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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF TERBUTALINE FLOATING TABLETS

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Abstract:

The present study outlines a systematic approach for designing and development of Terbutaline floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Floating tablets of Terbutaline have shown sustained release there by proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by using direct compression method. A floating drug delivery system (FDDS) was developed by using sodium bicarbonate as gas-forming agent and HPMC E5, Eudragit RLPO and Sodium carboxy methylcellulose as polymers. The prepared tablets were evaluated in terms of their physical characteristics, pre-compression parameters, in vitro release and buoyancy lag time. The results of the in vitro release studies showed that the optimized formulation (T7) could sustain drug release for 12 hrs by using Sodium carboxy methylcellulose in the concentration of 5mg. The in vitro drug release followed zero order kinetics.

Key words: *Terbutaline, HPMC E5, Eudragit RLPO and Sodium carboxy methylcellulose and Floating tablets.*

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INTRODUCTION:

Improved therapeutic feasibility, altered bioavailability, and action planning are all possible outcomes of ongoing research on terbutaline coasting tablets. As a focused supported release to prolong the stomach household time following verbal organization, terbutaline coasting pills have been proposed. The use of facilitate strain served to represent numerous nuances. Sodium carboxy methylcellulose and polymers such as HPMC E5 and Eudragit RLPO were used to develop a float-based medicine delivery system (FDDS). The gas-shaping operator was sodium bicarbonate. In this study, we assessed the real qualities, precompression limits, in vitro transport, and delicateness resting period of the suggested tablets. Restorative release appeared to be maintained for 12 hours under the adjusted criteria (T7), according to in vitro release concentrations employing 5 mg of sodium carboxy methylcellulose. In vitro drug release and the zero-deal criterion formed the basis of our strategy. The terms "floating pills," "terbutaline," "sodium carboxy methylcellulose," and "HPMC E5" are just a few instances.

MATERIALS AND METHODOLOGY:

Materials

Terbutaline Procured from Astra geneca Ltd, Bangalore, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad. HPMC E5Degussa India Ltd. (Mumbai, India). Eudragit RLPO from Arvind Remedies Ltd, Tamil nadu, India. Sodium carboxy methylcellulose, Micro crystalline cellulose and Sodium bicarbonate purchased from Merck Specialities Pvt Ltd, Mumbai, India. Citric acid purchased from Laser Chemicals, Ahmedabad, India. Magnesium Stearate purchased from Apex Chemicals, Ahmedabad, India. Talc purchased from S.D. Fine Chem., Mumbai, India.

Methodology

Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

10mg Terbutaline pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20, 25µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 220 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Pre-formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r$$

$\tan \theta$ = Angle of repose

h = Height of the cone,

r = Radius of the cone base

Table 1 Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk

density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table 2 Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of floating Tablets:

Procedure for direct compression method:

1) Drug and all other ingredients were individually passed through sieve no ¹60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method by using 6mm punch.

FORMULATION OF TABLETS:

Table 3 Formulation composition for Floating tablets

INGREDIENTS (MG)	FORMULATION CODE								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
Terbutaline	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
HPMC E5	5	10	15	-	-	-	-	-	-
Eudragit RLPO	-	-	-	5	10	15	-	-	-
Sodium carboxy methylcellulose	-	-	-	-	-	-	5	10	15
Citric acid	10	10	10	10	10	10	10	10	10
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Micro crystalline cellulose	54.5	49.5	44.5	54.5	49.5	44.5	54.5	49.5	44.5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Total Weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 4 Pharmacopoeia specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re- weighed, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W1] × 100

Where, W1 = Initial weight of tablets

W2 = Weight of the tablets after testing

Determination of drug content

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Terbutaline were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* Buoyancy studies:**

The in vitro buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* drug release studies**

Dissolution parameters:

Apparatus -- U S P - II, Paddle Method

Dissolution Medium -- 0.1 N HCL

RPM -- 50

Sampling intervals (hrs) - - 0.5,1,2,3,4,5,6,7,8,10,11,12

Temperature -- 37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 220 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics
To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.
In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model
The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Drug – Excipient compatibility studies
Fourier Transform Infrared (FTIR) spectroscopy
The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.
Analytical Method
a. Determination of absorption maxima
The standard curve is based on the spectrophotometer. The maximum absorption was observed at 220nm.
b. Calibration curve
Graphs of Terbutaline was taken in 0.1N HCL (pH 1.2)

Table 5 Observations for graph of Terbutaline in 0.1N HCL

Conc [µg/mL]	Abs
0	0
5	0.176
10	0.332
15	0.481
20	0.637
25	0.789

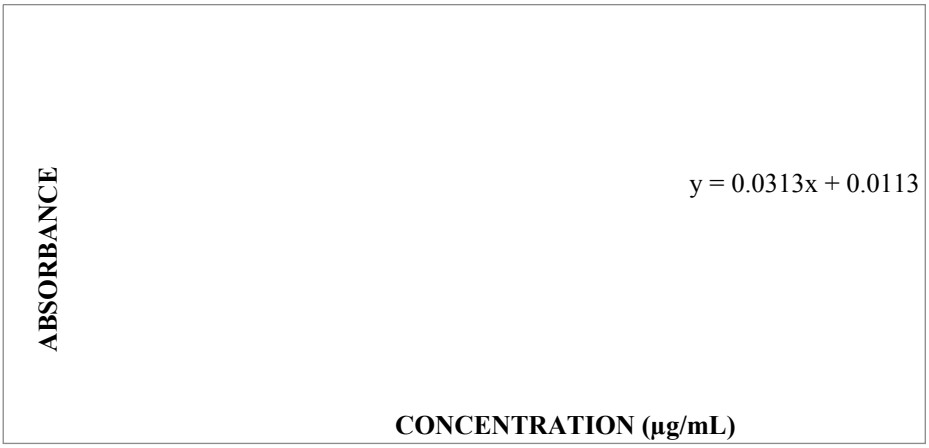

Figure 1 Standard graph of Terbutaline in 0.1N HCL

Standard graph of Terbutaline was plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig 8.1. The standard graph of Terbutaline showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Pre-formulation parameters of powder blend:

Table 6 Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
T1	29.35	0.538	0.649	17.10	1.20
T2	30.30	0.546	0.665	17.89	1.21
T3	31.65	0.576	0.672	14.28	1.16
T4	29.98	0.524	0.657	20.24	1.25
T5	29.66	0.564	0.677	16.69	1.20
T6	29.98	0.536	0.635	15.59	1.18
T7	30.32	0.576	0.650	11.38	1.12
T8	27.33	0.547	0.657	16.74	1.20
T9	30.62	0.567	0.678	16.37	1.19

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.524 to 0.576 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.635 to 0.678 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 20.24 which show that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.12 to 1.25 indicating the powder has good flow properties.

Quality control parameters for tablets

Tablet quality control tests such as weight variation, hardness, friability, thickness, Drug content and drug release studies were performed for floating tablets.

Table 7. *In vitro* quality control parameters

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time (Hrs)
T1	98.59	4.18	0.24	3.94	96.83	56	11
T2	96.32	4.92	0.58	3.20	99.67	43	10
T3	99.20	4.35	0.36	3.86	98.31	39	12
T4	97.45	4.12	0.18	3.42	96.40	32	11
T5	98.24	4.91	0.73	3.75	98.37	25	12
T6	97.69	4.18	0.62	3.59	99.13	20	12
T7	98.48	4.69	0.70	3.82	98.89	18	12
T8	99.14	4.17	0.46	3.14	98.11	28	12
T9	98.93	4.56	0.34	3.73	97.32	34	12

All the parameters for SR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

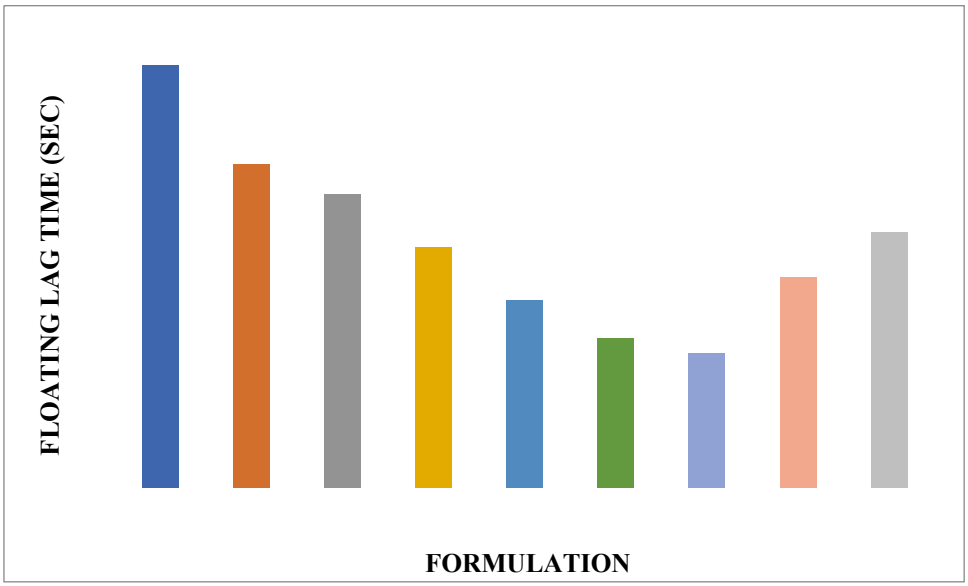

Figure 2 Floating lag time (sec)

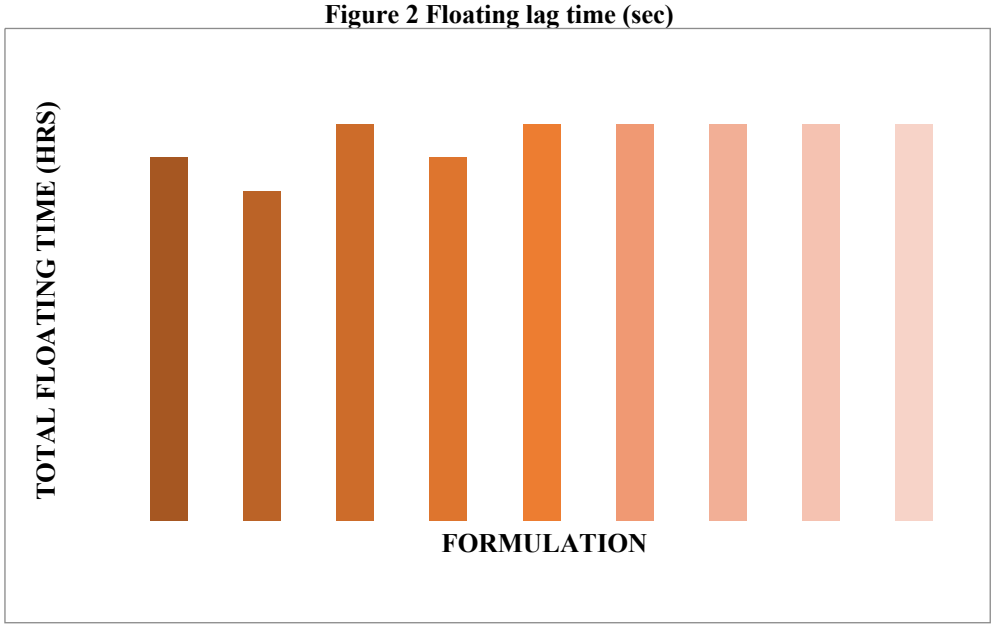

Figure 3 Total floating time (Hrs)

***In vitro* drug release studies**

Table no 8 Dissolution data of Floating tablets

TIME (HR)	CUMULATIVE PERCENTAGE OF DRUG RELEASE								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
0	0	0	0	0	0	0	0	0	0
1	28.92	15.58	13.29	20.99	15.82	11.34	16.50	10.29	06.91
2	36.34	28.25	18.13	26.63	20.90	18.26	21.32	15.72	10.30
3	40.68	38.71	23.96	38.24	28.35	22.54	28.11	22.90	18.61
4	58.15	43.90	28.14	42.81	37.45	28.87	35.08	28.38	23.52
5	67.76	50.65	35.20	56.60	45.76	36.93	40.96	35.27	28.81
6	76.50	59.12	42.87	64.32	50.81	45.27	48.60	40.12	37.32
7	90.31	65.08	49.73	70.41	57.96	50.71	56.14	46.90	45.60
8	96.83	78.70	56.51	87.88	66.75	59.56	61.73	54.63	51.97
9		89.36	68.09	96.59	71.31	66.81	75.69	61.28	58.82
10		97.18	76.80		85.85	73.04	83.82	67.12	64.35
11			88.66		98.91	77.10	91.09	76.30	70.82
12			93.37			90.17	99.59	89.27	78.99

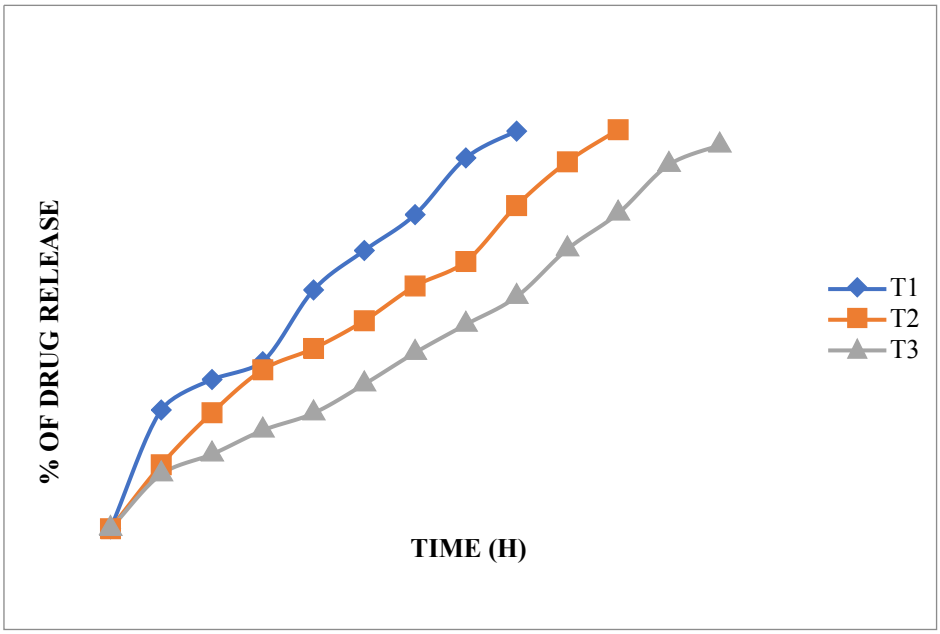

Figure 4 Dissolution data of Terbutaline floating tablets containing HPMC E5

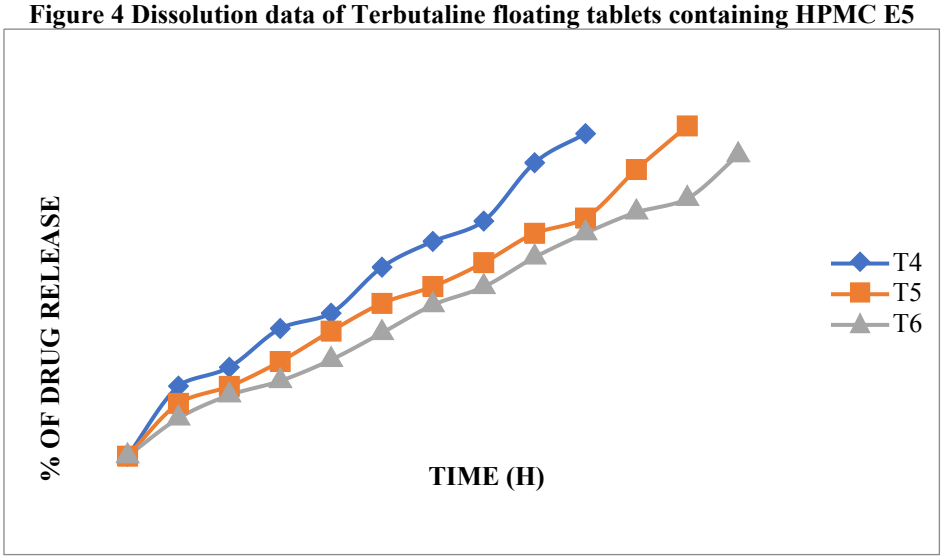

Figure 5 Dissolution data of Terbutaline floating tablets containing Eudragit RLPO

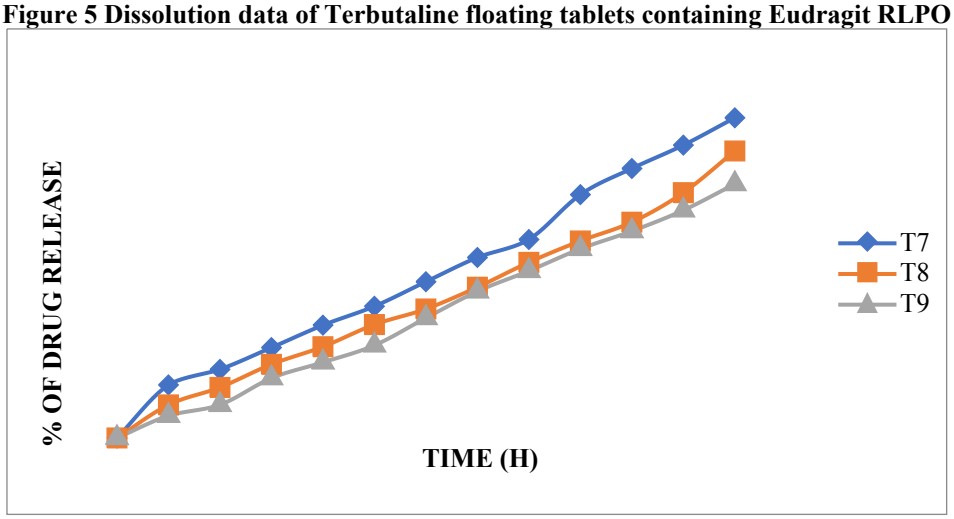

Figure 6 Dissolution data of Terbutaline Floating tablets containing Sodium carboxy methylcellulose

From the dissolution data it was evident that the formulations prepared with HPMC E5 as polymer were retarded the drug release 12 hours. In low concentration of the polymer the drug release was unable to retarded up to 12

hours. Whereas the formulations prepared with higher concentration of Eudragit RLPO retarded the drug release up to 12 hours in the concentration 15 mg. In lower concentrations the polymer was unable to retard the drug release up to 12 hours. Whereas the formulations prepared with Sodium carboxy methylcellulose were retarded the drug release in the concentration of 5 mg (T7 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.59 % in 12 hours with good retardation. Hence from the above dissolution data it was concluded that T7 formulation was considered as optimized formulation because good drug release (99.59%) in 12 hours.

Application of release rate kinetics to Dissolution data for optimised formulation:

Table 9 Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
16.5	1	1.000	1.217	0.000	1.922	16.500	0.0606	-0.783	83.5	4.642	4.371	0.271
21.32	2	1.414	1.329	0.301	1.896	10.660	0.0469	-0.671	78.68	4.642	4.285	0.357
28.11	3	1.732	1.449	0.477	1.857	9.370	0.0356	-0.551	71.89	4.642	4.158	0.484
35.08	4	2.000	1.545	0.602	1.812	8.770	0.0285	-0.455	64.92	4.642	4.019	0.623
40.96	5	2.236	1.612	0.699	1.771	8.192	0.0244	-0.388	59.04	4.642	3.894	0.748
48.6	6	2.449	1.687	0.778	1.711	8.100	0.0206	-0.313	51.4	4.642	3.718	0.923
56.14	7	2.646	1.749	0.845	1.642	8.020	0.0178	-0.251	43.86	4.642	3.527	1.115
61.73	8	2.828	1.790	0.903	1.583	7.716	0.0162	-0.210	38.27	4.642	3.370	1.272
75.69	9	3.000	1.879	0.954	1.386	8.410	0.0132	-0.121	24.31	4.642	2.897	1.745
83.82	10	3.162	1.923	1.000	1.209	8.382	0.0119	-0.077	16.18	4.642	2.529	2.112
91.09	11	3.317	1.959	1.041	0.950	8.281	0.0110	-0.041	8.91	4.642	2.073	2.568
99.59	12	3.464	1.998	1.079	-0.387	8.299	0.0100	-0.002	0.41	4.642	0.743	3.899

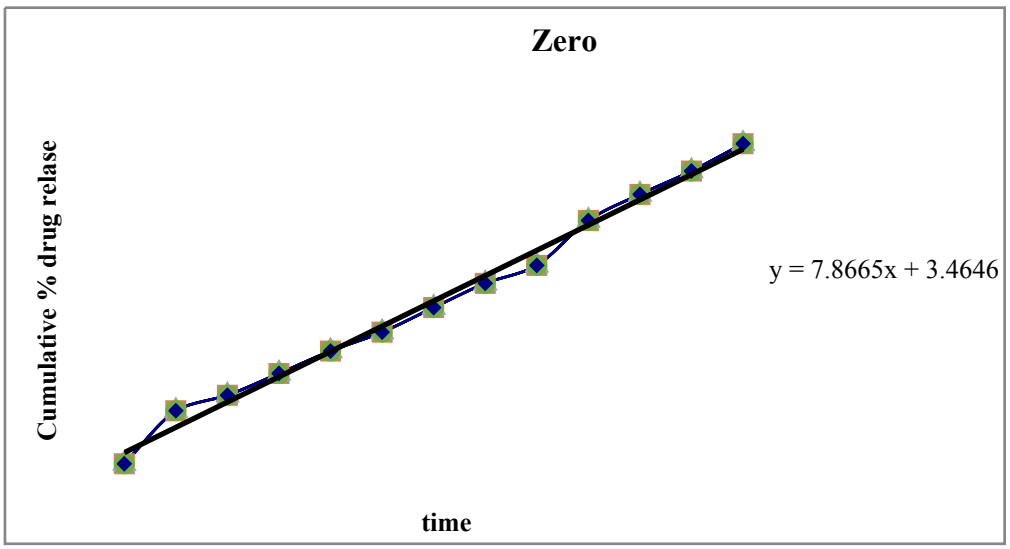

Figure 7 Zero order release kinetics

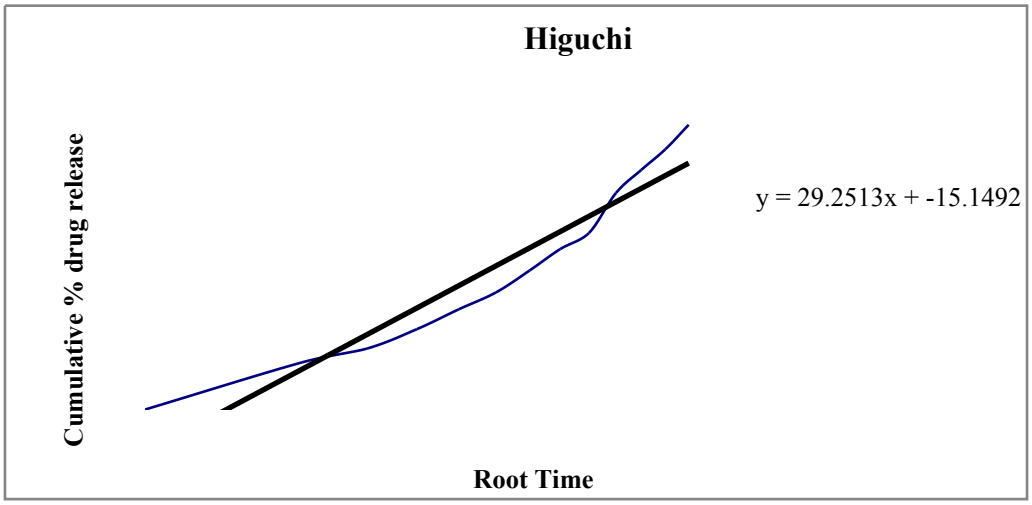

Figure 8 Higuchi release kinetics

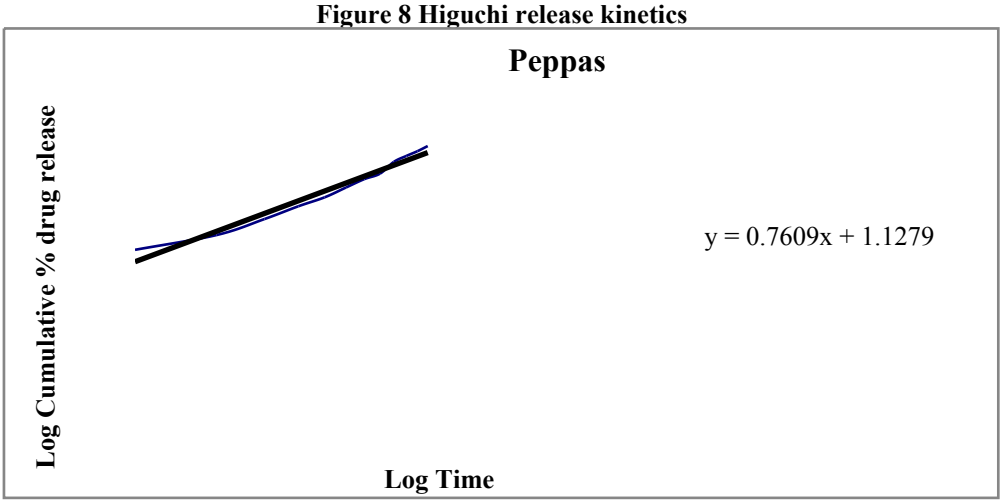

Figure 9 Kors mayer peppas release kinetics

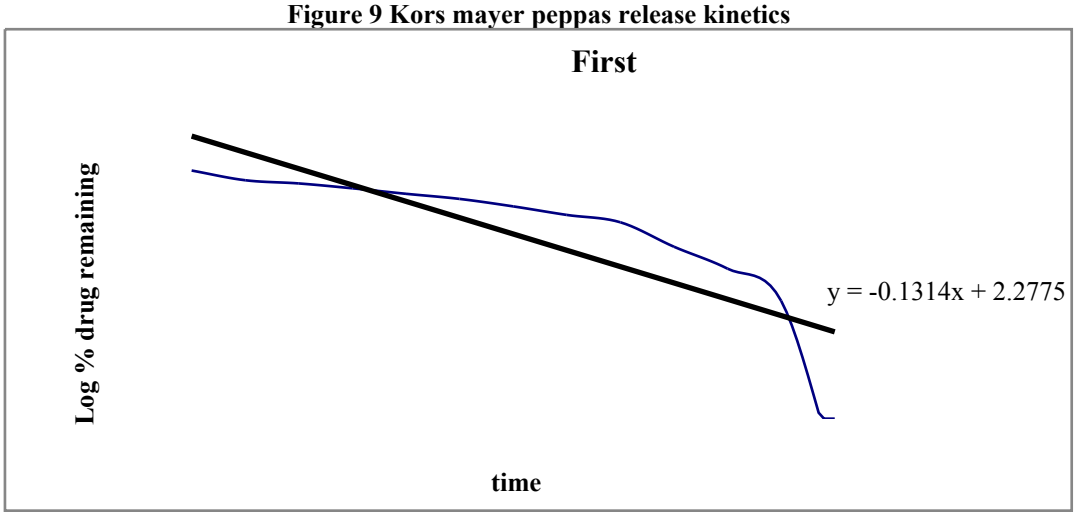

Figure 10: First order release kinetics

Optimised formulation T7 was kept for release kinetic studies. From the above graphs it was evident that the formulation T7 was followed Zero order release kinetics mechanism.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

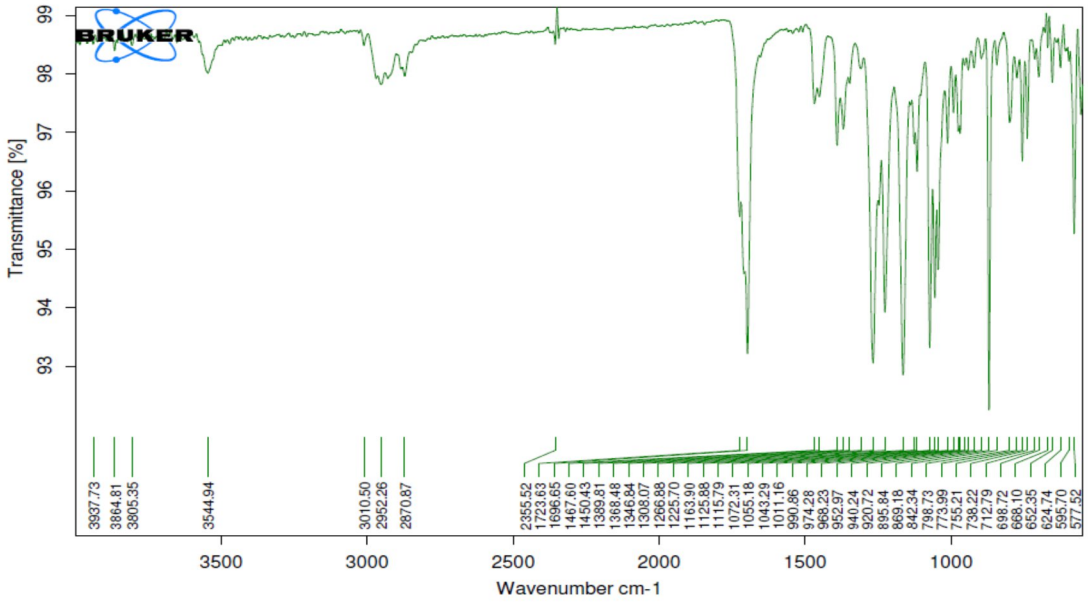

Figure 11 FTIR Spectrum of pure drug

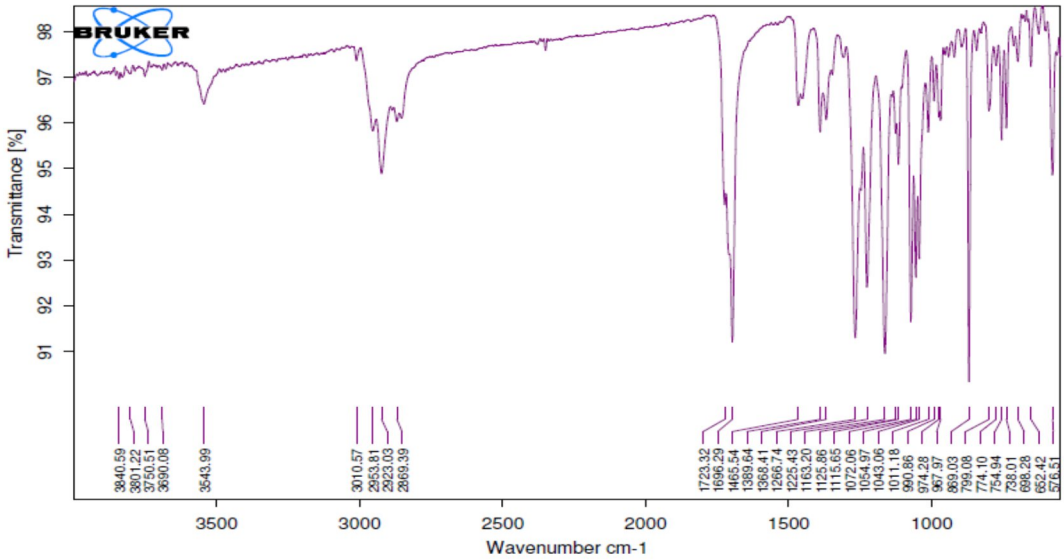

Figure 12 FTIR Spectrum of optimized formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions. Terbutaline are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION:

Floating tablets were formulated and evaluated using Terbutaline by using HPMC E5, Eudragit RLPO and Sodium carboxy methylcellulose use as polymers, by varying drug to polymer ratio. From the drug content and *in vitro* dissolution studies of the formulations, it was concluded that the formulation T7 shown best result i.e., the formulation prepared with Sodium carboxy methylcellulose, sodium bicarbonate, microcrystalline cellulose, magnesium stearate, talc retarded the drug release up to 12 hours in the concentration of 5mg of Sodium carboxy methylcellulose. *In-vitro* dissolution data was fitted to Zero order kinetics models to check the release kinetics. The best fit release was achieved with Zero order kinetics.

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