PREPARATION AND EVALUATION OF FLOATING TABLETS OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

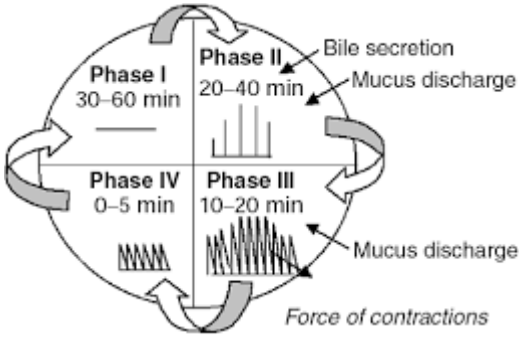
The purpose of this research was to formulate and evaluate the Floating sustained release tablets of Tramadol Hydrochloride 50mg, opioid pain medication. Tramadol Hydrochloride is a medication used to treat moderate to moderately severe pain. The tablets are prepared by direct compression method. The formulations were optimized by incorporating varying composition of Eudragit RSPO, HPMC K 100, Chitosan and Micro crystalline cellulose as diluent, Sodium bicarbonate as floating agents, Magnesium stearate agent as lubricant. All the excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. The Preformulation parameters such as bulk density, tapped density, compressibility index and Hausner's ratio were analyzed. The thickness, hardness, friability, weight variation, and drug content uniformity was evaluated for tablets. The effect of these variables on drug release also studied. The In-Vitro drug release studied were Performed in the USP dissolution apparatus-II (Paddle) using 0.1N HCL buffer as dissolution media at 50 rpm speed and temperature of 37°C ± 5°C. The sampling was done at periodic time intervals of 0.5,1,2,3,4,5,6,7,8,9,10,11 and 12 hours and was replaced by equal volume of dissolution media after each withdrawal. The cumulative amount of drug release at different intervals is estimated using UV spectrophotometer. Based on the evaluation result the formulations F-3 containing Eudragit RSPO were selected as best formulation. The tablets were found to follow Higuchi kinetics mechanism of drug release.

Key words: Tramadol Hydrochloride, Eudragit RSPO, HPMC K 100, Chitosan and Floatingtablets.

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 gastrointestinal tract (GIT).[1] Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drugsolubility 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 withfloating type gastroretentine drug delivery system.



Schematic Representation of Interdigestive MotilityPhase 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 treatcertain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H.Pylori infections.[12]

AIM

The aim of the present work is to formulate & evaluate gastro retentive floating tablets of Tramadol Hydrochloride 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.

In the present investigation floating tablets of Tramadol Hydrochloride were prepared by direct compression using various polymers.

Analyis

Analytical Method

Determination of absorption maxima

The standard curve is based on the

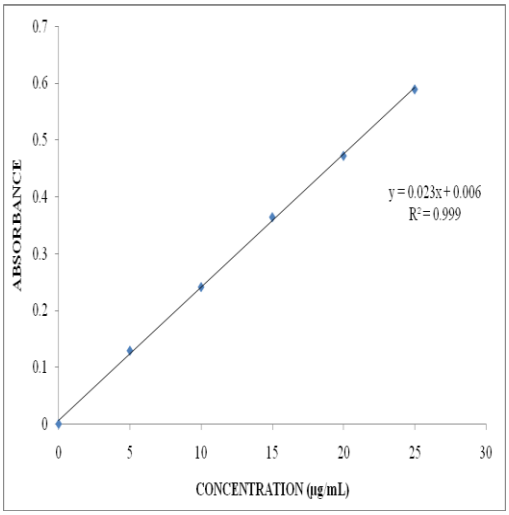
spectrophotometer. The maximum absorption was observed at215nm.

Calibration curve

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

Observations for graph of Tramadol Hydrochloride in 0.1N HCL

Conc [µg/mL]	Abs
0	0
5	0.129
10	0.241
15	0.364
20	0.472
25	0.589



Standard graph of Tramadol Hydrochloride in 0.1N HCL

Standard graph of Tramadol Hydrochloride 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 Tramadol Hydrochloride showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer-Lamberts" law.

Preformulation parameters of powder blend:

Pre-formulation parameters of blend

mulation Code	Angle of Repose	ulk density (gm/mL)	Tapped density (gm/mL)	's index(%)	usner's Ratio
F1	25.56±0.3	0.57±0.01	0.61±0.01	10.11±0.8	1.13±0.02
F2	24.67±0.3	0.53±0.01	0.68±0.03	10.23±0.5	1.12±0.03
F3	25.56±0.2	0.52±0.06	0.64±0.03	10.34±1.0	1.14±0.06
F4	23.30±0.1	0.50±0.21	0.66±0.12	10.23±0.5	1.12±0.06
F5	22.56±0.1	0.65±0.02	0.59±0.02	11.23±0.8	1.11±0.05
F6	23.89±0.2	0.50±0.04	0.68±0.04	11.34±0.6	1.14±0.03
F7	26.54±0.1	0.59±0.04	0.64±0.05	10.12±0.7	1.13±0.09
F8	23.67±0.3	0.58±0.12	0.58±0.04	10.23±1.0	1.11±0.07
F9	24.34±0.4	0.56±0.02	0.54±0.01	10.23±0.8	1.13±0.02

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 0.50±0.04 to 0.65±0.02 (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 0.54±0.01 to 0.54±0.01 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 10.34 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.11 to 1.14 indicating the powder has good flow properties.

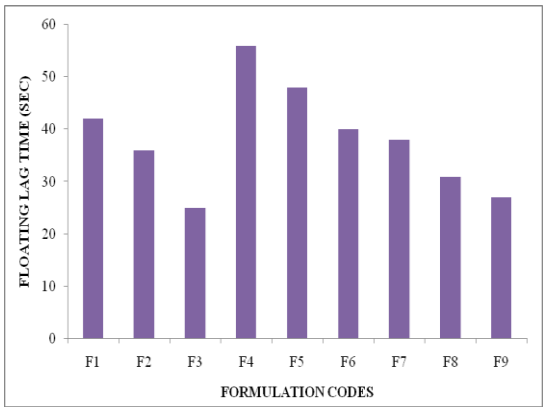
Quality Control Parameters For tablets:

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

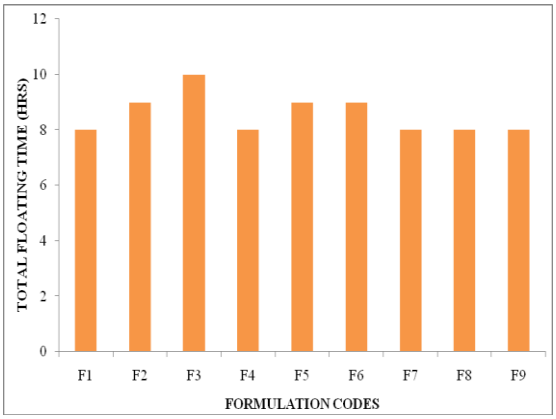
***In vitro* quality control parameters**

mulation codes	Weight variation (mg)	Hardness (kg/cm^2)	riability (%loss)	nickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time (Hrs)
F1	146.13	4.6	0.34	3.15	99.27	42	8
F2	145.37	4.8	0.46	3.69	98.64	36	9
F3	148.01	5.1	0.29	3.81	100.05	25	10
F4	149.75	4.0	0.62	3.79	99.82	56	8
F5	147.54	5.2	0.72	3.56	97.19	48	9
F6	150.07	4.9	0.69	3.11	98.52	40	9
F7	150.01	5.6	0.28	3.29	99.13	38	8
F8	148.69	4.5	0.47	3.50	97.68	31	8
F9	150.01	4.8	0.52	3.74	98.49	27	8

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



Floating lag time (sec)



Total Floating Time (Hrs)

***In vitro* drug release studies**

Dissolution data of Floating tablets

Time (H)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	32.62	28.38	16.23	44.97	21.82	20.31	11.22	13.49	9.07
1	45.81	33.14	24.38	60.65	36.31	32.38	17.38	15.21	13.31
2	52.20	46.63	35.79	78.16	41.23	36.43	22.45	19.07	21.03
3	56.39	52.82	40.88	80.98	56.96	41.86	29.59	26.17	24.12
4	63.85	60.40	47.54	86.29	64.35	59.75	37.83	35.56	31.13
5	70.34	68.09	58.17	92.73	72.02	65.46	43.26	42.58	39.09
6	87.13	75.46	64.62	97.22	80.75	71.13	53.15	51.27	48.17
7	90.91	81.02	73.93		88.13	78.16	61.29	59.68	55.24
8	98.28	88.59	78.87		96.84	85.77	66.76	67.37	64.36
9		92.36	82.26			90.85	73.27	71.77	68.81
10		98.11	87.15			93.49	78.19	77.42	75.63
11			91.02			98.88	84.64	82.12	79.43
12			100.15				95.49	89.28	87.19

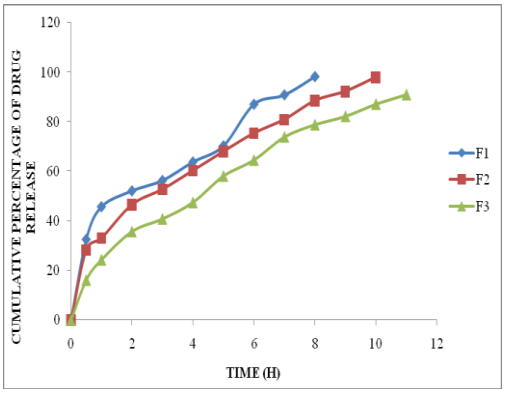


Fig 8.4: Dissolution data of Tramadol Hydrochloride Floating tablets containing EudragitRSPO

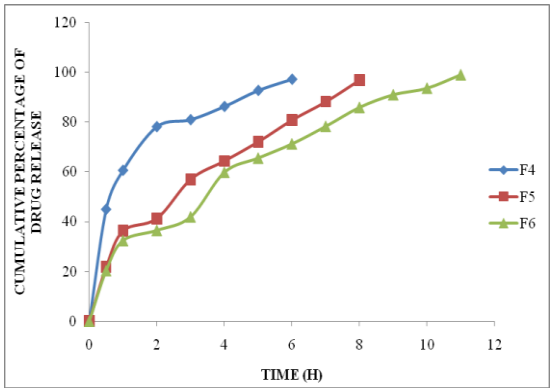
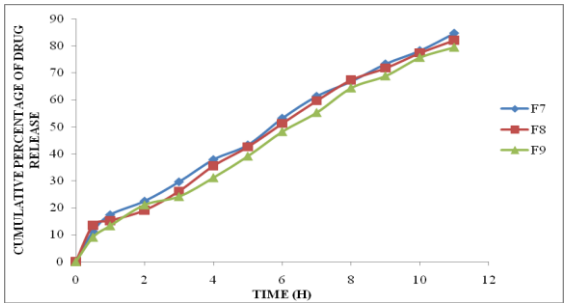


Fig: 8.5 Dissolution data of Tramadol Hydrochloride Floating tablets containing HPMC K100



Dissolution data of Tramadol Hydrochloride Floating tablets containing Chitosan

From the dissolution data it was evident that the formulations prepared with Eudragit RSPO as polymer were did not retarded the drug release 12 hours.

Whereas the formulations prepared with HPMC K 100 did not retarded the drug release up to 12 hours in the all ratios. In higher concentrations the polymer was unable to retard the drug release.

Whereas the formulations prepared with Chitosan were retarded the drug release in the concentration of 20 mg (F7 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 95.49 % in 12 hours with good retardation.

Hence from the above dissolution data it was concluded that F3 formulation was considered as optimized formulation because good drug release (100.15%) in 12 hours.

Application of release rate kinetics to Dissolution data for optimised formulation:Table no 8.5 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
16.23	0.5	0.707	1.210	-0.301	1.923	32.460	0.0616	-0.790	83.77	4.642	4.376	0.266
24.38	1	1.000	1.387	0.000	1.879	24.380	0.0410	-0.613	75.62	4.642	4.229	0.413
35.79	2	1.414	1.554	0.301	1.808	17.895	0.0279	-0.446	64.21	4.642	4.004	0.637

40.88	3	1.732	1.612	0.477	1.772	13.627	0.0245	-0.388	59.12	4.642	3.896	0.746
47.54	4	2.000	1.677	0.602	1.720	11.885	0.0210	-0.323	52.46	4.642	3.743	0.898
58.17	5	2.236	1.765	0.699	1.621	11.634	0.0172	-0.235	41.83	4.642	3.471	1.170
64.62	6	2.449	1.810	0.778	1.549	10.770	0.0155	-0.190	35.38	4.642	3.283	1.359
73.93	7	2.646	1.869	0.845	1.416	10.561	0.0135	-0.131	26.07	4.642	2.965	1.676
78.87	8	2.828	1.897	0.903	1.325	9.859	0.0127	-0.103	21.13	4.642	2.765	1.877
82.26	9	3.000	1.915	0.954	1.249	9.140	0.0122	-0.085	17.74	4.642	2.608	2.034
87.15	10	3.162	1.940	1.000	1.109	8.715	0.0115	-0.060	12.85	4.642	2.342	2.299
91.02	11	3.317	1.959	1.041	0.953	8.275	0.0110	-0.041	8.98	4.642	2.079	2.563
100.15	12	3.464	2.001	1.079		8.346	0.0100	0.001	-0.15	4.642	-0.531	5.173

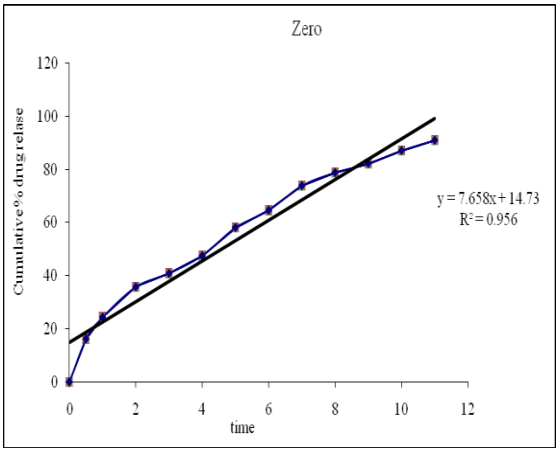


Fig no 8.7 : Zero order release kinetics

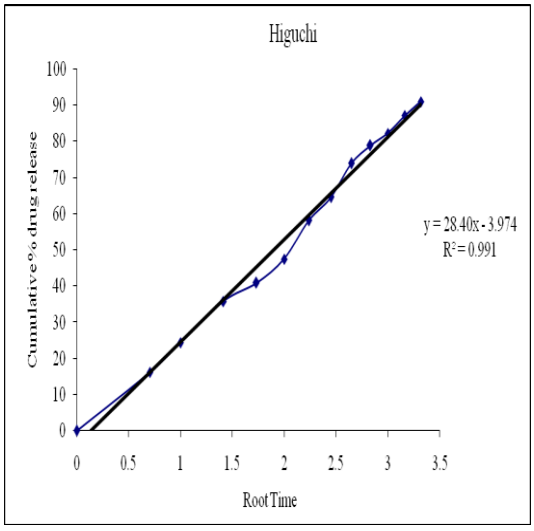


Fig no 8.8: Higuchi release kinetics

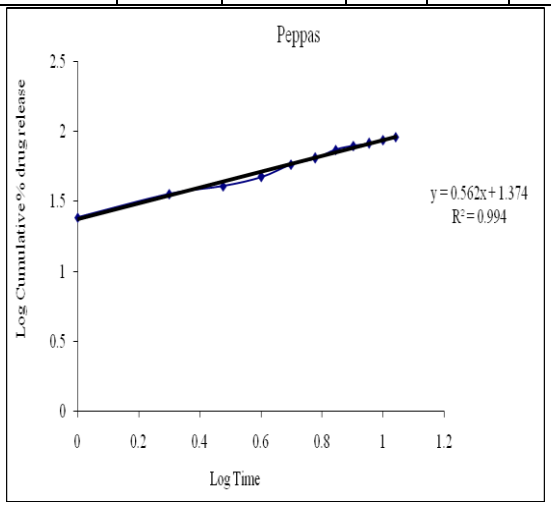
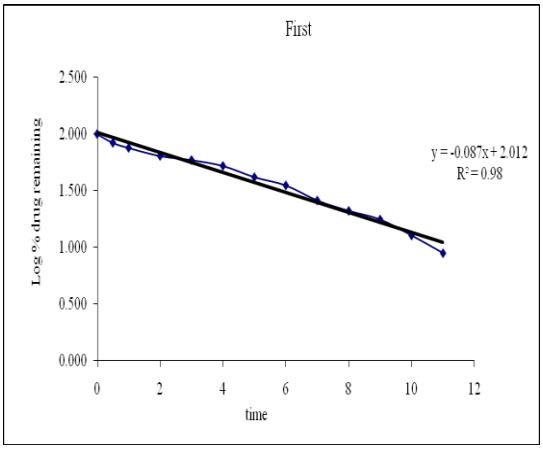
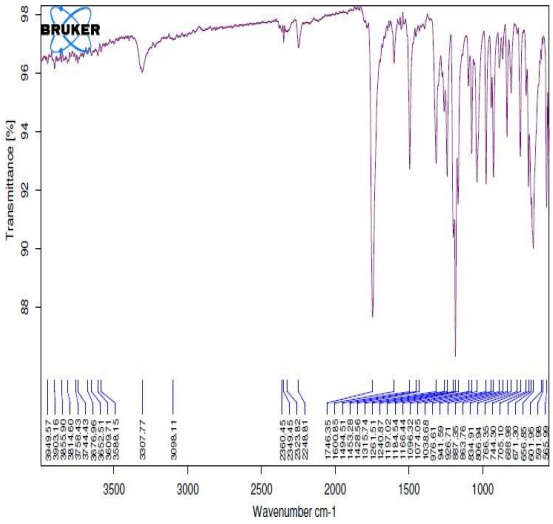


Fig8.9 : Kors mayer peppas release kinetics



First order release kinetics

Optimised formulation F3 was kept for release kinetic studies. From the above graphs it was evident that the formulation F3 was followed **Higuchi release kinetics** mechanism.



Drug – Excipient compatibility studies Fourier Transform-Infrared Spectroscopy:

Figure 8.11: FTIR Spectrum of pure drug

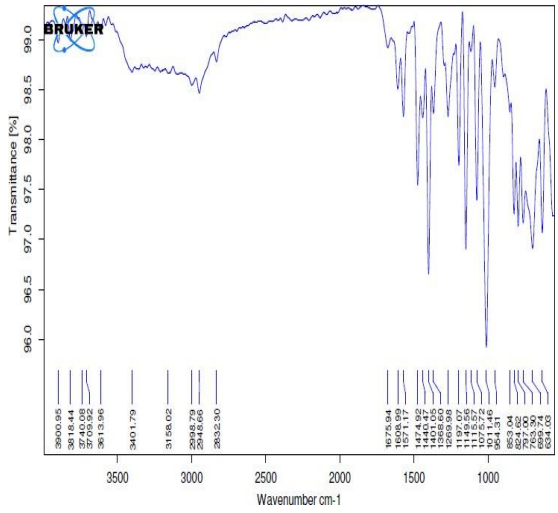


Fig 8.12 FTIR Spectrum of optimised formulation

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.

Tramadol Hydrochloride is 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

In the present study gastro-retentive floating tablets of Tramadol Hydrochloride were successfully prepared by direct compression method using a number of ingredients like Eudragit RSPO, HPMC K 100, Chitosan, Sodium Bicarbonate, Talc and Magnesium stearate. For each formulation blend of the drug and excipients were prepared and evaluated, the tablets were compressed by direct compression method. Compatibility study revealed that there was no interaction between the drug and the excipients in the formulation. Pre-compression parameters were tested for each and every formulation batch and were found to be satisfactory. *In-vitro* drug release studies were carried out for all prepared formulation and from that concluded F3 formulation has shown good results finally concluded release kinetics to optimised formulation (F3) has followed Higuchi release kinetics.

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