Research Article

Design and Evaluation of Gastroretentive Floating Matrix Tablets of Tramadol Hydrochloride

M. Mohan Varma* and GEVN. Kumar

Shri Vishnu college of Pharmacy, Vishnupur, Bhimavaram, Andhra Pradesh, India.

ABSTRACT

Tramadol HCl is a synthetic opioid analgesic,it has the elimination half-life of 4-6 hours. The purpose of this research was to formulate the floating drug delivery system of tramadol HCl.The floating matrix tablets were prepared to prolong the gastric residence time and to increase its bioavailability.The rapid gastro-intestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to poor bioavailability of the drug.The floating tablets were formulated using various polymers:HPMC (K4M,K15M,K100M),sodium CMC, and ethyl cellulose.The tablets were prepared by direct compression.The formulated tablets were evaluated for weight variation,hardness,friability, floating lag time,total floating time and the dissolution rate in pH 1.2.The floating tablets extended the drug release up to 12 hours.The drug-polymer interaction was evaluated by fourier transform infrared spectroscopy(FTIR).The FTIR study indicated the lack of drug-polymer interaction.The drug release from the optimized formulation(batch F8) followed first order kinetics(correlation coefficient, r value 0.957) and non-fickian diffusion(n=0.483).

Keywords: Tramadol HCl, Floating tablets, polymers, Dissolution.

INTRODUCTION

Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process[1].Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region with in the GI tract for either local or systemic action[2].It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. 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 (GRDFs or GRDS). Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transittime and improves the oral bioavailability of the drugs that are having site specific absorption from the stomach or upper part of the small intestine[3,4].Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems,swelling and expanding systems,floating systems and delayed gastric emptying devices[5,6].The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release[7,8].From the discussion of the physiological factors in stomach, to achieve gastro retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease.

Tramadol Hydrochloride[9,10] is a centrally acting synthetic opioid analgesic,it is freely soluble in water. Tramadol has an absolute bioavailability of 75%.Tramadol has a volume of distribution of approximately 2.7 L/kg and is 20% bound to plasma proteins.The drug is administered orally,

initially at a dose of 50mg, 3-4 tissues/day gradually increased to a maximum dose of 200mg/day in divided doses.It has an elimination half life of 4-6 hours and has an absorption zone from the upper intestinal tract.Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone.Tramadol requires multiple daily drug dosage in order to maintain adequate plasma concentrations.Therefore,it is a suitable drug for gastroretentive formulation.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 the gastrointestinal tract.These systems help in continuously releasing the drug before it reaches the absorption window ,thus ensuring optimum bioavailability.

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[11,12] action.Aim of the study is to formulate and evaluate Tramadol hydrochloride floating tablets[13,14] using different polymers:HPMCK4M, HPMC15M, HPMC K100M,sodium CMC and ethyl cellulose in different ratios.The sodium bicarbonate[15-18] was used as the gas-generating agent.

MATERIALS AND METHODS

Tramadol HCl was obtained as the gift sample from S.K.Parenterals, Tanuku, AndhraPradesh. HPMC (K4M, K15M, and K100M), ethylcellulose, sodium CMC, and sodium bicarbonate were procured from S.D Fine Chem Ltd., Mumbai.

Estimation of Tramadol HCl

A spectrophotometric method based on the measurement of absorbance at 271 nm in 0.1N HCl was used for the estimation of tramadol HCl.The 100 mg of the pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution 1000µg/ml), from this 10ml of solution was taken and the volume was adjusted to 100 ml with 0.1 N HCl (100µg/ml).The above solution was subsequently diluted with 0.1N HCl to obtain the series of dilutions containing 2,4,6,8,10,15,20,30, 40, 50, 60, 70, 80, 90 µg/ml of tramadol HCl solution. The absorbance of the above dilutions was measured at 271 nm by using the UV-spectrophotometer(Lab.India) using 0.1N HCl as the blank. Then a graph was plotted by taking concentration on x-axis and absorbance on y-axis which gives a straight line.

Preparation of Floating Tablets

All the formulations were prepared by using the different polymers(HPMC,sodium CMC,ethyl cellulose) in various ratios (designated as F1 to F20 inTable-1).The tramadol HCl and all other ingredients were individually passed through sieve ≠ 60.All the ingredients were mixed thoroughly by triturating up to 15 min.The powder mixture was lubricated with talc.The tablets were prepared by using the direct compression method[19].

Evaluation of Floating Tablets

The formulated tablets were evaluated for the following physicochemical characteristics[20].

Hardness

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force required for the tablet to break.

Weight Variation

The 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Friability test
The 20 previously weighed tablets were placed in the friability apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,

Percentage friability = initial weight-final weight /initial weight × 100

Drug content
The 20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of tramadol HCl was transferred in to a 100 ml volumetric flask and the volume was adjusted to 100 ml with 0.1N HCl. The sample was filtered to remove the insoluble excipients.Further, 1ml of the above solution(filtrate) was diluted to 100 ml with 0.1N HCl and the absorbance of the resulting solution was observed at 271 nm.

In vitro Buoyancy studies
The in vitro buoyancy was determined by floating lag time and total floating time as per the method described by Rosa et al[21].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 the duration of the time the tablet constantly floats on the dissolution medium was noted as the total floating time respectively (TFT).

Dissolution Study
The 900ml of 0.1 HCl(pH 1.2)was placed in the vessel and the USP apparatus –II (paddle method) was assembled. The medium was allowed to equilibrate to the temperature of 37 $\pm$ 0.5°C. The tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 12 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fresh dissolution fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically(Lab.India) at 271 nm.

Release Kinetics
The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, diffusion and Peppa's-Korsemeyer equations. The order of drug release from the matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's- Korsemeyer equation.

Zero Order Release Kinetics
It defines a linear relationship between the fraction of drug released versus time. $Q = k_o t$.Where, Q is the fraction of drug released at time t and $k_o$is the zero order release rate constant.A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics
Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is $\ln (1-Q) = - K_1 t$.Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.Thus, a plot of the logarithm of the fraction of drug undissolved against time will be linear if the release obeys first order release kinetics.

Higuchi equation
It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time. $Q=K_2 t^{½}$ .Where, K2 is the release rate constant.A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation[22].

Power Law
In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power

Law).$M_t/M_\alpha = K.t^n$.Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the $M_t/M_\alpha$is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent. A plot between log of M_t/M_α against log of time will be linear if the release obeys Peppa's and Korsemeyer equation and the slope of this plot represents "n" value[23].

FTIR studies

The FTIR studies were carried out to evaluate the drug-polymer interaction.The FTIR spectra of the drug (alone) and the drug-polymer (physical mixture) were recorded by the potassium bromide pellet method (Bruker model FTIR was used).

RESULTS AND DISCUSSION

Buoyant drug delivery systems have a bulk density lower than gastric fluids[24] and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate[25]. 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[26]. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentrations[27].

Tramadol HCl is a synthetic opioid analgesic.The absorption window of tramadol is confined to the upper part of the GI tract. It has the elimination half-life of 4-6 hours and its absolute bioavailability is reported to be about 75% of the administered oral dose.The tablets were formulated using various concentrations of polymers such as HPMC K4M, HPMC K15M, HPMC K100M, Ethyl cellulose, Sodium CMC either alone or in combination. The effervescing agent, sodium bicarbonate was used.

Evaluation of tablets

The objective of the present study was to prepare floating tablets of tramadol HCl. These tablets were developed to prolong the gastric residence time and to increase the bioavailability of the drug.Tramadol HCl was chosen as the drug because it is better absorbed in the stomach than in the lower gastro intestinal tract. The tablets were prepared by direct compression technique, using polymers such as HPMC K 15M, HPMC K15M,HPMC K 100M,sodium CMC,ethyl cellulose either alone or in combination.Tablets were evaluated for physical characteristics such as weight variation,hardness,friability,drug content, floating lag time and total floating time. The in vitro release characteristics were evaluated for 12hrs.

All the formulations fulfilled the compendial specifications of the various quality control parameters (Table 2): weight variation, hardness, friability, drug content, floating lag time, total floating time and the matrix integrity. The values of hardness of the different formulations ranged from 7.5-8.2kg/cm^2.The friability values of the different batches ranged from 0.512%-0.711%.All the tablet formulations exhibited uniformity of drug content(Table 2).The values of floating(buoyancy)lag time of all the formulations(Table 2)ranged from 3-10 minutes.The total floating time of all the formulations ranged from 05-12 hours.All the formulations exhibited good matrix integrity up to 12 h,except the formulations:F13,F14 which exhibited the matrix integrity only up to 5h.The sodium bicarbonate was used as a gas generating agent in order to float the tablet.The sodium bicarbonate induces CO_2 generation in the presence of dissolution medium (0.1N HCl).The gas generated is trapped and protected within the gel formed by hydration of the polymer,thus decreasing the density of the tablet below 1gm/mL,and the tablet becomes buoyant.

Dissolution study

The dissolution studies were carried out in 0.1N HCl(pH1.2)for 12 hours.The amount of drug released from all the formulations depends upon the concentration of the polymer used. As the concentration of the polymer was increased in the different formulations,the rate of drug release was decreased.The dissolution parameters of the formulated floating tablets are enlisted in Table 3.Based on $T_{50\%}$(hr) values,(time taken for 50% of drug release),the order of drug release from the formulations can be indicated, as:

F14>F13>F15=F1>F11>F12>F3>F2>F4>F16>F5>F7>F8=F6=F17>F10>F18>F9>F19>F20.Similarly,based on $T_{75\%}$(hr)values(time taken for 75% of drug release),the order of drug release from the different formulations can be arranged as: F13>F14>F11>F12>F1>F15>F2>F3=F4=F16>F5>F17>F6=F7>F9>F18>F8>F10>F19>F20.Based on the $T_{90\%}$(hr)values(time taken for 90% of drug release),the order of the drug release can be arranged as F13>F14>F11>F12>F1>F15>F2>F3>F4>F5=F16>F17>F6>F7>F10>F8.Thebatches:F9,F18,F19,F20 did not attain the values of $T_{90\%}$ after the 12 hr of the dissolution study.Among all the batches, the F8 (Drug:HPMC K100M, 1:1.5) batch is considered to be the optimized formulation ($T_{50\%}$ = 4.5h,$T_{75\%}$ = 9.3h, $T_{90\%}$ = 12h). Thedissolution profiles of the different formulations are depicted in Fig.1-8.

The hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH independent. In the present study, HPMC was used as a hydrophilic matrix polymer because it forms a strong viscous gel on contact with the aqueous media, which may be useful in controlled delivery of highly water-soluble drugs. In an attempt to prolong the release of drug, the concentration of HPMC was increased. Faster release of the drug from the hydrophilic matrix was probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecules. Further, ethyl cellulose was incorporated in the hydrophilic matrix.Incorporation of ethyl cellulose was found to control the drug release to some extent, which could be attributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer leading to decreased diffusion of the drug from the matrix. Ethyl cellulose has been used as a release retardant polymer in controlled release matrix dosage forms. Presence of hydrophobic polymer(ethyl cellulose) along with the HPMC was found to reduce the drug release further, possibly due to the reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethyl cellulose present in the tablet.

In vitro drug release studies revealed that the release of Tramadol hydrochloride from different formulations varies with characteristics and composition of matrix forming polymers as shown in Fig.1-8.The release rate of Tramadol hydrochloride decreased with increasing concentration of HPMC K4M, HPMC K15 M, HPMC K100M, Ethyl cellulose, Sodium CMC and the combination of polymers respectively. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to delay in the release of the drug from the device. In the present investigation, the results indicated that as the polymer concentration and the viscosity of the polymer was increased, there was a reduction in the rate of drug release. Formulations containing higher methocel viscosity grades. i.e., F7 to F9 showed slower drug release rates when compared to formulations with lower methocel viscosity grades i.e.F1, F3 and combination of polymers (HPMC and ethyl cellulose) Also,formulations containing higher viscosity grades, i.e., F19 and F20 showed slower rate of drug release when compared to formulations containing lower viscosity grades i.e., F15, F16, F17, and F18. Also,F13, F14 containing Sodium CMC exhibited faster rate of drug release compared to other formulations. Because the Sodium CMC was more hydrophilic than the other polymers, it rapidly absorbs the water and increases the swelling leading to more drug release from the formulation. The matrix integrity of the formulation was less, and the total floating time was also decreased.The amount of drug released from all the formulations depends on the concentration of polymer used. Finally, the amount of drug released from all the formulations was found to be in the order:

Sodium CMC > Ethyl Cellulose > HPMC K4M > HPMC K15M > HPMC K100M.

Formulation F13, F14 which contains high amounts of sodium CMC,gets eroded during dissolution study before the stipulated study period. Thus, higher concentration of Sodium CMC cannot be incorporated into such formulations for sustaining the release.

Release kinetics

The data was fitted to Korsemeyer equation; and the value of diffusion exponent ‘n’

(0.483) indicated that the drug release from the batch F8(optimized formulation) shows non-fickian diffusion(Table 3). The values of n(diffusion exponent),K(release rate constant)and the dissolution parameters:T_{25}(time taken to release 25% of the drug),T_{50}(time taken to release 50% of the drug) and T_{75} (time taken to release 75% of the drug)computed for all the controlled release floating tablets are represented in Table 3. Release of Tramadol hydrochloride from the prepared formulations was found to follow first order kinetics (correlation coefficient, r = 0.95 to 0.97),except the batches:F13,F14 which exhibited zero order kinetics(r >0.9) . Also, Higuchi plot of the different formulations showed an "r" value of 0.99, suggesting that diffusion and erosion is the predominant mechanism in controlling the drug release. Drug release data was fitted to Korsemeyer-Peppa's equation; and the value of diffusional exponent 'n' (0.48 to 0.61) of the different batches indicated that the drug release from the different formulations followed the non-fickian diffusion mechanism. The Table 4 enlists the coefficient of correlation (r) values of the different formulations. Release of tramadol from the optimized formulation (F8) was found to follow first order kinetics (correlation coefficient, r value, 0.957).Higuchi plot showed an r valve of 0.994 for formulation F8, suggesting that the diffusion and erosion plays an important role in the controlled release.

FTIR Studies

The FTIR studies of the pure drug,drug:HPMC K100M(1:1.5) physical mixture was carried out to study the interaction between the drug and the polymer.The FTIR spectrum of the pure drug shows the characteristic FTIR peaks at 3345.87cm^{-1} (O-H stretching), 3017.49cm^{-1}(C-H aromatic stretching),1404.72cm^{-1}(C=C aromatic stretching),1161.78cm^{-1} (C-N stretching), 2860.92cm^{-1} (C-H stretching),1437.05cm^{-1} (CH_2 bending).The FTIR spectrum of the pure drug (alone)and the drug:HPMC K100M physical mixture are depicted in the Fig. 9a and the Fig.9b respectively. All the FTIR peaks of the drug were observed in the drug: HPMC physical mixture. From the infrared spectra it is clearly evident that there were no interactions of the drug and the polymer. This confirms the undisturbed structure of the drug in the formulation. The FTIR studies demonstrated the absence of drug-polymer interaction in the solid state.

Table 1: Composition of different formulations of floating tablets

Formu Lation No.	Tramadol HCl (mg)	HPMC K4M (mg)	HPMC K15M (mg)	HPMC K100M (mg)	Ethyl Cellulose (mg)	Sodium CMC (mg)	$NaHCO_3$ (mg)	Mag. Stearate (mg)	Talc (mg)
F1	100	100	-----	-----	-----	-----	30	12	08
F2	100	150	-----	-----	-----	-----	40	15	10
F3	100	200	-----	-----	-----	-----	50	18	12
F4	100	-----	100	-----	-----	-----	30	12	08
F5	100	-----	150	-----	-----	-----	40	15	10
F6	100	-----	200	-----	-----	-----	50	18	12
F7	100	-----	-----	100	-----	-----	30	12	08
F8	100	-----	-----	150	-----	-----	40	15	10
F9	100	-----	-----	200	-----	-----	50	18	12
F10	100	-----	-----	-----	100	-----	30	12	08
F11	100	-----	-----	-----	150	-----	40	15	10
F12	100	-----	-----	-----	200	-----	50	18	12
F13	100	-----	-----	-----	-----	100	30	12	08
F14	100	-----	-----	-----	-----	150	50	18	12
F15	100	100	-----	-----	100	-----	50	18	12
F16	100	100	-----	-----	200	-----	70	20	12
F17	100	-----	100	-----	100	-----	50	18	12
F18	100	-----	100	-----	200	-----	70	20	12
F19	100	-----	-----	100	100	-----	50	18	12
F20	100	-----	-----	100	200	-----	70	20	12

Table 2: Quality control parameters of tramadol HCl floating tablets

Formulation No.	Avg. Weight,mg (Mean±S.D) (n=20)	Hardness (kg/cm^2) (n=3)	% Friability (Mean±S.D) (n=20)	% Drug content (mg)	Buoyancy Lag time (min)	Total floating Time(hrs)	Matrix Integrity
F1	252±3.1	8.0±1.5	0.612	99±0.7	7.0	12	+
F2	313±2.8	8.0±2.1	0.612	100±0.5	7.2	12	+
F3	378±3.5	8.0±1.8	0.644	100±0.6	7.5	12	+
F4	251±3.1	8.0±1.5	0.611	99±0.6	6.1	12	+
F5	313±2.8	8.0±2.1	0.625	99±0.6	5.0	12	+
F6	378±3.5	8.0±2.1	0.655	99±0.5	7.4	12	+
F7	252±2.1	8.0±1.8	0.711	100±0.3	8.5	12	+
F8	313±2.8	8.0±3.0	0.702	100±0.4	8.6	12	+
F9	378±3.5	8.0±2.1	0.699	100±0.3	7.7	12	+
F10	252±3.1	8.0±3.0	0.622	99±0.6	8.5	12	+
F11	313±2.8	8.0±2.2	0.589	99±0.8	8.9	12	+
F12	378±3.5	8.0±1.8	0.640	100±0.4	7.0	12	+
F13	252±3.0	7.5±2.0	0.532	100±0.5	6.5	05	-
F14	378±3.5	8.0±2.5	0.512	100±0.6	6.3	05	-
F15	378±3.5	8.2±1.8	0.611	99±0.4	9.0	12	+
F16	498±2.1	8.1±2.2	0.511	99±0.5	8.5	12	+
F17	378±3.5	8.1±1.9	0.533	99±0.6	10.0	12	+
F18	498±2.1	8.2±2.0	0.589	99±0.5	11.1	12	+
F19	378±3.5	8.2±1.2	0.599	100±0.3	11.5	12	+
F20	498±2.1	8.1±2.2	0.600	99±0.7	11.0	12	+

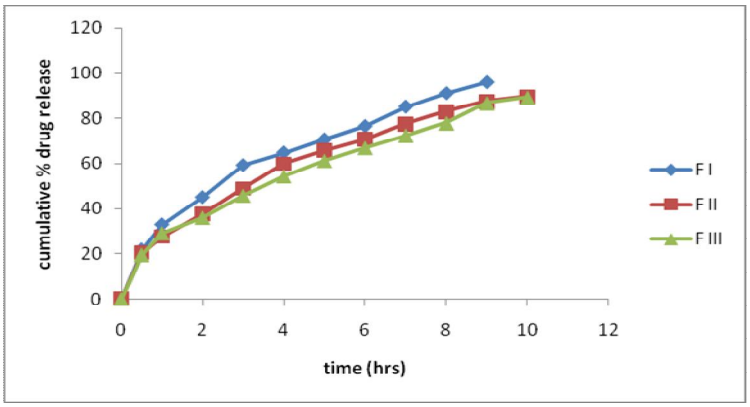

Fig. 1: Dissolution profile of TRAMADOL HCl floating tablets (F1, F2, F3 formulations)

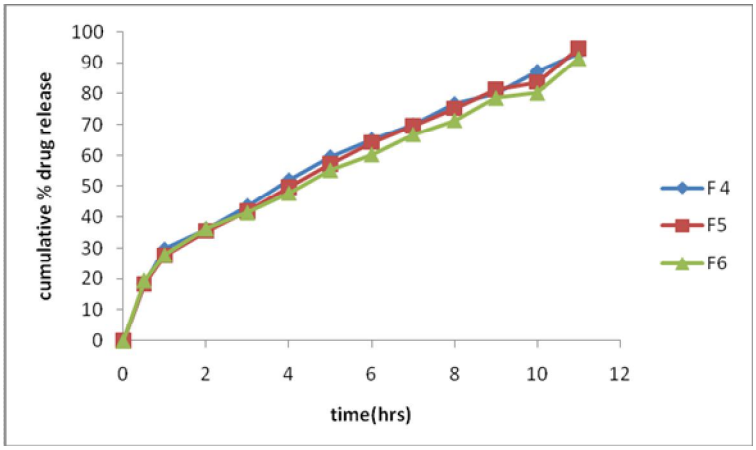

Fig. 2: Dissolution profile of TRAMADOL HCl floating tablets (F4, F5, F6 formulations)

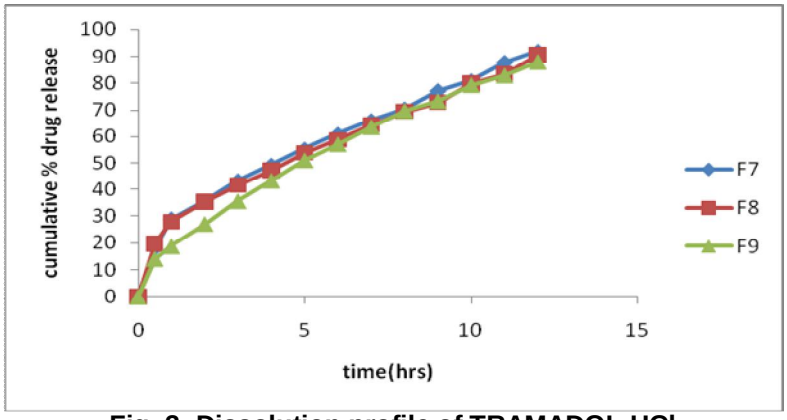

Fig. 3: Dissolution profile of TRAMADOL HCl floating tablets (F7, F8, F9 formulations)

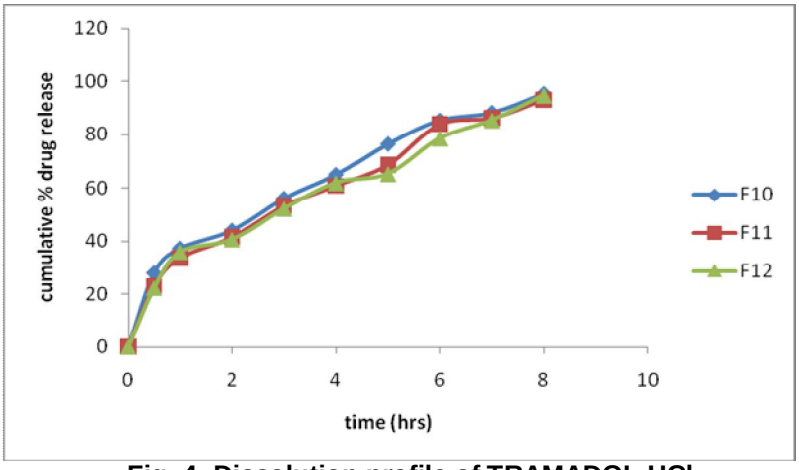

Fig. 4: Dissolution profile of TRAMADOL HCl floating tablets (F10, F11, F12 formulations)

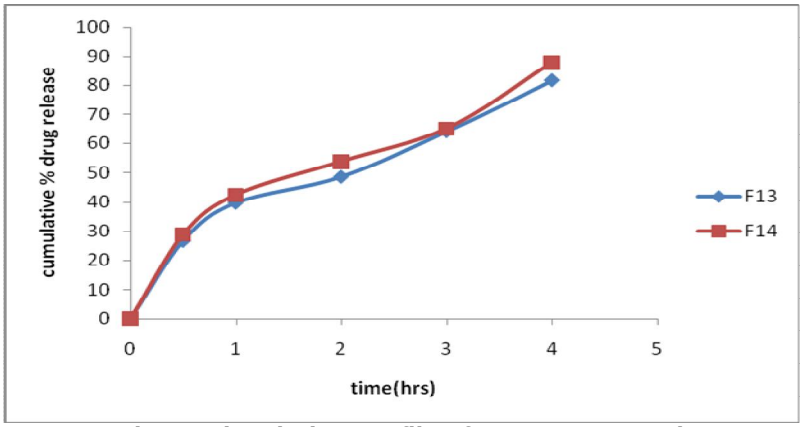

Fig. 5: Dissolution profile of TRAMADOL HCl floating tablets (F13, F14 formulations)

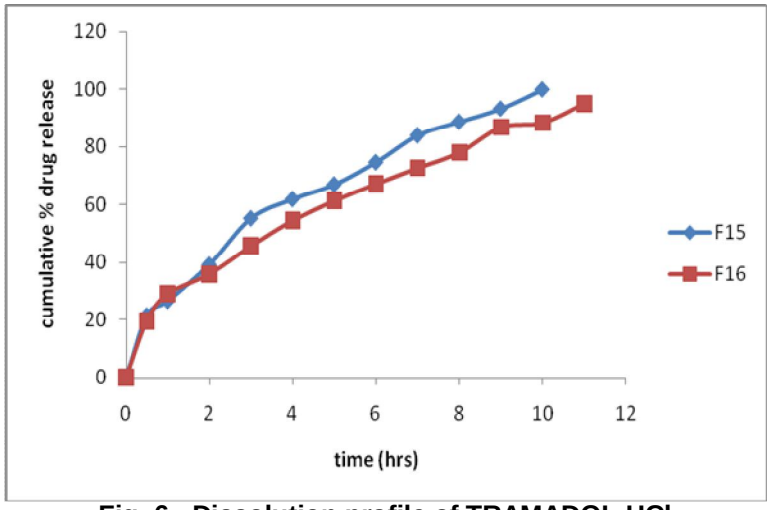

Fig. 6: Dissolution profile of TRAMADOL HCl floating tablets (F15, F16 formulations)

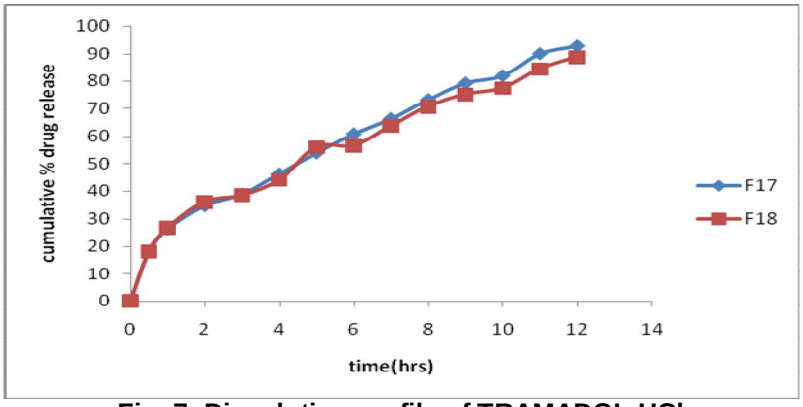

Fig. 7: Dissolution profile of TRAMADOL HCl floating tablets (F17, F18 formulations)

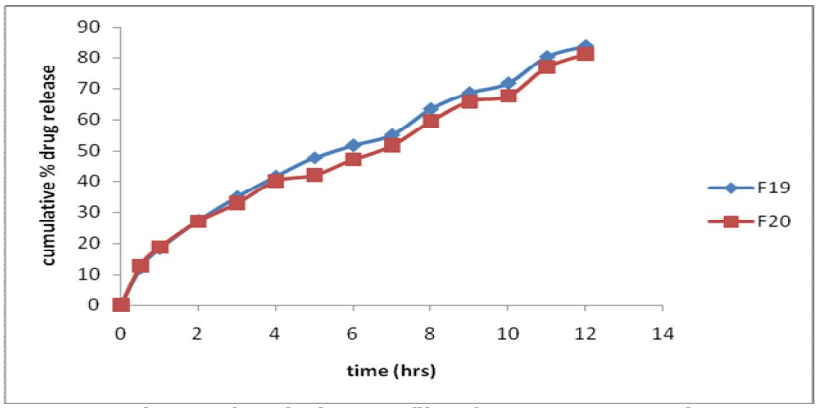

Fig. 8: Dissolution profile of TRAMADOL HCl floating tablets (F19, F20 formulations)

Table 3: Dissolution parameters of tramadol HCl tablets

Formulation	Dissolution Parameters					
	n	$K_{0(mg/hr)}$	$K_{1(hr^{-1})}$	$T_{50(hr)}$	$T_{75(hr)}$	$T_{90(hr)}$
F1	0.507	9.375	0.301	2.5	5.8	8.0
F2	0.514	7.775	0.248	3.6	6.8	10.0
F3	0.507	7.604	0.223	3.5	7.5	10.1
F4	0.505	7.424	0.204	3.8	7.5	10.2
F5	0.507	7.268	0.186	4.0	8.1	10.5
F6	0.479	6.593	0.175	4.5	8.5	11.1
F7	0.479	5.861	0.151	4.0	8.5	11.2
F8	0.483	6.563	0.175	4.5	9.3	12.0
F9	0.610	6.762	0.179	5.1	9.1	>12
F10	0.459	10.6	0.354	5	9.5	11.9
F11	0.500	10.43	0.299	2.6	4.8	7.2
F12	0.486	10.32	0.299	2.8	5.5	7.8
F13	0.530	16.94	0.502	2.1	3.5	4.8
F14	0.495	18.92	0.453	2.0	3.8	4.9
F15	0.535	9.431	0.267	2.5	6.0	8.5
F16	0.503	7.895	0.199	3.8	7.5	10.5
F17	0.510	6.817	0.181	4.5	8.2	11.0
F18	0.487	6.421	0.149	5.0	9.1	>12
F19	0.604	6.188	0.142	6.1	10.2	>12
F20	0.617	5.867	0.122	6.3	11.2	>12

Table 4: Release kinetics: coefficient of correlation (r) values of different batches of Tramadol HCl floating tablets

Formulation	Zero order	First order	Higuchi's	Peppa's
F1	0.920	0.946	0.997	0.996
F2	0.931	0.936	0.997	0.996
F3	0.948	0.957	0.996	0.994
F4	0.949	0.958	0.995	0.991
F5	0.957	0.964	0.996	0.993
F6	0.950	0.958	0.994	0.990
F7	0.937	0.968	0.993	0.992
F8	0.947	0.957	0.994	0.992
F9	0.963	0.972	0.991	0.992
F10	0.932	0.941	0.992	0.981
F11	0.944	0.953	0.990	0.988
F12	0.942	0.955	0.992	0.984
F13	0.957	0.913	0.983	0.978
F14	0.923	0.917	0.981	0.974
F15	0.940	0.971	0.995	0.990
F16	0.944	0.976	0.996	0.994
F17	0.952	0.979	0.990	0.987
F18	0.950	0.960	0.988	0.983
F19	0.961	0.974	0.997	0.997
F20	0.961	0.975	0.983	0.985

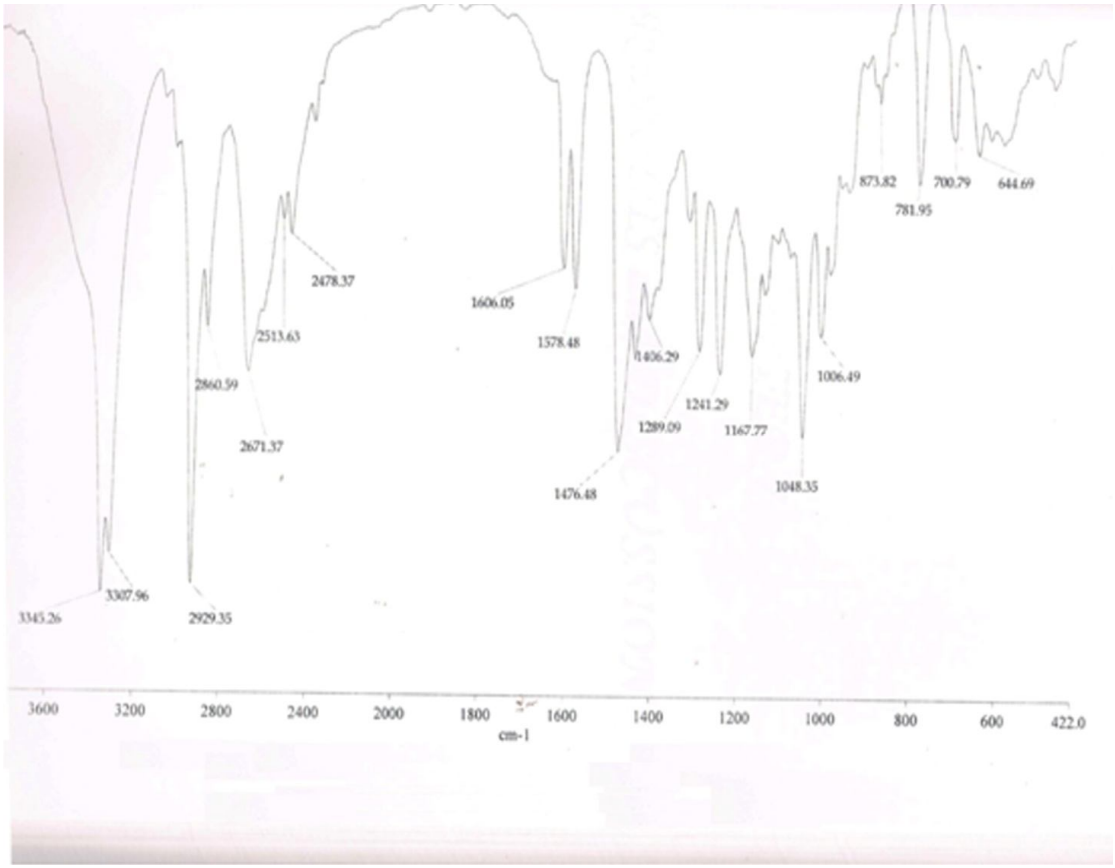

Fig. 9a: FTIR spectrum of Tramadol HCl

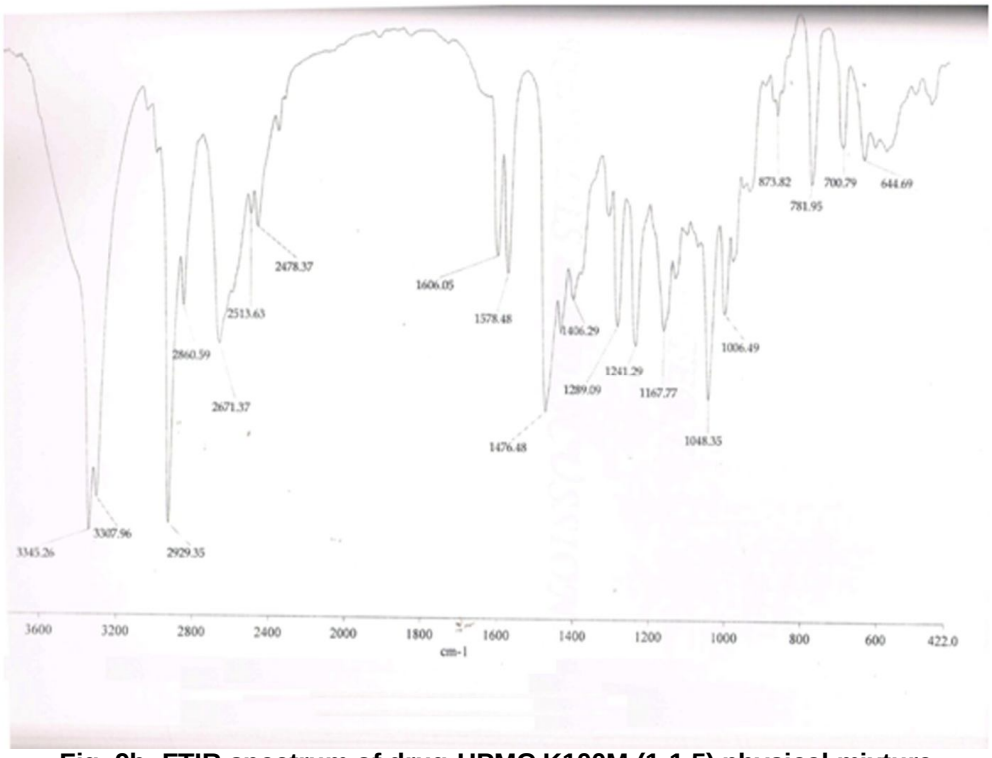

Fig. 9b: FTIR spectrum of drug-HPMC K100M (1:1.5) physical mixture

CONCLUSIONS

From the foregoing investigation it may be concluded that the release rate of the drug from the floating tablets can be governed by the type of polymer and the concentration of the polymer employed in the preparation of tablets. The effervescent based floating drug delivery is a promising approach to achieve in vitro buoyancy by using gel–forming polymer HPMC K100M and gas generating agent sodium bicarbonate. Floating matrix tablets containing the polymer, HPMC K100M(batch F8) could control the Tramadol release effectively for 12 hours.The tablets exhibited good floating time for 12 hours.The FTIR study revealed the absence of the drug-polymer interaction.The best formulation F8 can successfully be employed as a controlled release floating drug delivery system. The floating tablets can control the fluctuations in the plasma drug concentration, increase the gastric residence time and eventually improve the bioavailability of tramadol.

ACKNOWLEDGEMENT

The authors are thankful to the management of the shri vishnu college of pharmacy for providing the necessary facilities to carry out this work.

REFERENCES

1. Deshpande A.A.,Rhodes,C.T.,Shah,N.H. and Malick,A.W.Controlled drug delivery systems for prolonged gastric residence:an overview.Drug Dev.Ind. Pharm.1996:22:531-539.
2. Arora,S.,Ali,J.,Ahuja,A.,Khar,R.K.and Baboota,S. Floating Drug Delivery Systems: A Review. AAPS Pharmscitech.2005: 47: 268-272.
3. Desai, S.and Bolton, S. A Floating Controlled Release System: In-vitro and In-vivo evaluation. J. Pharm. Res.1993: 10:1321-1325.
4. Deshpande, A.A., Shah, N.H.and Rhodes, C.T. Development of a Novel Controlled Release System for Gastric Retention. Pharm. Res.1997:14: 815-819.
5. Davis,S.S.,Siockwell,A.F.,Taylor,M.J. and Hardy J.G. The effect of density on the gastric emptying on single and multiple unit dosage forms. J. Pharm Res.1986: 3:208-213.
6. Gangadharappa,H.V.,Kumar,T.M.P. and Shivakumar, H.G.Floating Drug Delivery System for Prolonged Gastric Residence time: A review. Ind. J. Pharm. Edu.Res. 2007:41:295-305.
7. Singh, B.N.and Kim,K.H. Floating drug delivery system an approach to control drug delivery via gastric retention. J. Control. Release.2000: 63:235-259.
8. Whitehead,L.,Fell,J.T.,Collet,J.H.Sharma,H.L.and Smith,A.M.Floating dosage forms:an in vivo study demonstrating prolonged gastric retention.J.Control.Release.1998:55: 3-12.
9. Goodman Gilman's.The Pharmacological Basis of Therapeutics, 10th edn, New York, USA,2001, pp.1765.
10. Thripati, K.D.Essential of Medical Pharmacology, 5th edn, New Delhi,2003, pp. 248-49.
11. Ichikawa, M. Watanabe, S.and Miyake, Y. A new multiple-unit oral floating dosage system: Preparation and in-vitro evaluation of floating and sustained-release characteristics. J. Pharm. Sci.1991:80:1062-1066.
12. Rouge, N.and Allemann ,E.Buoyancy and Drug release patterns of floating mini tablets containing Piretanide and Atenolol as model drugs. Pharm. Dev.Technol.1998: 3: 3-84.
13. Menon, A.Wolfgang, A.R.and Saks, A. Development and evaluation of a monolithic floating dosage form for Furosemide. J. Pharm. Sci.1998:83:239-245.
14. Xu, X.and Sun, M. Floating matrix dosage form phenylpropanolamine HCl based on gas forming agent. Int. J. Pharm.2006: 25:324-332.
15. Srivastava, A.K.andWadwa ,S. Oral sustain delivery of Atenolol from floating matrix tablets and invitro evaluation.Drug. Dev. Ind. Pharm.2005:31: 367-374.
16. Streubel, A., Siepmann ,J.and Bodmeier, R.Floating matrix tablets based on low density foam powder:

effects of formulation and processing parameters on drug release. Eur. J. Pharm. Sci.2003:18 : 37-45.
17. Nur, O.A.and Zhang, J.S.Captopril floating and/or bioadhesive tablets: design and release kinetics, Drug Dev. Ind. Pharm.2000: 26:965-969.
18. Shah, S.,Quaqish, R., Patel, V.and Amiji, M. Evaluation of the factors influencing stomach specific delivery of antibacterial agents for H.pylori infections. J. Pharm. Pharmacol.1999:51:667-672.
19. Aldrete, M.E.and Vilfuence, R.L. Influence of the viscosity grade and the particle size of HPMC on Metronidazole release from matrix tablets. Eur. J. Pharm. Biopharm.1997:43:173-178.
20. Ingani, H.M.,Timmermans, J.and Moes, A.J. Concept and in-vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int. J. Pharm.1987:35:157-164.
21. Rosa, M., Zia, H.and Rhodes, T.Dosing and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. Int. J. Pharm.1994:105:65-70.
22. Higuchi, T.Mechanism of Sustained-action medication. Theoretical Analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci.1963: 51:1145-1149.
23. Peppas, N.A. Analysis of Fickian and Non-Fickian drug release from polymers. Pharma Acta.Helv.1985:60:110-111.
24. Basak, S.C.,Rao, K.N., Manavalan,R. and Rao, P.R. Development and invitro evaluation of oral matrix floating tablets formulation of Ciprofloaxacin, Ind. J. Phram. Sci.2004: 66:313-316.
25. Rajinikanth PS,Balasubramaniam J and Mishra B.Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori.Int. J Pharm. 2007;335:114-122.
26. Dave, B.S. Amin,A.F.and Patel, M.M. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in-vitro evaluation, AAPS Pharm. Sci. Tech.2004:5:1-6.
27. Patel, V.F.and Patel, N.M. Studies on formulation and evaluation of Ranitidine floating tablets. Ind. J.Pharm.Sci.2005:25:333-341.