International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 2, Issue 4, 2010

Research Article

DESIGNING AND *IN-VITRO* STUDIES OF GASTRIC FLOATING TABLETS OF TRAMADOL HYDROCHLORIDE

DEBAJYOTI RAY, AMRESH K PRUSTY[2]

P.G. Department of Pharmaceutics, Sri Jaydev College of Pharmaceutical Sciences, Bhubaneswar, Orissa, India, 752101, St. Mary's College of B. Pharmacy, A.D.B. Road, Surampalem, Peddapuram, A.P., India-533437 Email: drayphd@gmail.com

Received: 20 Jun2010, Revised and Accepted: 24 July 2010

ABSTRACT

The objective of this study is to develop floating drug delivery system; specially floating tablet of Tramadol Hydrochloride (TH). Floating delivery system of TH was prepared using different grades of HPMC as drug release retarding polymer and sodium bicarbonate as source for carbon dioxide which helps tablets to float. From FTIR studies no interactions were found between TH and polymers. The flow properties of the granules were studied and formulation F5 was found to have comparatively good compressibility index and hausner ratio than other formulations. From the swelling study of the formulations, formulation F5 was found to have good swelling properties (220%). From the dissolution studies of the formulations, formulation F5 was found to have better drug release profile than other formulations. From the drug release kinetic study, Higuchi model was found to be best fit. So it could be predicted that release of TH from the floating drug delivery formulations were of diffusion type.

Keywords: Floating drug delivery, Tramadol hydrochloride, Swelling, Drug release, Release kinetic

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.[1] Thus; small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion,[2,3] flotation,[4] sedimentation,[5,6] expansion,[7,8] modified shape systems,[9,10] or by the simultaneous administration of pharmacological agents[11,12] that delay gastric emptying. The gastroretentive drug-delivery system can be retained in the stomach and assists in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GI tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Several approaches are currently used to prolong gastric retention time. These include floating drug-delivery systems, swelling and expanding systems, polymeric bioadhesive systems, high-density systems, and other delayed-gastric-emptying devices.[13] The principal of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for dosage form and sustained drug release[14].

TH is a centrally acting oral analgesic that blocks pain through opoid receptor binding and inhibition of nor epinephrine& serotonin reuptake. TH is having short plasma half life (6h) [15] which is suitable for developing gastro retentive floating drug delivery system. The present system of preparing floating drug is that, it will remain in gastric region for longer duration causing increase in gastric residence time, which may cause improve bioavailability& reduces drug waste.

MATERIALS & METHODS

Materials

TH was procured from Matrix Laboratories, Bangalore. HPMC K 15M, HPMC 100 LV were procured from Merck Chemicals Ltd. Germany. Other ingredients like Sodium biocarbonate, gum tragacanth, starch, talc, magnesium stearate were procured from S.D. Fine chemicals, Mumbai.

Method

Preparation of gastro retentive controlled release tablets

Floating hydrophilic matrix tablet were prepared by direct compression technique using different grades of polymer with varying concentration as ell as different concentrations of sodium bicarbonate and varying amount of starch, gum tragacanth. All the ingredients (Table 1) 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, the weight of tablets was kept constant for tablets of all batches, i.e. 420 mg with hardness about 5 kg/cm^2.

Characterization of tablets

Pre compression parameters

Fourier Transform Infrared (FTIR) studies

FTIR studies of formulation along with pure drug (TH) were carried out at room temperature by FTIR spectrophotometer (FTIR, Paragon-500) using KBr pellet. All the spectra were recorded in the range of 400-4000 cm $^{-1}$.

Bulk density

The power sample under test was screened through sieve no.18 and the sample equivalent to 25 gm was weighed and filled in a 100 ml graduated cylinder and the power was leveled and the unsettled volume, V_o was noted.

The bulk density was calculated in g/cm^3 by the formula.

Bulk density = M/V_o
M = Powder mass
V_o = apparent unstirred volume

Tapped density

The power sample under test was screened through sieve no.18 and the weight of sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder was carried out using tapped density tester at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume V_o was noted. Tapping was proceeding further for an additional tapping 750 times and tapped volume, V_b was noted. The difference between two tapping volume was less the 2%, V_b was considered as a tapped volume V_f. The tapped density was calculated in g/cm^3 by the formula,

Tapped density=M/V_f
M =weight of sample power taken
V_f =tapped volume

Compressibility index

The bulk density, tapped density was measured and compressibility index was calculated using formula,

C.I.= (Pt -Po)/(Pt)x 100
P_t=tapped density
P_o=bulk density

Hausner ratio

Hausner ratio of the blend was calculated using the following formula,

Hausner ratio=P_t/P_o
P_t=tapped density
P_o=bulk density

Characterization of post compression parameters of tablets

Hardness and friability test

The crushing strength (Kg/cm^2) of tablets was determined by using Monsanto type hardness tester. Friability was determined by weighing 10 tablets after dusting, placing them in the friabilator (Roche Friabilator) and rotating the plastic cylinder vertically at 25rpm for 4 min. Aft er dusting, the total remaining weight of the tablets was recorded and the percent friability (PF) was calculated using formula

PF = (Weight original – Weight final) / Weight original X 100.

Weight variation test

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

Drug content

Drug content was determined by taking 5 tablets in a glass mortar and powdered; 100 mg of this powder was placed in a 100 mL stopper conical flask. The drug was extracted in 0.1 N HCl with vigorous shaking on a mechanical shaker (100 rpm) for 5 hours and filtered into 50 mL volumetric flask through cotton wool and filtrate was made up to the mark by double distilled water through filter, further appropriate dilution were made and absorbance was measured at 272nm using 0.1 N HCl as blank solution by UV-Visible double beam spectrophotometer (Genesis-2, USA).

Floating property study

The time taken for dosage form to emerge on surface medium called floating lag time (FLT) and duration of time by which it constantly emerge on surface of medium is called total floating time (TFT).The tablets from each formulation batch were placed in USP type II dissolution apparatus(Disso 2000, Labindia) containing 900 ml 0.1 N HCl of pH 1.2 using paddle at a rotational speed of 100 rpm. The temperature of medium and the duration of time by which the tablet constantly remain on surface of medium were noted.

Swelling behavior study of the Tablets

Swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in swelling of particles. The extent of swelling can be measured in terms of %weight gain by the tablet. For each formulation batch, tablets were weighed and placed in a beaker containing 200 ml 0.1 N 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 not performed for batch F1, F2 and F3 as the tablet of these batches did not float. The % weight gain by the tablet was calculated by the formula,

Swelling Index (S.I.) = (Wt -Wo) / Wo x 100
W_t =weight of tablet at time t hour
W_o =weight of tablet before immersion

***In-vitro* dissolution studies**

Dissolution of tablets of each batch was carried out using USP type II dissolution apparatus (Disso 2000, Labindia) using paddle. 900 ml of 0.1 N HCl (pH 1.2) was filled in a dissolution vessel and the temperature of medium were set at 37±0.5^{0}C. Tablets were placed in dissolution vessel and the rotational speed of paddle was set at rpm 100. The 10 ml of sample was withdrawn at predetermined time interval and same volume of fresh medium was replaced. The samples were analyzed for drug contain against 0.1 N HCl as a blank at wavelength of 272 nm using double beam UV-Visible spectrophotometer (Genesis-2,USA). The content of drug was calculated using the equation generated from standard curve. The %cumulative drug release was calculated.

Kinetics of drug release

Different mathematical models may be applied for describing the kinetics of the drug release process from the formulation matrix; the most suited being the one which best fits the experimental results. The kinetics of TH release from tablets was determined by finding the best fit of the dissolution data (drug release *vs.* time) to distinct models: Zero order[eq.1], first-order [eq.2] and Higuchi [eq. 3] .

$Q_t = k_0 t$ [1]
$Q_t = Q_\infty (1-e^{-k_1 t})$ [2]
$Q_t = k_H t^{1/2}$ [3]

where Q_∞ being the total amount of drug in the matrix, k_0 the zero order kinetic constant, k_1 the first order kinetic constant and k_H representing the Higuchi rate constant.

RESULTS AND DISCUSSION

FTIR studies of the pure drug (TH) and the formulation (F5) 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 3460, 2910,1601,1575, 1284,1238,1042,702 cm^{-1} (Fig.1a) .In the F5 formulation, major peaks of TH were found to be at 3406,2912,1600, 1565,1280, 1040, 702 cm^{-1}(Fig.1b). Other peaks were due to presence of excipients. So no interactions were found between drug and excipients in the formulation.

The flow properties of the granules were studied and formulation F5 was found to have comparatively good compressibility index and hausner ratio than other formulations (Table 2).From the results of floating properties it was shown that all tablets except of batch F1, F2, F3 had good floating properties, which might be due to absence of sodium bicarbonate in these three formulations (Fig 2). From the results of swelling study it was concluded that swelling index increases as time passes because the polymer gradually absorbed water due to hydrophilic in nature and swell. The swelling index increases with time up to 2 hours in some batches which might due to low viscosity of polymer and after 2 hours, the polymer chain relaxation was dominating phenomenon as swelling reaches

thresholds resulting in lowering of swelling index. Thus the viscosity of polymer had a major role on swelling process, matrix integrity as well as floating capability. The higher swelling index was found for tablets which are due to HPMC K 15 M which is having nominal viscosity of 15000 cps. Thus it was concluded that linear relationship may be there in between swelling process and viscosity of polymer. From the swelling study of the formulations, formulation F5 was found to have good swelling properties.

The *in vitro* dissolution was carried out for all batches except F 1, F2, and F3 as the tablets of these had no floating properties. From the dissolution studies of the formulations, formulation F5 was found to have better drug release profile than other formulations (Fig.4). Formulation F5 was also found to have better swelling capacity and floating time than other formulations. The drug release was extended upto 12 hours from the floating drug delivery formulations.

To determine the mechanism of drug release from floating tablet matrices, different kinetic models like zero order kinetic, first order kinetic, Higuchi model were used. Regression coefficient (R^2) values of each kinetic models were compared to find out the best fit model. By comparing the R^2 values of different models, Higuchi model was found to be best fit (Table 3). So it could be predicted that release of TH from the floating drug delivery formulations were of diffusion type.

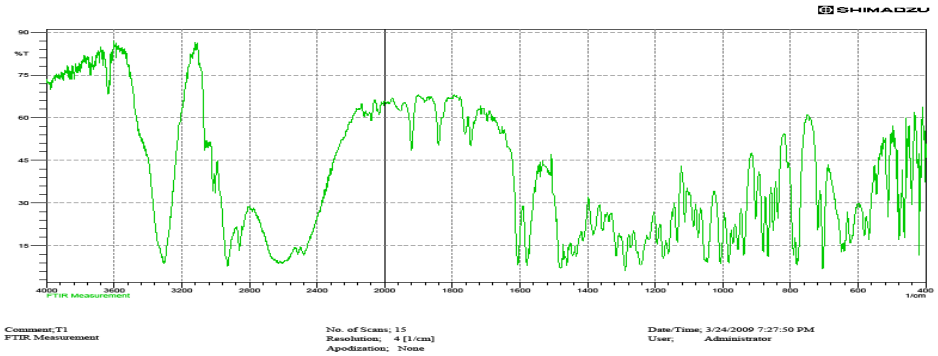

Fig. 1a: FTIR spectra of pure drug (TH)

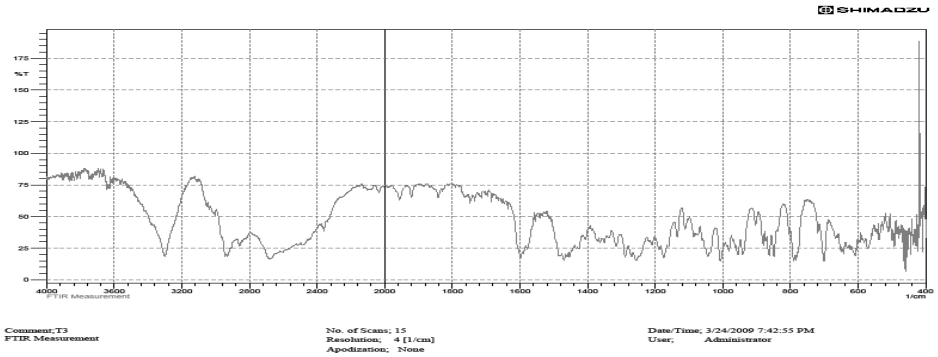

Fig. 1b: FTIR spectra of formulation F5 containing TH

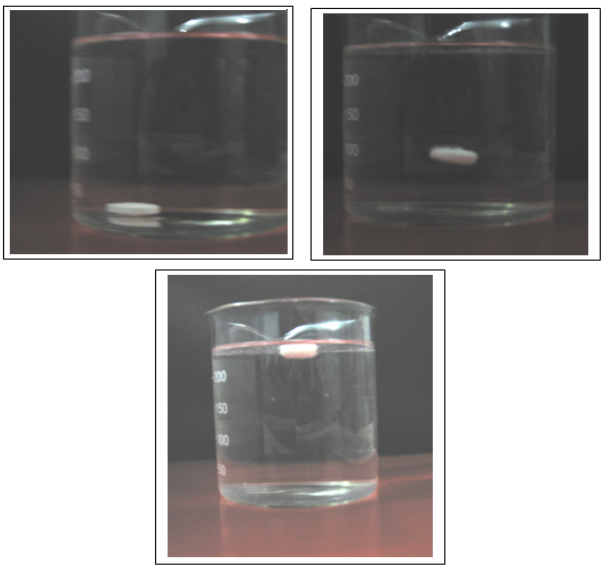

Fig. 2: Stepwise floating of formulation F5

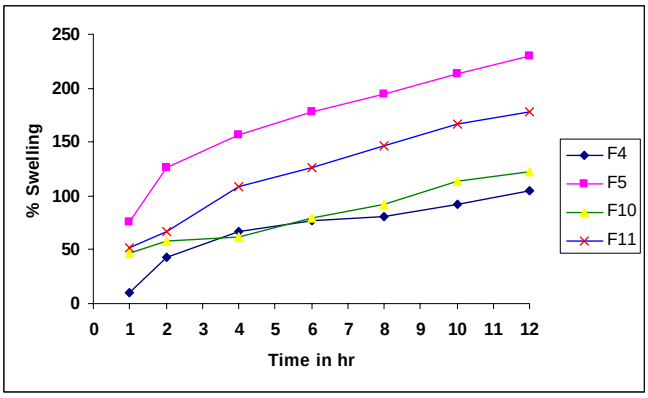

Fig. 3: Swelling behavior study of the tablets

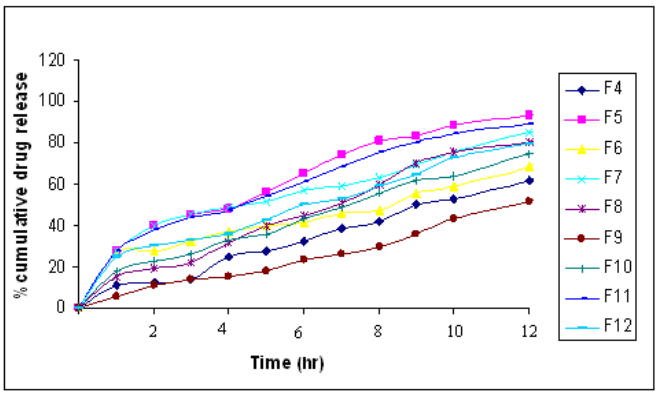

Fig. 4: *In-Vitro* dissolution studies of the formulations

Table 1: Formulation of gastro retentive controlled release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (TH)	220	220	220	220	220	220	220	220	220	220	220	220
HPMC K 15 M	120	120	-	110	100	90	100			90	110	-
HPMCK100 LV	-	-	120	-	-	-	-	110	110	-	-	110
Sodium biocarbonate	-	-	-	40	40	40	50	40	60	60	40	50
Gum tragacanth	70	-	-	40	50	60	-	-	-	-	-	-
Gum acacia	-	70	-	-	-	-	40	40	40	-	-	30
Starch	-	-	70	-	-	-	-	-	-	40	40	-
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5

Table 2: Characterization of precompresion parameters of tablet

Batch	Bulk density (g/cm³)	Tapped density (g/cm³)	Compressibility index	Hausner ratio
F5	0.482	0.561	14.08	1.06
F6	0.300	0.348	20.37	1.26
F10	0.300	0.480	39.63	1.59
F11	0.333	0.526	36.67	1.58

Table 3: Fitting results of experimental TH release data of floating tablet formulations F_5-F_{11} to different kinetic equations

Formulation	Zero order (k_0)	R^2	First order (k_1)	R^2	Higuchi (k_H)	R^2
F_5	7.211	0.8665	0.416	0.9920	49.721	**0.9991**
	(1.031)	(0.010)	(0.039)	(0.004)	(1.116)	**(0.0009)**
F_{10}	7.182	0.9011	0.061	0.9938	19.571	**0.9971**
	(1.046)	(0.011)	(0.068)	(0.0013)	(1.261)	**(0.0001)**
F_{11}	7.139	0.9102	0.066	0.9951	21.061	**0.9969**
	(1.141)	(0.005)	(0.114)	(0.0004)	(1.174)	**(0.001)**

Values in parenthesis mean S.D., R^2 is the regression coefficient. Best results in bold.

CONCLUSION

Floating delivery system of TH was prepared using different grades of HPMC as drug release retarding polymer and sodium bicarbonate as source for carbon dioxide which helps tablets to float. From FTIR studies no interactions were found between TH and polymers. The flow properties of the granules were studied and formulation F5 was found to have comparatively good compressibility index and hausner ratio than other formulations. From the swelling study of the formulations, formulation F5 was found to have good swelling properties. From the dissolution studies of the formulations, formulation F5 was found to have better drug release profile than other formulations.

From the drug release kinetic study, Higuchi model was found to be best fit . So it could be predicted that release of TH from the floating drug delivery formulations were of diffusion type.

REFERENCES

1. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol. 1985;19: 77S-83S.
2. Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate system for oral delivery to the gastrointestinal tract. Adv Drug Del Rev. 1998; 34:191-219.
3. Lenaerts VM, Gurny R. Gastrointestinal Tract- Physiological variables affecting the performance of oral sustained release dosage forms. In: Lenaerts V, Gurny R, eds. Bioadhesive Drug Delivery System. Boca Raton, FL: CRC Press; 1990.p.281-283.
4. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res.1997;14:815-819.
5. Rednick AB, Tucker SJ. Sustained release bolus for animal husbandry. US patent 3 507 952. April 22, 1970.
6. Davis SS, Stockwell AF, Taylor MJ. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm Res.1986;3:208-213.
7. Urguhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US patent 4 434 153. February 28,1994.
8. Mamajek RC, Moyer ES. Drug dispensing device and method. US Patent 4 207 890. June 17, 1980.

9. Fix JA, Cargill R, Engle K. Controlled gastric emptying. III. Gastric residence time of a non-disintegrating geometric shape in human volunteers. PharmRes. 1993;10: 1087-1089.
10. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. J Control Rel. 1999;58:195-205.
11. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm. 1984;10:527-539.
12. Yeole PG, Khan S, Patel VF. Floating drug delivery systems: need and development. Indian J Pharm Sci. 2005; 67:265-272.
13. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS PharmSciTech. 2005; 6:E372-E390.
14. Groning R, Heun G. Dosage forms with controlled gastrointestinal passage—studies on the absorption of nitrofurantion. Int J Pharm. 1989;56:111-116.
15. Anthony C M, Osselton MD, Brian W. Clarke's Analysis of Drugs and Poisons.3rd ed. London: Pharmaceutical press; 2005.