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TRAMADOL HYDROCHLORIDE FLOATING TABLETS: FORMULATION, IN-VITRO STUDIES AND INFLUENCE OF POLYMER INCIPIENT

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ABSTRACT

The purpose of this research is to formulate the floating drug delivery system of Tramadol HCl, a synthetic opioid analgesic. The present investigation describes the influence of content of hydroxyl propyl methyl cellulose (HPMC) in Gastro retentive floating tablets by using different grades of hydroxyl propyl methyl cellulose along with the detailed study of the effect of various factors like drug polymer ratio, drug disintegrating agent, sodium bicarbonate ratio and polymer grade on formulation properties. The prepared tablets were also evaluated for physical parameters like weight variation, friability and hardness, disintegration test, dissolution test,buoyancy test, swelling index etc. In addition, effect of floating properties like buoyancy lag time (BLT) and total floating time (TFT) of the floating matrix tablet were also studied. To study the release pattern of drug from these formulations using suitable in vitro model. The floating matrix tablets were prepared to prolong the gastric residence time and to increase its bioavailability. The drug-polymer interaction was evaluated by Fourier transform infrared spectroscopy (FTIR), which indicated the lack of drug-polymer interaction.

KEY WORDS

Tramadol HCl, Floating tablets, Polymers, Dissolution Study, Swelling Index.

INTRODUCTION

Tablets are solid dosage forms in which powder, crystalline or granular from of drug is compressed in a disk or molded. It is the most frequently used means of administering a drug.(1) Most of the tablet is administered orally. However, the tablet for application as implant, solution, vaginal use and external use are also available. Oral tablet is designed to release the drug within the gastrointestinal tract for absorption into the circulation or more rarely for local effect. The goal of drug therapy is to produce drug concentration that elicit desired pharmacological action and minimize incidence and severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen.

In conventional oral drug delivery systems, there is little or no control over the release of the drug, and effective concentration of grossly excessive doses. This kind of dosing pattern results in constantly changing, unpredictable, and often sub or supra therapeutic plasma concentrations, leading to marked side effects in some cases. Moreover, the rate and extent of absorption of drug from conventional formulations may vary greatly, depending on factors such as physio-chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal (GI) tract, GI motility and so on.

Uncontrolled rapid release of drug may cause local GI or systemic toxicity. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentration versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half-life ($t_{1/2}$) and duration of pharmacological effect. The rate of dosing may also be affected by therapeutic index of a drug.

Thus, conventional oral controlled drug delivery systems has not been suitable for a variety of important drugs which has any of above-mentioned characteristics, which is mainly due to the relatively short transit time of the dosage form in the stomach and upper part of small intestine. The overall results are accompanied my lesser bioavailability. Furthermore, the relatively brief gastric emptying time in humans, which normally range from 2 to 3 hours through the major absorption zone (stomach or upper part of intestine), can result in incomplete drug release from the dosage form leading to diminished efficacy of the administered dose. Thus, control of placement of drug delivery system in a specific region of the GI tract offers numerous advantages.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the Gastric Residence Time (GRT), i.e. Gastro Retentive Dosage Form (GRDF).(2) GRDF extend significantly the period of time over which the drugs may be released.(3) They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Floating Drug Delivery Systems (FDDS) is one such GRDF which can increase the GRT. These FDDS have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. (4, 5) While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. (6, 7). These floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.(8) A floating dosage form is a feasible approach(9) especially for drugs which has absorption sites in the upper small intestine. (10)

In the context of the above principles, a strong need was recognized for the development of a dosage form to deliver tramadol in the stomach and to increase the efficiency of the drug, providing controlled release action. Aim of this study is to formulate and evaluate Tramadol hydrochloride floating tablets using different polymers: HPMCK4M, HPMC15M, HPMC K100M, sodium CMC and ethyl cellulose in different ratios. Sodium bicarbonate was used as the gas generating agent.Polymers such as HPMC K100 has been found to be beneficial in improving floating properties. Use of these hydrophilic polymer have been reported to slowly forms thick gel, retaining the formulation integrity as well as promoting drug release through thick gel which controls the release.(11) Hence, both the drug and polymers were found to fulfill the required characteristics, which indicate its suitability for fabrication into the floating drug delivery system.

MATERIALS AND METHODS

Drugs and Instruments:

Tramadol hydrochloride, HPMC K4M, HPMCK100 M, Carboxy methyl cellulose. The UV spectra were recorded in using aShimadzu UV spectrophotometer. Compatibility studies of Tramadol HCl and the carriers were carried out by using FT-IR spectra of the samples were obtained in the range of 400 to 4000 cm^{-1} using a PERKIN ELMER – FT-IR 8201 PC spectrophotometer by the KBr disc method.

Direct compression method:

Floating Tramadol hydrochloride hydrophilic tablet were prepared by using direct compression technique using different grades of polymers with varying concentration as well as different concentration of sodium bicarbonate and varying amount of gum acacia. All the ingredients given in the above (table) except magnesium stearate were shifted and blended in mixer uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate were added and further mixed for additional 2- 3

minutes. The tablets were compressed using 12 mm concave punch on a single stroke punching machine with hardness about 5 kg/cm^2 .

Characterization of tablets:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations. Following parameters were evaluated

A) Hardness

Hardness indicates the ability of a tablet to with stand mechanical shocks while handling. The hardness of tablet was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets are randomly picked and hardness of the tablet was determined.

b) Friability Test

The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0 - initial) and transferred in to Friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_t - final). The % friability was then calculated by.

$$\% F = (1-W_0/W_f) \times 1$$

% Friability of tablets less than 1% were considered acceptable

c) Weight variation test

Twenty tablets were selected randomly from each batch and weighed individually to Check for weight variation. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage and none deviate by more than twice the percentage. The percentage deviation in weight

Floating parameter:

(a) Dissolution Study of floating tablets

Dissolution Study of floating tablets was performed using Dissolution test apparatus (USP XXIII). USP type 2 apparatus (paddle method) was employed using 0.1N HCl as Dissolution medium. Dissolution volume was maintained at 900 ml at 37 $\pm$ 0.5 °C and a speed 50 rpm.

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 5, 6 hour intervals and same volume of fresh medium was replaced .The samples were analyzed for drug content analysis against 0.1N HCl as a blank.

The absorbance was measured at 270nm using UV visible Spectrophotometer. The content of drug is calculated using the equation generated from the standard curve. The percentage cumulative drug release was calculated.

(b) Swelling study:

Swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the may be due to saturation of capillary species within the particle or hydration of micromolecule. The liquid enters the particle through pores and bind to large molecule breaking the hydrogen bond and resulting in swelling of particle. The extent of swelling can be measured in terms in % weight gain by the tablet. For each formulation batch, tablets were weighed and place in a beaker containing 200 ml of 0.1N HCl of pH 1.2. After each hour the tablets were removed from beaker and weighed again up to 12 hours. The swelling study was performed for batch F1, F2, F3, F4 and F5 as the tablet of these batches float. The % weight gain by the tablet was calculated by the formula.

$$\text{Swelling Index (S.I)} = (W_t - W_{0)} / W_0 \times 100$$

W_t = weight of tablet at time t hour

W_0 = weight of tablet at before immersion.

RESULTS AND DICUSSION

Floating tablet of Tramadol Hydrochloride was prepared by direct compression method. The microscopic examination of the tablets from each formulation batches has showed cylindrical shape (oval) with no cracks. The floating tablets were prepared using different polymer grades like HPMC K4M, & HPMC K100M polymers.

Table 1: Formula for Tramadol hydrochloride floating tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Tramadol HCl	220	220	220	220	220	220	220	220
HPMCK4M	150	100	300	200	-	-	-	-
HPMCK100M	-	-	-	-	150	100	300	200
SCMC	50	100	100	200	50	100	100	200
Sodium bicarbonate	40	40	40	40	40	40	40	40
Citric acid	10	10	10	10	10	10	10	10
MCC	89	89	80	80	89	89	80	80
Gum acacia	30	30	40	40	30	30	40	40
Magnesium stearate	5	5	8	8	5	5	8	8
Aerosil	2	2	2	2	2	2	2	2
Target wt (mg)	600	600	800	800	600	600	800	800

Table 2: Weight variation test

Average weight of tablet (mg)	Percentage deviation
130 mg or less	**10**
>130 mg & less than 324 mg	**7.5**
324 mg or more	**5**

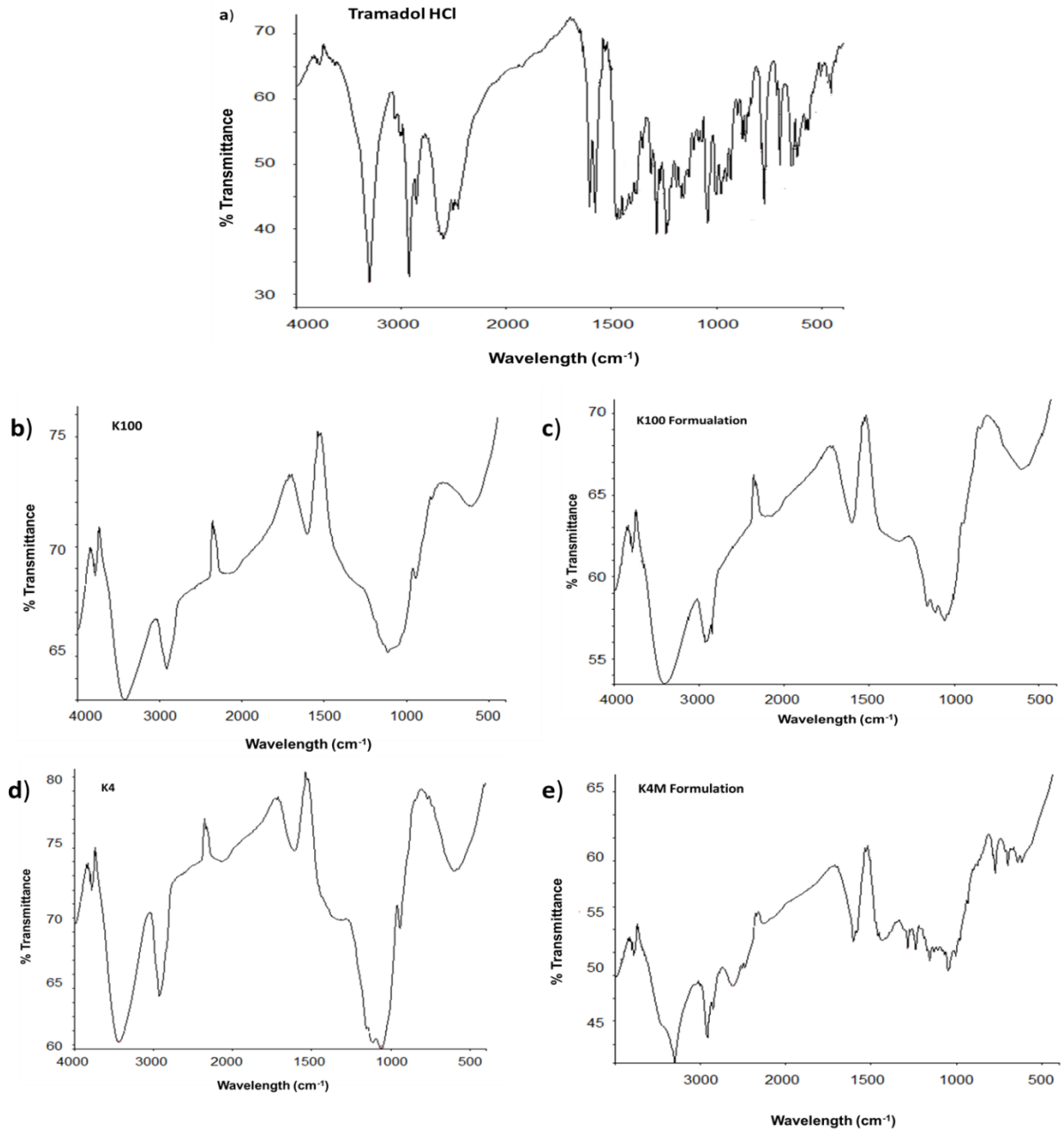

Figure 1: FT-IR of a) Pure drug Tramadol HCl, b) Polymer HPMCK100M, c) Formulation using HPMCK100M, d) Polymer HPMCK4M, e) Formulation using HPMCK4M

Compatibility studies were performed using FT-IR spectrophotometer. The FT-IR spectrum of pure drug and physical mixture of drug and polymer were studied. FT-IR studies of the pure drug (TH) and the formulations were carried out to study the interaction between drug and excipients in the formulation. From the study, major peaks of drug (TH) were found to be at 3305, 2930,2602,1607, 1579, 1285,1242,1045,776, 702 cm^{-1} (**Fig.1a**) . The major peaks in the polymers HPMC K100M (**Fig.1b**) were observed at around 3429, 2916, 2173, 1605, 1117 and 609 cm^{-1}. These FT-IR peaks representing the polymer were found to be unaffected by the presence of the drug in the formulation (**Fig.1c**). In the formulation containing

polymer HPMCK4M also (**Fig.1e**), major peaks of the polymers were found to be undisturbed by the presence of the drug. Other peaks observed were due to excipient or the drug present in the formulation. Hence, the peaks obtained in the spectra's of each formulation correlated with the peaks of the polymer spectrum. From the FT-IR spectrum, it was concluded that no significant difference in peak pattern in IR spectrum of drug, polymer, excipients.

Studying the drug release profiles it was found that different grades of HPMC lead to the increase in the viscosity and hence lead to an increase in the time of drug release time (decrease the drug release). From the in-vitro drug profiles, it was also found that drug release rate increased as the concentration of HPMC K100 was increased.

The Tablets were also subjected to various evaluation parameters such as physical property, floating property, swelling property & in - vitro drug release studies. The measured hardness of tablet of each batch range between 2.5 to 3.1 kg/cm^2. The friability values was found to be less than 1% in all cases and considered to be satisfactory.

It was revealed that all batches had acceptable physical parameters. All tablet formulation adds good floating property along with swelling behaviors& in – vitro drug release. Higher swelling index was found for tablets formulation F5 containing HPMCK100 M. Formulation 1 which had the same formulation as formulation F5, but had used HPMCK4M showed the lowest swelling index. As the polymer HPMCK4M amount was increased from formulation F1 to F4, a change in the swelling index as well as the drug release % was also observed. F3 containing the highest amount of polymer HPMCK4M showed the lowest drug release profile. Doubling the SCMC amount in F3 to F4 lead to increase in swelling index. Thus, the concentration of polymer and ratio of SCMC had influence on swelling process, matrix integrity, as well as floating capability.

Table 3: In-vitro Dissolution Profile of Tramadol HCl Floating Tablet

S.No	Time (h)	Percentage Cumulative Drug Release				
		F1	F2	F3	F4	F5
1	0.5	24.0	29.76	23.15	25.5	28.2
2	1	26.5	36.6	42.68	38.21	45.20
3	2	52.75	50.9	52.3	51.5	53.0
4	3	59.92	60	56.17	58.0	62.3
5	4	74.09	72.09	62.04	73.5	76.9
8	5	80.33	79.09	68.83	81.22	83.7
9	6	80.91	85.3	72.39	88.0	86.5

Table 4: Standard graph of Tramadol HCl.

S.No	Concentration(µg/ml)	Absorbance(nm)
1	20	0.104
2	40	0.201
3	60	0.297
4	80	0.401
5	100	0.530

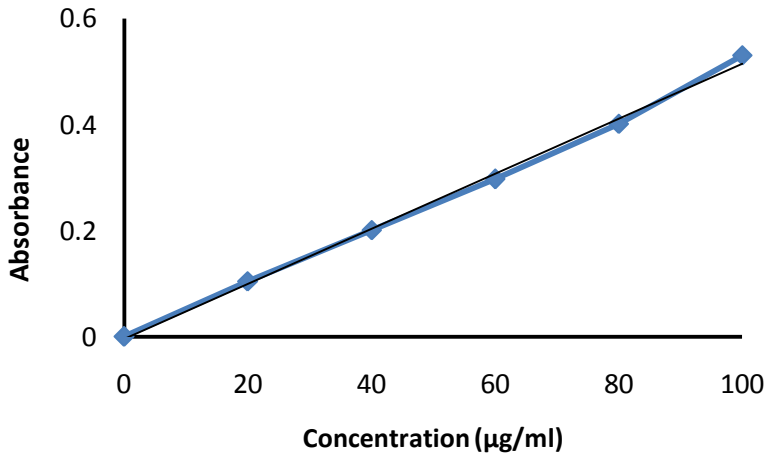

Figure 2: Calibration curve of Tramadol HCl.

Table 5: Physical Properties of Tramadol HCl Floating Tablet.

Batch Code	Evaluation Parameters			
	Weight variation (mg)	Hardness (kg/cm²)	Percentage Friability (%)	Drug Content (%w/w)
F1	1.033±1.21	3.2	0.546	80.91
F2	1.043±0.49	3.4	0.578	85.32
F3	1.093±1.42	3.5	0.652	72.39
F4	1.022±1.11	4.2	0.582	88.0
F5	1.045±1.99	4.2	0.416	86.5

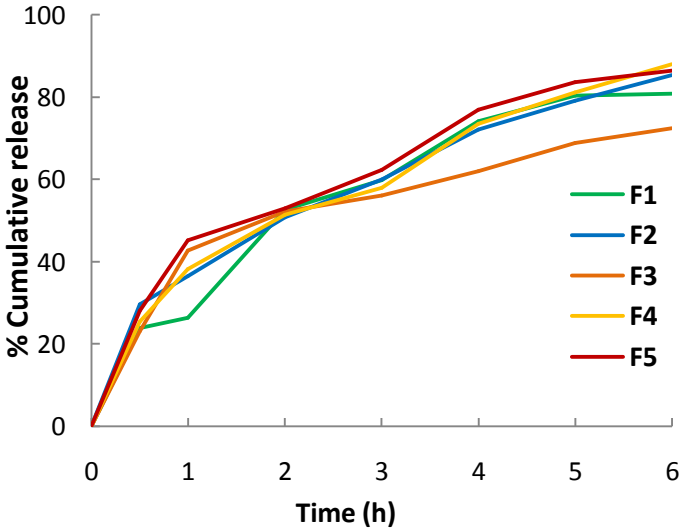

Figure 3: In-vitro Dissolution Profile of Tramadol HCl Floating Tablet.

Table 6: Degree of Swelling of Tramadol HCl Floating Tablet.

Time (h)	F1	F2	F3	F4	F5
1	56.66	80	80	78.33	80
2	56.6	108.33	92.5	126.66	116.25
3	106.66	120	115	155	140
4	120	140	130	186	168
5	123.3	152	136.25	151.6	232

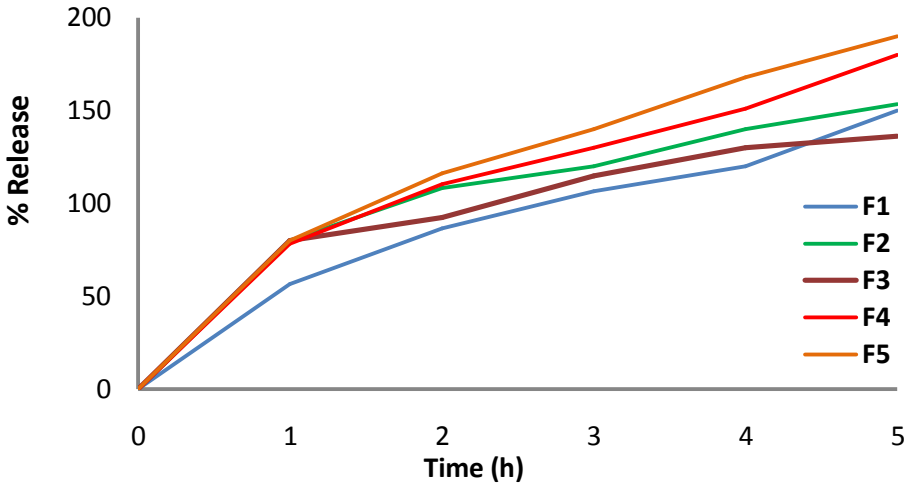

Figure 4: Degree of Swelling of Tramadol HCl Floating Table.

CONCLUSIONS

Attempt to deliver Tramadol Hydrochloride via Floating drug delivery system was successfully formulated as an approach to increase gastric residence time & there by improve its bio-availability. The gastric retentive system of Tramadol Hydrochloride were prepared with different grades of HPMC as drug release retarding polymer and Sodium bicarbonate as source for Carbon dioxide which helps tablet to float. FT-IR studies confirmed that there were no interactions found between Tramadol Hydrochloride and polymers.

The flow properties of the granules were studied and formulation F5 was found to have comparatively good swelling index properties. From the dissolution studies of the formulations, formulation F5 was found to have better drug release than other formulations. Tablets were also subjected to various evaluation parameters such as physical property, floating property, swelling property & in - vitro drug release studies. It was revealed that all batches had acceptable physical parameters. All tablet formulation adds good floating property along with swelling behaviors & in – vitro drug release.

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