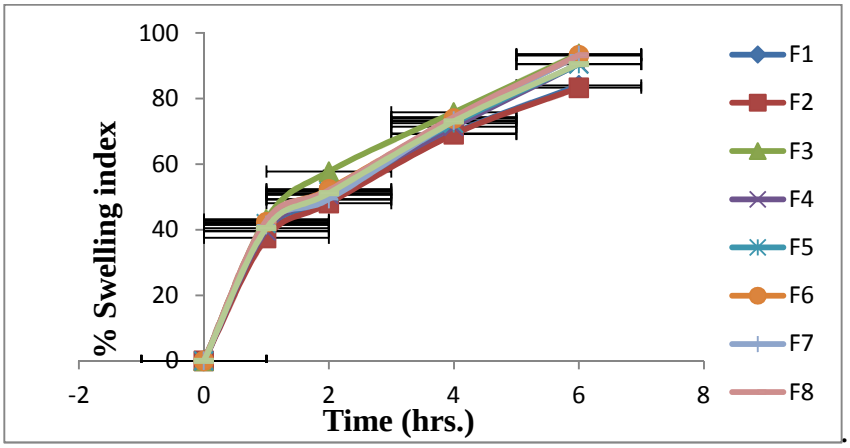

Figure 5: Time v/s swelling index (%) curve (F1-F9)

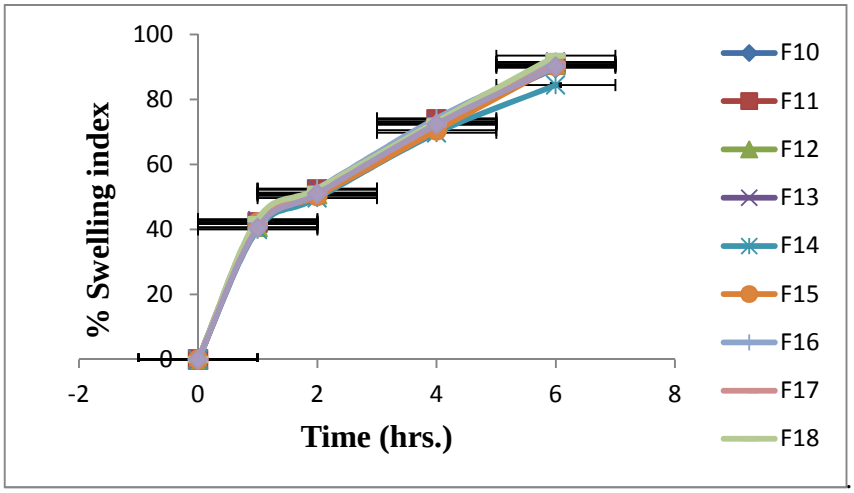

Figure 6: Time v/s swelling index (%) curve (F10-F19)

Simulated salivary fluid (pH 6.75) was preferred for this study. When buccal tablet came into the contact with fluid got swelled with time. According to result, the carbopol shows the maximum swelling index i.e. formulation F3 and least swelling showed by formulation F2 that contain ethyl cellulose. But HPMC and Na-CMC showed more swelling then ethyl cellulose. Carbopol has 'fluffy' nature, so it swelled more than other polymers. When concentrations of cellulose derivatives (HPMC, EC, Na-CMC) were increased, the swelling index was decreased. Its mean cellulose derivatives have low swelling index comparison to carbopol.

C. *In-vitro* drug release:

Same environment conditions were maintain for all formulation of terbutaline sulphate. Different concentrations of polymers were used in buccal tablet formulation. Drug release data for 8 hrs are shown in above tablet.

According to release data, cellulose derivatives showed high release in 8hrs. Carbopol was insoluble in solvent due to cross linked structure, so it showed lowest release of drug (79% for F3) in 8 hrs. On reducing carbopol concentration, drug release was increased. Although Na-CMC showed highest drug release (93.69%)

In whole experiment the formulation F5 was considered as best on the basis of various parameters like drug release, bioadhesion, swelling index and hardness. Some of these formulations were showing the low hardness which could create transportation problems. So hardness was also remembered for optimization of formulation. F5 had all the parameters in the range including SD which satisfy the pharmacopoeia specifications.

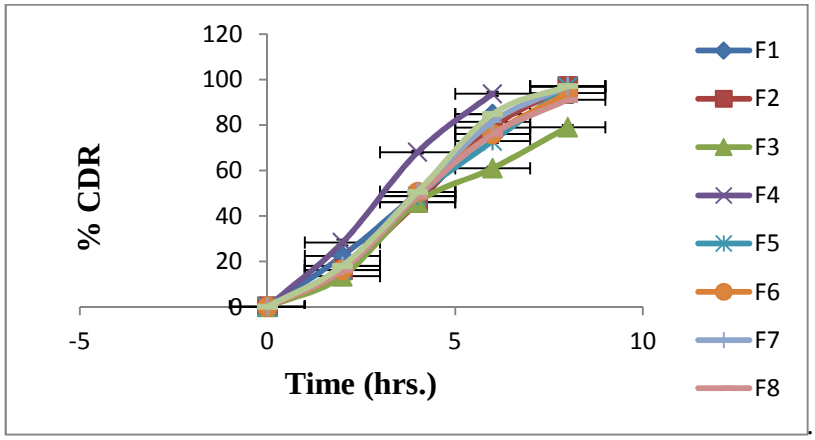

Figure 10: Drug release curve (F1-F9)

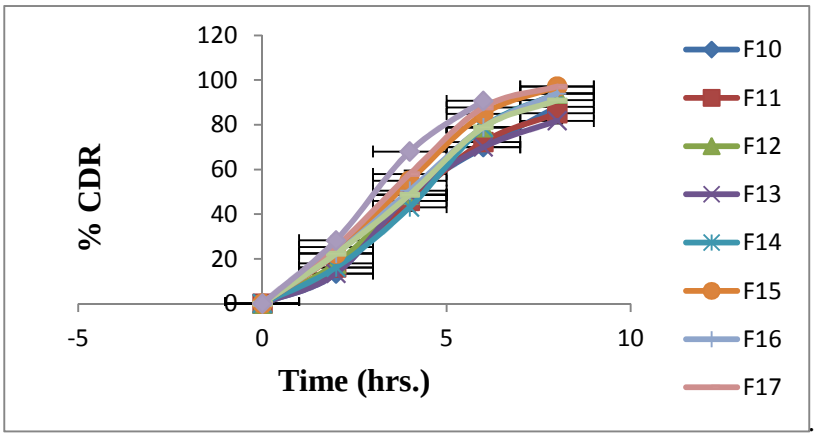

Figure 10: Drug release curve (F10-F19)

D. Drug release kinetics:

Table No. 4: Data of release kinetics

Formulation	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) M/L.S	R^2	K_H	R^2	n
F1	0.991	14.12	0.261	0.385	0.870	34.62	0.893	1.04
F2	0.987	12.82	0.005	0.044	0.871	34.28	0.919	0.78
F3	0.982	10.27	0.221	0.263	0.894	27.93	0.916	0.85
F4	0.993	16.03	0.103	0.236	0.915	38.26	0.869	1.00
F5	0.992	12.52	0.008	0.056	0.880	34.26	0.914	0.78
F6	0.987	12.39	0.043	0.117	0.889	33.25	0.911	0.79
F7	0.986	12.87	0.003	0.036	0.890	34.30	0.903	0.78
F8	0.985	12.09	0.080	0.156	0.889	32.20	0.910	0.80
F9	0.979	13.04	0.002	0.026	0.885	34.30	0.904	0.78
F10	0.982	11.63	0.086	0.165	0.882	31.12	0.922	0.82
F11	0.984	11.32	0.008	0.055	0.895	30.11	0.906	0.83
F12	0.987	12.44	0.111	0.181	0.892	33.24	0.899	0.79
F13	0.971	11.00	0.153	0.216	0.890	28.90	0.917	0.85
F14	0.982	12.53	0.038	0.111	0.866	33.22	0.917	0.79
F15	0.982	12.83	0.024	0.099	0.916	34.32	0.875	0.77
F16	0.991	12.23	0.042	0.113	0.918	33.25	0.872	0.77
F17	0.975	12.84	0.0008	0.016	0.930	34.35	0.859	0.77
F18	0.987	11.92	0.078	0.153	0.917	32.17	0.871	0.79
F19	0.990	15.59	0.165	0.293	0.921	37.02	0.830	0.92

The data were treated according to zero order, first order, higuchi model and korsmeyer peppas pattern for kinetics of drug release during dissolution process. The regression equation of optimized formulation F5 was find out according to zero order equation 0.880, first order equation 0.008 and higuchi model 0.880 respectively.

According to this model a value of n<0.45 indicates fickian release, n>0.45 but n<0.89 for non-fickian (anomalus) release and n>0.89 indicates super case II generally refers to the erosion of the polymeric chain and anomalous transport (non-fickian) refers to a combination of both diffusion and erosion controlled drug release. The 'n' value described in table no. 4. On the basis of n value the best formulation (F5) exhibited non-fickian type drug release.

CONCLUSION

Terbutaline sulphate buccal tablets were successfully formulated using the mixture of bioadhesive polymer HPMC $K_{100}M$, ethyl cellulose, carbopol 934-p and Na-CMC. Carbopol was found very useful polymer for adhesion and swelling. Purpose of current study (article) was to formulate buccal tablet of terbutaline sulphate by increasing bioavailability of the drug and it was very helpful and easy approach to obtain high bioavailability by avoids the first pass metabolism and enzymatic degradation.

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REFERENCES

[1] AH Shojaei; RK Chang; BA Burnside; RA Couch. *Ind. J. Pharm. Pharm. Tech*., **2001**, 6, 70-81.
[2] D Duchene; G Ponchel. *Eur. J. Pharm. Biopharm.*, **1997**, 44(1), 15-23.
[3] G Praveen. *The Pharm. Innov*., **2012**, 1(5), 63-70
[4] S Shanmugan; R Chakrahari; K Sundaramoorthy; T Ayyappan. *Int. J. Pharm. Tech. Res*., **2012**, 3(1), 526-534.
[5] YG Kumar; J Sreekanth; D Satyavati; P Chaitanya; B Swetha. *Int. J. Pharma. Tech. Res.*, **2013**, 5(3), 332-344.
[6] S Giri; S Velmurgan; S Chowdary. *Int. J. Pharm. Pharm. Sci.*, **2013**, 5(1), 354-360.
[7] B Kaur; S Sharma; G Sharma; R Saini; S Singh; M Nagpal; et al. *Asian J. Biomed. Pharm. Sci.*, **2013**, 3(24), 1-6.
[8] S Shukla; A Patidar; S Agrawal; R Choukse. *Int. J. Pharm. Biologic. Arch.*, **2011**, 2(6), 1561-1568.
[9] S Dhiman; G Singh; AK Rehni; S Sood; S Arora. *Asian J. Pharm. Clin. Res.*, **2011**, 4(1), 5-13.
[10] SR Lahoti; S Iftequar; M Sabina; MH Dehghan; S Shoaib; S Mohiuddin. *Int. Res. J. Pharm.*, **2011**, 2(11), 50-57.
[11] VN Deshmukh; JK Jadhav; DM Sakarkar. *Asian J. pharm*., **2009**, 3(1), 54-58.
[12] SS Shindhaye; PV Thakkar; NM Dand; VJ Kadak. *A. A. P. S. Pharm. Sci Tech.*, **2010**, 11(1), 416-424.
[13] PV Swamy; P Singh; SN Hiremath; SB Shirsand; SA Raju. *Ind. Drugs.*, **2007**, 44, 137-139.
[14] SB Shirsand; S Sarasija; GG Keshavshetti; PV Swamy; PVR Reddy. *Int. J. Pharm. Investig.*, **2012**, 2(1), 34-41.
[15] HG Choi; CK Kim. *J. Cont. Rel.*, **2000**, 68(3), 397-404.
[16] A Gupta; S Garg; RK Khar. *Ind. Drugs*, **1992**, 29(13), 586-593.
[17] A Avachat; V Kotwal. *A. A. P. S. Pharm. Sci. tech.*, **2007**, 8(4), 88-96.
[18] K Rajesh; P Suraj; AA Agarwal. *Drug Dev. Indust. Pharm.*, **1997**, 23(8), 831-837.
[19] A Chandel; K Chauhan; B Parashar; H Kumar; S Arora. *Int. Curr. Pharma. J.*, **2012**, 1(5), 110-118.
[20] S Bouckaert; JP Remon. *J. Pharm. Pharmacol.*, **1993**, 4, 504-507.
[21] VM Vaidya; JV Manwar; NM Mahajan; DM Sakarkar. *Int. J. Pharm. Tech. Res.*, **2009** 1(3), 588-597.