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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, precompression 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.

Keywords: Terbutaline, HPMC E5, Eudragit RLPO and Sodium carboxy methylcellulose and Floating tablets.

INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinaltract (GIT).[1] Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment[2] Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach[3] , low density (floating) systems that causes buoyancy in gastric fluid[4,5,6], mucoadhesive systems that causes bioadhesion to stomach mucosa[7], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[8,9],superporous hydrogel systems[10] magnetic systems[11]etc. The current review deals with floating type gastroretentine drug delivery system.

Basic gastrointestinal tract physiology

The stomach is divided into 3 regions anatomically: fundus, body, and antrum pylorus. The proximal part is the fundus and the body acts as a reservoir for undigested material, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states but the pattern of motility is distinct in the 2 states. During the fasting state an interdigestive series

of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided into following 4 phases.[12]

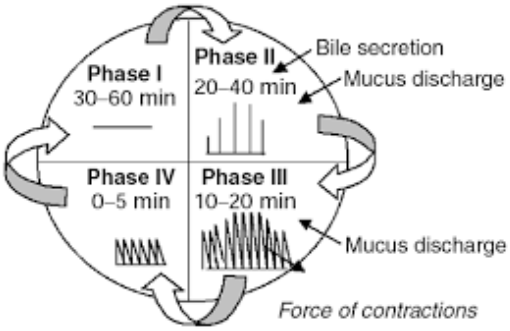

Figure 1: Schematic Representation of Interdigestive Motility

Phase I: This period lasts about 30 to 60 minutes with no contractions.

Phase II: This period consists of intermittent contractions that increase gradually in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III: This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10 to 20 minutes these contractions, also known as ‘‘house-keeper wave,’’ sweep gastric contents down the small Intestine.

Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase

Need For Gastroretention

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H.Pylori infections.[12]

Factors controlling gastric retention of dosage forms

There are several factors that can affect gastric emptying of an oral dosage form which include density, size and shape of dosage form, feeding state, biological factors such as age, gender, posture, body mass index, disease state etc.

Aim and objectives

Aim

The aim of the present work is to formulate & evaluate gastro retentive floating tablets of Terbutaline using various polymers.

Objectives

The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

Objectives of the study

1. Analytical method development for an Anti-asthmatic agent.
2. To evaluate compatibility between drug-polymers and other excipients.
3. To carry out pre-formulation studies.
4. To develop and formulate controlled release floating delivery system.
5. To evaluate post compression parameters like weight variation, hardness, friability, content uniformity, Floating lag time, etc.
6. Evaluation of developed formulation for *in-vitro* drug release studies.

MATERIALS AND METHOD MATERIALS

Terbutaline Provided by SURA LABS, Dilsukhnagar, Hyderabad. HPMC E5, was gift sample from Degussa India Ltd., Eudragit RLPO was purchased from Arvind Remedies Ltd, Tamil nadu, India., Sodium carboxy methylcellulose was purchased from Merck Specialities Pvt Ltd, Mumbai, India, Citric acid was purchased from Laser Chemicals, Ahmedabad, India., Sodium bicarbonate was purchased from Merck Specialities Pvt Ltd, Mumbai, India, Magnesium Stearate was purchased from Apex Chemicals, Ahmedabad, India.and Talc was purchased from S.D. Fine Chem., Mumbai, India.

Methodology

Formulation of tablets

Table 1: Formulation composition for Floating tablet

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

RESULTS AND DISCUSSION

Analytical Method

Determination of absorption maxima

The standard curve is based on the spectrophotometer. The maximum absorption was observed at 220nm.

Calibration curve

Graphs of Terbutaline was taken in 0.1N HCL (pH 1.2)

Table 2: 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

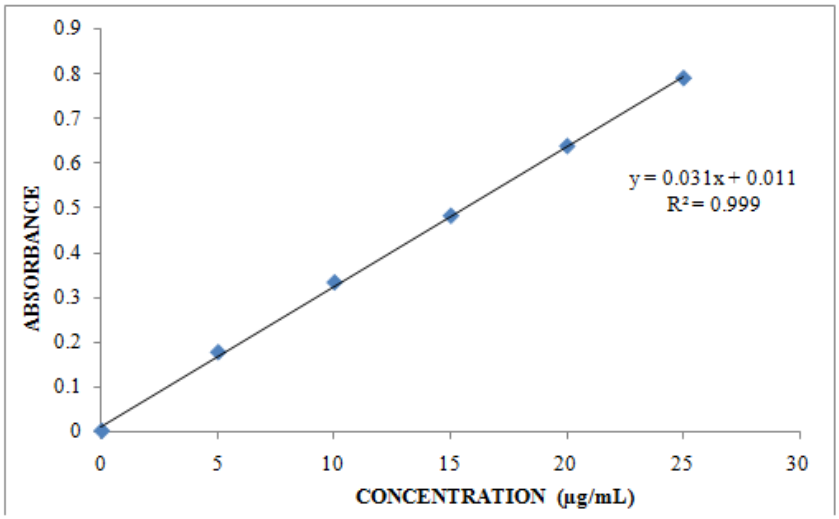

Fig 2: Standard graph of Terbutaline in 0.1N HCL

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.

Preformulation parameters of powder blend

Table 3: 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 4: *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.

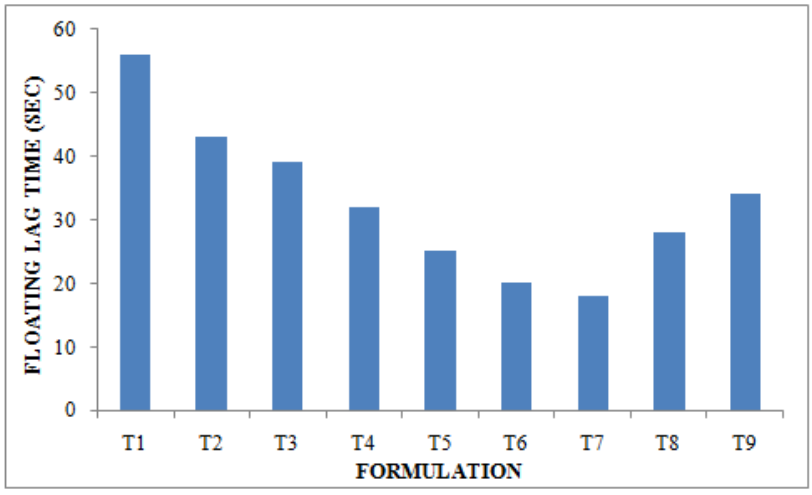

Figure 3: Floating lag time (sec)

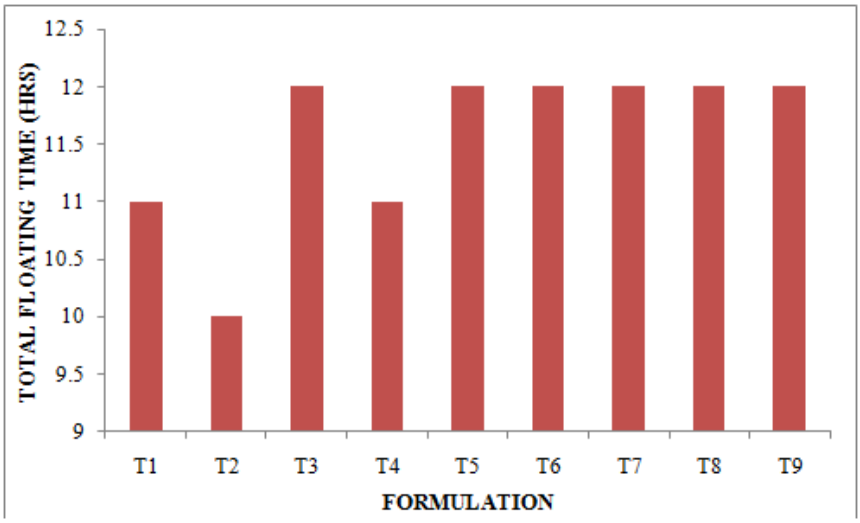

Figure 4: Total floating time (Hrs)

In vitro drug release studies

Table 5: 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

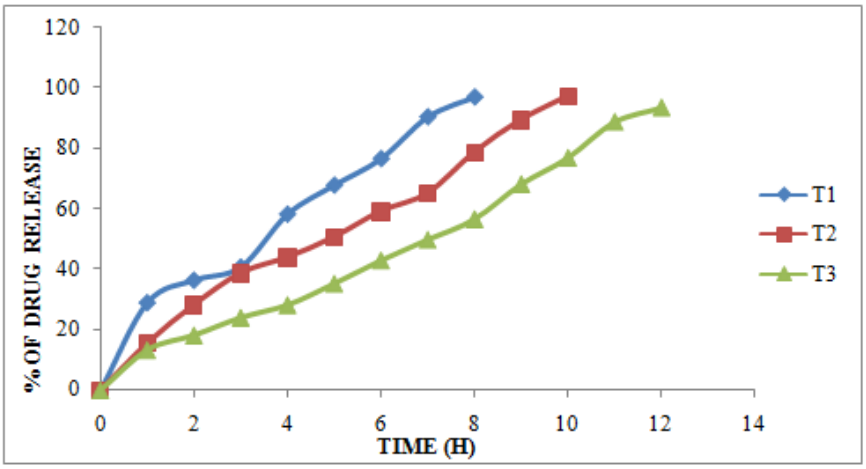

Fig 5 : Dissolution data of Terbutaline floating tablets containing HPMC E5

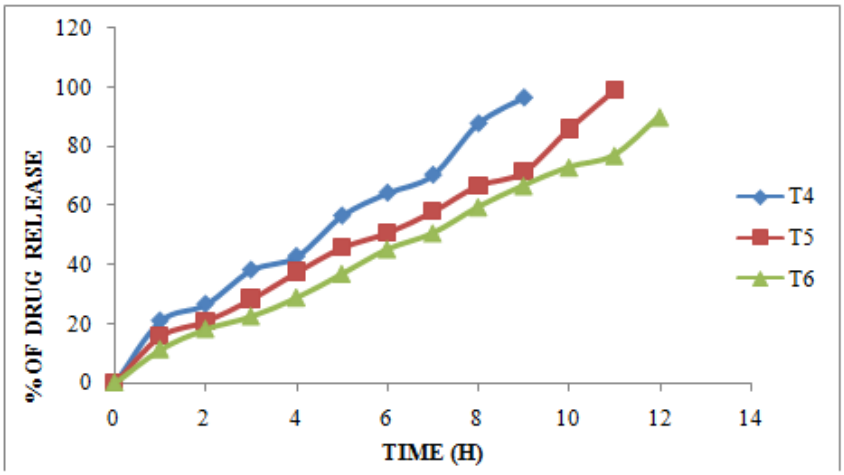

Fig 6: Dissolution data of Terbutaline floating tablets containing Eudragit RLPO

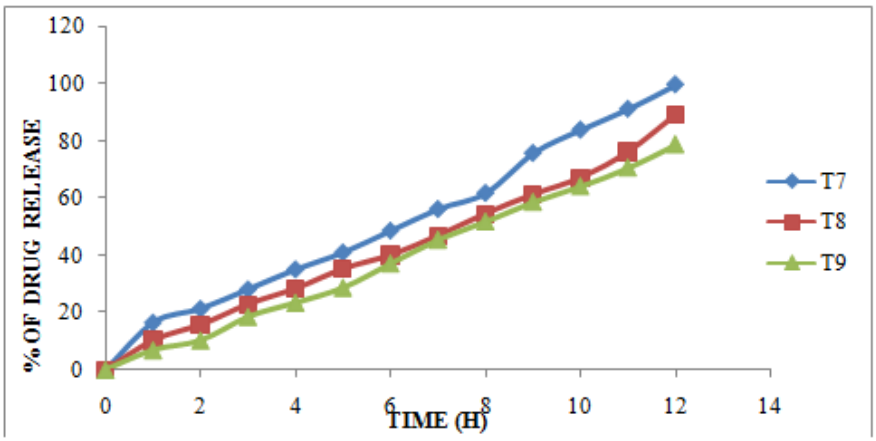

Fig 7: Dissolution data of Terbutaline Floating tablets containing Sodium carboxy methylcellulose

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 optimised formulation because good drug release (99.59%) in 12 hours.

Application of release rate kinetics to Dissolution data for optimised formulation

Table 6: 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	Q0 1/3	Qt 1/3	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

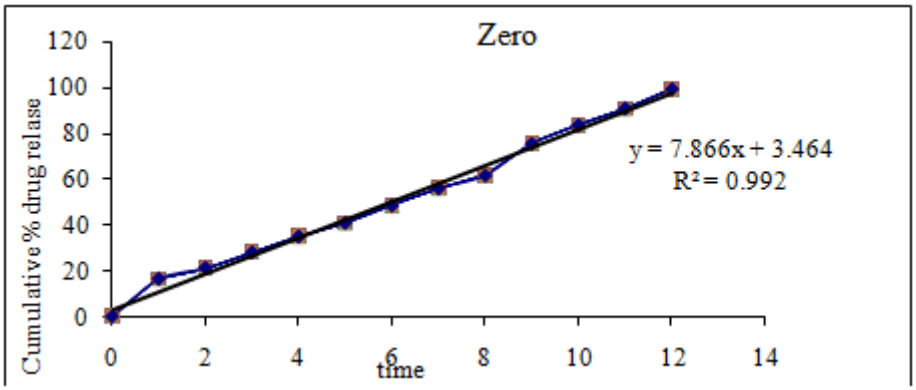

Fig 7 : Zero order release kinetics

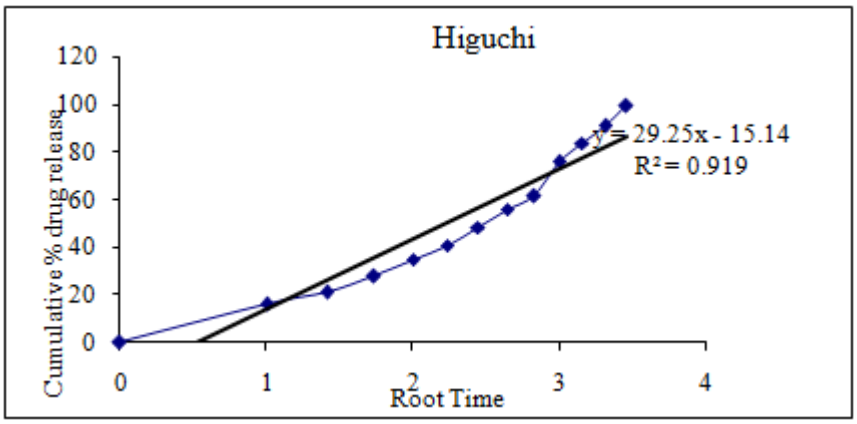

Fig 8: Higuchi release kinetics

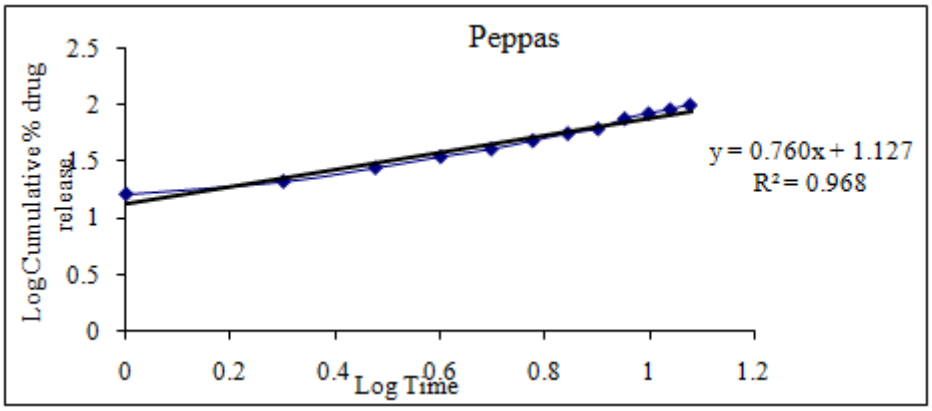

Fig 9: Kors mayer peppas release kinetics

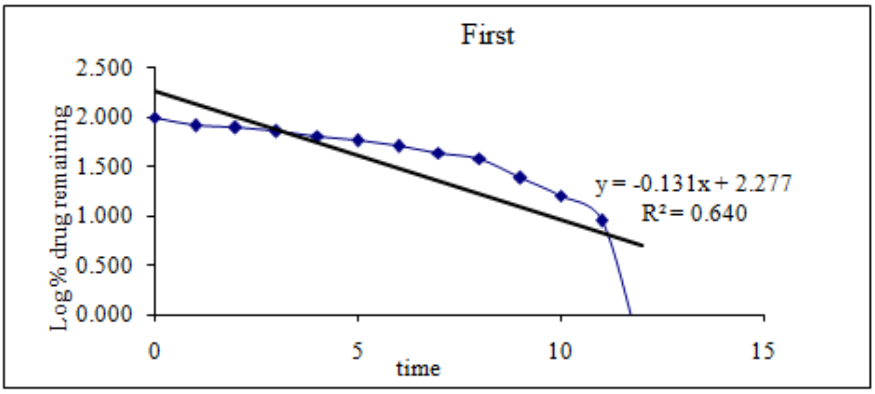

Fig 10 : First order release kinetics

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

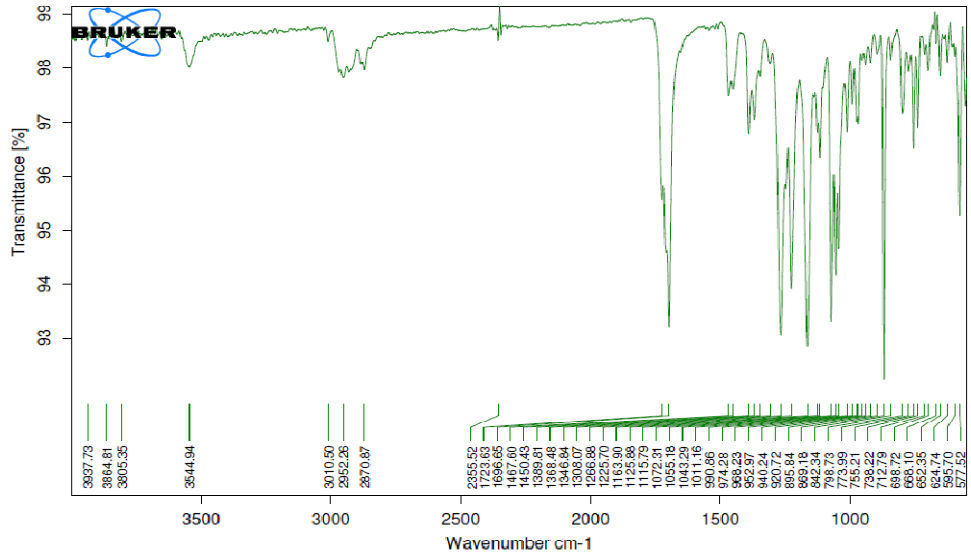

Figure 11: FTIR Spectrum of pure drug

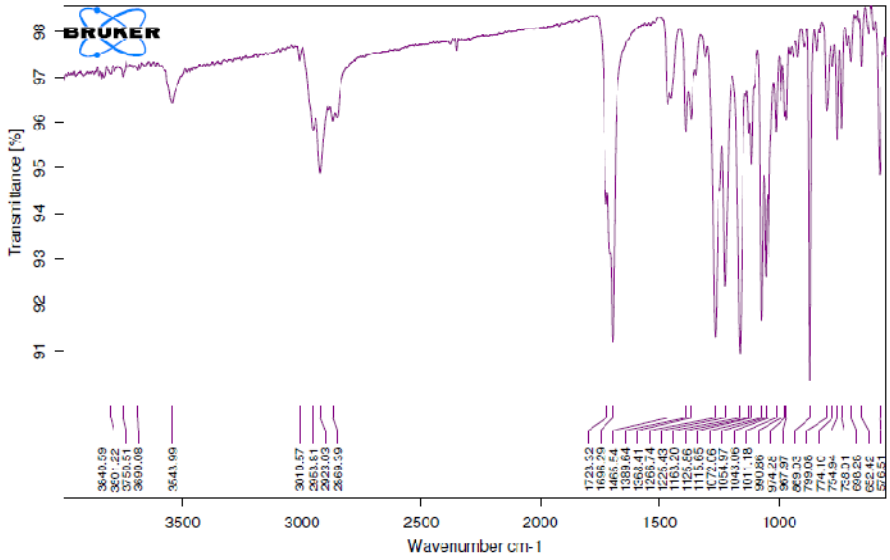

Fig12 : FTIR Spectrum of optimised formulation

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.
- ✓ All the formulations were prepared by using direct compression method.
- ✓ The pre compression parameters of all formulations show good flow properties and these can be used for tablet manufacturing.
- ✓ The post compression parameters of all formulations were determined and the values were found to be satisfactory.
- ✓ Sodium bicarbonate is used as gas generating agent. Citric acid is used to achieve buoyancy effect under the elevated pH, which results an enhancement in drug release.
- ✓ The shapes of the tablets of all the formulations were found to be white, smooth, flat faced circular with no visible cracks.
- ✓ The tablets prepared with low viscosity grade Sodium carboxy methylcellulose (i.e.T7) exhibited short Floating Lag Time and longer Floating Time, when compared with the formulations containing high viscous grade.
- ✓ It is concluded that the formulations prepared with low viscous Sodium carboxy methylcellulose (T7) showed desirable buoyancy time.
- ✓ It is observed that, in all the formulations as the concentration of polymer increases, the amount of drug release was found to be decreased, because the amount of drug binded in the polymer could be more.
- ✓ 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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