CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.220872

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS OF TAPENTADOL HCL

K. Venkateswara Reddy[1*], Shimoga Nagaraj Sriharsha[1] and S. Sujatha[2]

[1] Faculty of Pharmacy, Pacific Academy of Higher Education and Research, Udaipur-313003.

[2]Department of Pharmaceutics, Narayana Pharmacy College, Nellore, Andhra Pradesh-524 002.

Abstract:

The objective of the present study is to evaluate HPMC K100M, HPMC K15M and carbopol 934P as matrix formers in this design of floating tablets of tapentadol, a poorly water soluble drug. Floating tablet s of tapentadol (100 mg) were formulated employing (i) HPMC K100M (ii) HPMC K15M and (iii) Carbopol 934P as matrix formers at 30% and 50% strength, sodium bicarbonate at 7.5%, 10% & 12.5% strength as gas generating agent and the tablets were evaluated for floating and drug releases characteristics. Tapentadol floating tablets formulated employing HPMC K100M and HPMC K15M as matrix formers at 50% strength and containing sodium bicarbonate (12.5%) as gas generating agent exhibited floating over 36 to 48 h with a floating lag time of less than 1 min. These floating tablets also gave slow and controlled release of tapentadol over 24 h and were found suitable for once a day administration (24 h). HPMC K100M and HPMC K15M were better suitable as matrix formers than Carbopol 934P for floating tablets of tapentadol, a poorly water soluble drug.

Key Words: *Floating tablets, tapentadol Hydrochloride, HPMC K100M, Carbopol, and zero order release.*

Corresponding Address:

K. Venkateswara Reddy*

Faculty of Pharmacy,

Pacific Academy of Higher Education and Research,

Udaipur-313003,

Rajasthan, India.

QR code

Please cite this article in press as K. Venkateswara Reddy et al, ***Formulation and Evaluation of Floating Matrix Tablets of Tapentadol Hcl****, Indo Am. J. P. Sci, 2016; 3(12).*

INTRODUCTION:

The oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has certain problems such as unpredictable gastric emptying rate, short gastr o-intestinal transit time (8-12 h) and existence of an absorption window in the gastric and upper small intestine for several drugs [1,2] leading to low and variable oral absorption over shorter period of time. The real issue in the development of oral drug delivery systems is to prolong the residence time of the dosage form in the stomach or upper gastrointestinal tract until the drug is completely released and absorbed. Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems [3], swelling and expanding systems [4,5] floating systems [6,7] and other delayed gastric emptying devices [8,9]. The principle of floating tablets offers a simple and practical approach to achieve increased gastric residence time to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer. The objective of the present study is to evaluate HPMC K100M, HPMC K4M and Carbopol 934P as matrix formers in the design of floating tablets of tapentadol, a poorly water soluble drug.

Tapentadol is a centrally-acting opioid analgesic, having potency between morphine and tramadol [10]. Tapentadol has been approved as immediate release tablets in 50 mg, 75 mg and 100 mg formulations, every 6 hours with a maximum dosage 600 mg/day by the USFDA. After oral administration 32% of the drug is absorbed. It is widely distributed in the body. The plasma protein binding is low (approximately 20%). The activity of Tapentadol is independent of metabolic activation and resides in a single enantiomer which readily crosses the blood-brain barrier; hence, tapentadol displays a rapid onset of action after administration. The half life is 4 h and peak effect is attained after 1 h and duration of action is 4-6 h. The drug undergoes extensive first pass hepatic metabolism i.e. 97% and its metabolites shown no analgesic activity [6,8]. To reduce the frequency of administration and to improve patient compliance especially for chronic pain, an extended-release formulation of tapentadol hydrochloride is desirable. The drug is freely soluble in water and hence selection of release retarding polymers is necessary to achieve a constant *in-vivo* input rate of the drug.

Floating tablets of tapentadol were designed in the present study to enhance its bioavailability and to achieve controlled release over 24 h for once a day administration. Floating tablets of tapentadol were designed employing HPMC K100M, HPMCK15M and Carbopol 934P as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer and the tablets prepared were evaluated for floating and drug release characteristics.

MATERIALS AND METHODS:

Drugs and Excipients

Tapentadol HCl obtained from MSN Laboratories ltd., Hyderabad, India as a gift sample. HPMC K100M, HPMCK15M and Carbopol 934P were obtained from Cipro Pharmaceuticals Ltd., Hyderabad, India as a gift samples. All other reagents used were of analytical grade.

Pre-formulation studies

Identification of the drug (Tapentadol) by organoleptic evaluation, melting point determination, solubility profile were carried out as per literature methods and Indian Pharmacopoeia, 2007 [11,12]. The standard calibration curve of Tapentadol for UV spectrophotometric study was carried out in Phosphate buffer media (pH 6.8) at 225 nm as per standard methodology [13,14]. The percentage purity of Tapentadol was calculated from calibration curve.

Drug-polymers compatibility study by FTIR

An IR spectrum of pure drug (Tapentadol) and properly blended mixtures of Tapentadol with the polymers used were recorded in FTIR spectrophotometer in the scanning range of 500 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. The basic purpose of FTIR was to observe any changes in the spectrum pattern of the drug due to polymers and thus identify the chances of any chemical interactions [15-17].

Evaluation of micromeritic properties of powder blend

The powder blends were evaluated for flow properties by measuring Angle of Repose (fixed funnel method); Bulk Density (BD) and Tapped Bulk Density (TBD) by Cylinder method; Carr's Compressibility Index using the equations (Equations 1-4)are given below:

$$\text{Bulk density } (D_O) = \frac{\text{Weight of powder}}{\text{Volume of powder}} \quad \textbf{(1)}$$

$$\text{Tapped density } (D_F) = \frac{\text{Weight of powder}}{\text{Volume of powder after tapping}} \quad \textbf{------ (2)}$$

$$\text{Compressibility } \% = \frac{D_F - D_O}{D_F} \times 100 \quad \textbf{---- (3)}$$

$$\text{Hausner's ratio} = \frac{D_F}{D_O} \quad \textbf{---------- (4)}$$

Where 'D_F' is tapped density; 'D_O' is loose bulk density.

Table1: Formulation of Tapentadol floating tablets

S.No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Tapentadol HCl	116.47	116.47	116.47	116.47	116.47	116.47	116.47	116.47	116.47	116.47
2.	HPMC K100M	__	300	__	100	__	200	200	100	210	210
3	HPMC K15M	300	__	__	200	200	__	100	100	40	50
4	Carbopol 934P	__	__	300	__	100	100	_	100	50	40
5	MCC	100	100	100	100	100	100	100	100	100	100
6	NaHCO3	100	100	100	100	100	100	100	100	100	100
7	Citric acid	50	50	50	50	50	50	50	50	50	50
8	PVP	10	10	10	10	10	10	10	10	10	10
9	Mg. stearate	10	10	10	10	10	10	10	10	10	10
10	Talc	5	5	5	5	5	5	5	5	5	5
11	Aerosil	8.53	8.53	8.53	8.53	8.53	8.53	8.53	8.53	8.53	8.53
12	Total weight(mg)	700	700	700	700	700	700	700	700	700	700

Preparation of floating tablets

Matrix tablets each containing 100 mg of tapentadol were formulated employing(i) HPMC K100M (ii) HPMC K15M and (iii) Carbopol 934P, each at 30 and 50 % concentration in the formula. Sodium bicarbonate was used as gas generating agent at 7.5%, 10% and 12.5 % strength in each case.

The required quantities of drug, HPMC K100M or HPMC K15M, sodium bicarbonate, lactose were thoroughly mixed in a mortar by following geometric dilution technique. The granulating fluid (a mixture of water and alcohol in 1: 1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 2 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No. 60 on to the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16-station tablet punching machine (M/s Cadmach Machineries Pvt. Ltd., Ahmedabad) to a hardness of 7-9 Kg/cm2. In the case of Carbopol 934P the tablets were prepared by direct compression method. The formulation is given in table1.

Evaluation of tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was determined using a thermonic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids.

Estimation of tapentadol

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 229 nm in 0.1 N hydrochloric acid was used for the estimation of tapentadol. The method obeyed Beer-Lambert's law in the concentration range of 1-10 µg/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.65% and 1.75%, respectively. No interference from the excipients used was observed.

Floating lag time and floating time

In vitro buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 mL glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration in which the tablet remains floating was determined as floating time.

Drug content estimation

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 10 mg was added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by HPLC[23, 24].

HPLC analysis of the Tapentadol-floating tablets

HPLC analysis of the formulated Tapentadol floating tablets was carried out using C18 column (4.6 x 150mm, 3.5 µm ID)and the HPLC Chromatogram was depicted in fig.1.

Tapentadol hydrochloride analysis:

Mobile phase was prepared by a mixture of water:methanol:acetonitrile (60:10:30 v/v) and pH was adjusted to 3.5 by using acetic acid. The chromatographic column is agilent, C18 (150×4.6 mm; 3.5 to 5 µm particle size), the flow rate was 0.9 mL/min, the column temperature was 29°C, injection

volume was 20 µL, retention time was 3.01 min and at the wavelength of 272 nm.

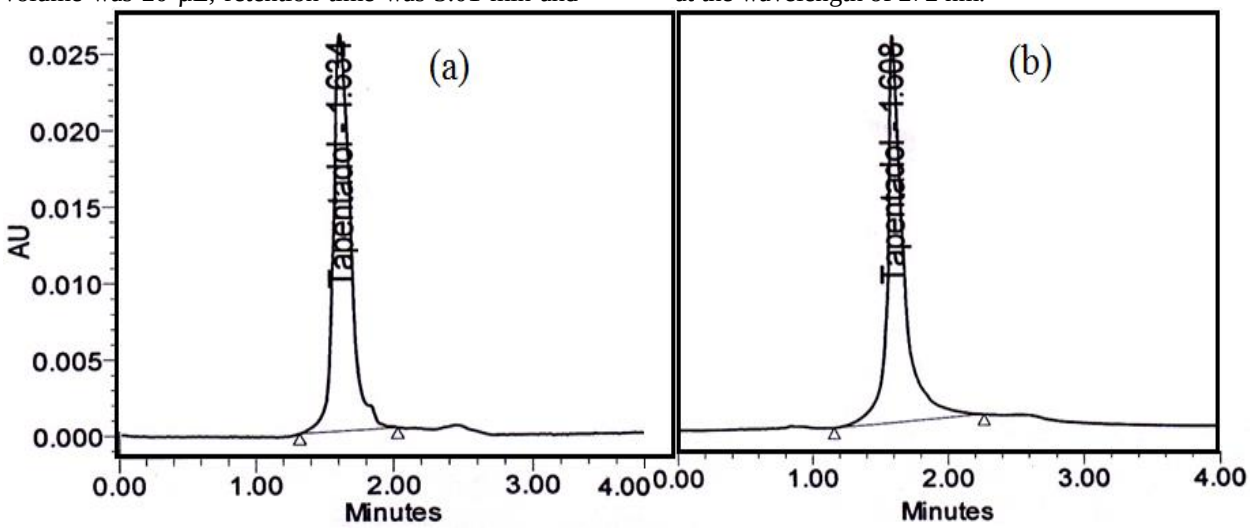

Fig 1: HPLC analysis of (a) Tapentadol hydrochloride standard; (b) Tapentadol sustains released formulation as test sample.

Standard preparation:

About 10 mg of tapentadol hydrochloride was weighed and transferred to 10 mL volumetric flask. It was dissolved in methanol and the solution was made up to volume with methanol to obtain 1000 µg/mL of stock solution. The sample solution was further diluted with mobile phase to obtain standard solutions of different concentrations containing 20-200 µL of tapentadol. The solution was filtered through 0.45 µm nylon membrane filter and 20 µL of were injected in HPLC system under the chromatographic conditions as described above. Six replicate injections were performed and the area under the curve was determined at 272 nm. The amount of drug present in the sample solutions was determined using calibration curve of standard tapentadol. The correlation coefficients, slopes and y-intercepts of the calibration curve were determined.

Sample preparation

Equivalent of 25 mg of tapentadol was transferred to a 10 mL of volumetric flask, extracted with methanol, sonicated for 30 min, diluted to volume with same solvent. It was further diluted with mobile phase. The solution was filtered through 0.45 µm nylon membrane filter and 20 µL aliquots were injected in six times in to the HPLC system under conditions explained above. The peaks were measured at 272 nm and concentrations in the samples were determined using multi level calibration curve developed on the same HPLC system under the conditions using the linear regression equation.

***In-vitro* drug release study**

In-vitro release rate of Tapentadol from the floating tablets was carried out using USP Type I rotating paddle apparatus. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). Experimentation was performed at 37ºC ± 0.5ºC with a rotation speed of 50 rpm. 5 mL of samples were withdrawn at one hour intervals and analyzed for Tapentadol content in spectrophotometer at 225 nm. The amount withdrawn was replaced with the same volume of the dissolution media. Experimentation was carried out up to 24 h [25].

In order to understand the kinetics and mechanism of release of Tapentadol from the floating tablets, the results of the in vitro drug release study were fitted with various kinetic equations like zero order (cumulative percent drug release vs. time); first order (log cumulative percent drug retained vs. time); Higuchi (cumulative percent released vs. √time); Peppas (log of cumulative percent drug release vs. log time). The kinetic model that best fits the dissolution data were evaluated by comparing the regression coefficient values (r) obtained in various models. The N values (release exponent) in Peppas model were used to characterize different release mechanisms, where values of n=0.5 for Fickian diffusion and values between 0.5-1.0 for non-Fickian diffusion and n=1 for zero order [26,27].

Zero order kinetics: $F = k_0 t_{(5)}$ ---------- **(5)**

First order kinetics: $1n(1-F) = -k_1 t$ ---------- **(6)**

To describe the drug release behavior from polymeric systems, the dissolution data were also fitted

according to the well-known exponential Korsmeyer-Peppas equation (Korsmeyer et al., 1983) as.

Korsmeyer-Peppas: $\frac{M_t}{M_\infty} = kt^a$ ------ (7)

Where $\frac{M_t}{M_\infty}$ is the fraction of drug release at time 't', and 'k' is the kinetic constant, 'a' is the release exponent (indicating the general operating release mechanism). For tablets, depending on the aspect ratios, 'a' value between 0.43 and 0.5 indicating Fickian (case I) diffusion-mediated release, non-Fickian (Anomalous) release, coupled diffusion and polymer matrix relaxation, occurs if 0.5<n <0.89, purely matrix relaxation or erosion-mediated release occurs for n=1 (zero-order kinetics), and super case II type of release for n>0.89.

RESULTS AND DISCUSSION:

From the point of organoleptic evaluation, it is a white to off white powdery substance, odorless and tasteless. Melting point of Tapentadol was found to be 209.7ºC which complies with the USP specification limits where the melting point range for Tapentadol is between 209-210ºC. Tapentadol was found to be highly soluble in water and ethanol. λmax of Tapentadol in phosphate buffer (pH 6.8) was found at 520 nm. The compatibility study between drug (Tapentadol) and excipients or polymers were carried out by Fourier Transforms Infra-Red (FTIR) spectroscopy. From the Fig. 2, it was observed that, peaks due to the major functional group in the spectras of Tapentadol (fig.2a) with all the polymers remain unchanged (fig.2b) as compared with spectra of Tapentadol alone. So from the above IR interpretations it can be inferred that there was no interaction between drug and polymers used in the formulations. Fig. 3 shown the DSC theromogram in pure form (fig. 3a) and optimized dosage form (fig. 3b), revealed that the no interaction was occurred after formulation of floating tablets with hydrophobic and hydrophilic polymer combination. Further FTIR and DSC studies concluded that there was no possible negative interaction was noted with the above composition of controlled release floating tablets.

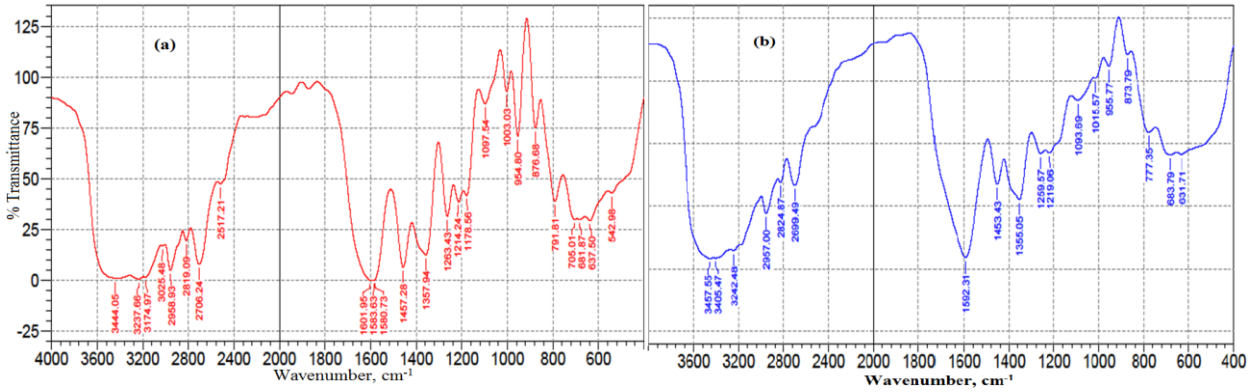

Fig 2: FTIR Spectral comparison of (a) Tapentadol hydrochloride (b) Tapentadol floating tablet formulation.

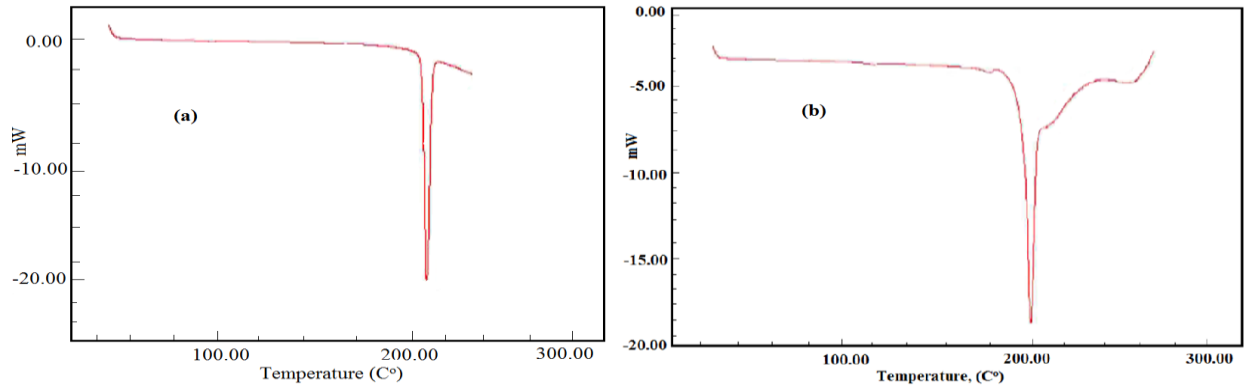

Fig 3: DSC thermogram of (a) Tapentadol hydrochloride (b) Tapentadol optimised floating tablet

The composition of Tapentadol matrix floating Tablets is presented in Table 1. Basing on the preformulation studies, details of the micromeritic properties of the powder blend are provided in Table 3. From the results of BD, TBD, Hausner's ratio, Carr's Compressibility Index and Angle of repose it can be inferred that the powder blend exhibited good flow properties. Hausner's ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow [18-20]. Hence all the formulations have shown good flow except F3-F7, then these were accepted for industrial purposes in future.

The Tapentadol floating matrix tablets formulated (F1-F10) didn't show any visual defects like capping, chipping and lamination after punching. The results of physico-chemical evaluations of the Tapentadol floating matrix tablets (Table.3) showed that tablets indicated good mechanical strength, the percentage friability of all the formulations were found to be less than 1%, percentage deviation from average tablet weight for all the formulations ranged from 0 to 1.25% which are within the Indian Pharmacopoeial specified limits. Uniform percentage of drug content among different batches of tablets was as per limits given in Indian Pharmacopoeia.

Table 2: Precompression parameters of the powder blend

Formulation	Bulk density gm/ml	Tapped density	Compressibility index (%)	Hausner's ratio	Angle of repose(Θ)
F1	0.423±0.02	0.536±0.05	24.5±0.1	1.14±0.02	31.15±0.1
F2	0.403±0.01	0.603±0.009	25.4±0.2	1.15±0.01	28.44±0.4
F3	0.427±0.01	0.597±0.01	24.6±0.3	1.16±0.05	27.21±0.3
F4	0.408±0.02	0.560±0.01	24.5±0.4	1.16±0.02	27.22±0.2
F5	0.465±0.03	0.569±0.03	22.4±0.3	1.15±0.04	27.10±0.1
F6	0.420±0.03	0.540±0.04	25.6±0.1	1.13±0.01	30.18±0.4
F7	0.445±0.01	0.535±0.01	25.8±0.3	1.13±0.01	27.09±0.3
F8	0.455±0.04	0.520±0.03	25.4±0.2	1.14±0.02	32.16±0.3
F9	0.469±0.05	0.568±0.02	26.4±0.3	1.14±0.01	32.34±0.2
F10	0.468±0.03	0.581±0.01	28.8±0.1	1.14±0.02	31.04±0.1

Table 3: Physico chemical parameters of prepared floating tablets

S.No	Batch code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight variation (mg)	% Assay	Floating lag time(sec)	Total Floating time(hours)
1	**F1**	6.3±0.23	4.22±0.03	0.23±0.15	698±0.22	97.9±0.2	60.41±0.1	12
2	**F2**	6.5±0.34	4.42±0.14	0.32±0.03	700±0.13	97.5±0.3	75.52±0.02	12
3	**F3**	5.8±0.17	4.37±0.19	0.44±0.06	701±0.34	98.2±0.1	55.22±0.09	12
4	**F4**	6.2±0.38	4.43±0.12	0.46±0.082	702±0.12	97.1±0.3	65.38±0.01	20
5	**F5**	6.2±0.14	4.25±.0.9	0.22±0.15	699±0.15	98.3±0.1	61.56±0.09	22
6	**F6**	6.2±0.17	4.52±0.15	0.25±0.19	698±0.24	98.4±0,2	45.43±0.08	20
7	**F7**	6.3±0.34	4.33±0.20	0.28±0.09	699±0.16	101.4±0.5	54.66±0.04	18
8	**F8**	6.8±0.05	4.53±0.17	0.44±0.08	701±0.13	98.1±0.7	10.71±0.04	24
9	**F9**	6.3±0.01	4.55±0.13	0.36±0.018	702±0.12	98.4±0.2	16.52±0.06	24
10	**F10**	6.2±0.13	4.72±0.5	0.22±0.017	498±0.14	98.2±0.1	30.66±0.23	18

In-vitro drug release studies revealed that the release of drug from different formulations varies with the characteristics and composition of matrix forming polymers. The release rate of Tapentadol decreased with increasing concentration of HPMC.

Table 4: Kinetics of drug release from Tapentadol floating matrix tablets

Formulation Code	Zero order	First order	Higuchi	Korsemeyer –peppas	
					N
F1	0.97	0.698	0.939	0.989	0.863
F2	0.964	0.857	0.916	0.979	1.043
F3	0.945	0.724	0.75	0.982	2.131
F4	0.941	0.745	0.741	0.978	2.289
F5	0.924	0.961	0.964	0.944	0.965
F6	0.931	0.915	0.961	0.975	0.873
F7	0.984	0.729	0.957	0.994	0.892
F8	0.987	0.678	0.934	0.986	0.773
F9	0.934	0.945	0.96	0.973	0.905
F10	0.984	0.824	0.957	0.995	0.889

Further to characterize the release mechanism of Tapentadol from floating matrix tablets, the dissolution data was fitted to different models like zero order, first order, Korsemeyer peppas and Higuchi diffusion models. The optimized formulation (F8) shown the results, zero-order (r2=0.985), first-order (r2=0.678), Higuchi equation (r2=0.934) and korsemeyer-peppas (r2=0.986 & n=0.776), which explains drug release follows zero-order,.in-vitro release profile of drug from all the formulations could be best expressed by Higuchi's equation, as the plot showed high linearity (r2=0.934). To conform the diffusion mechanism, the data was fitted into Korsmeyer peppa's plot with linearity. 'n' value (0.776) indicates anomalous diffusion i.e, coupling of diffusion and erosion mechanisms. Results were showed in table.4.

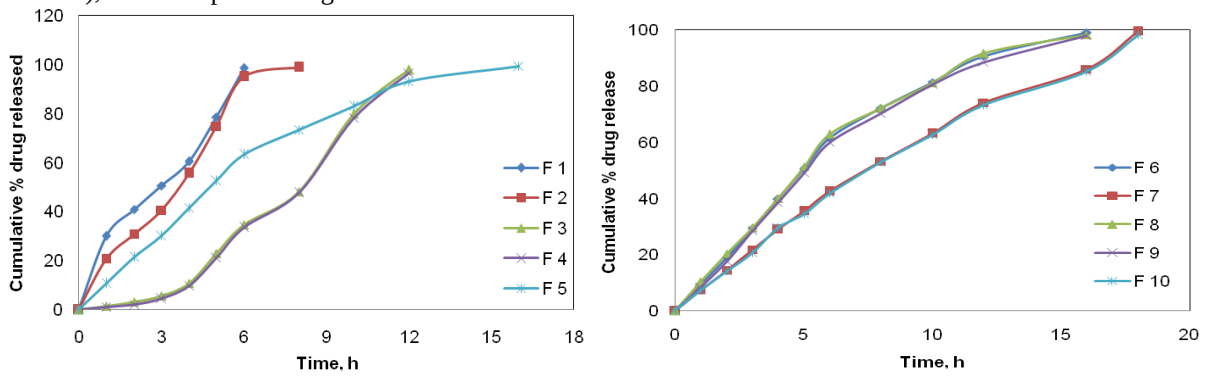

Fig 4: Release profile of Tapentadol floating tablets from (a) F1 to F5, (b) F6 to F10.

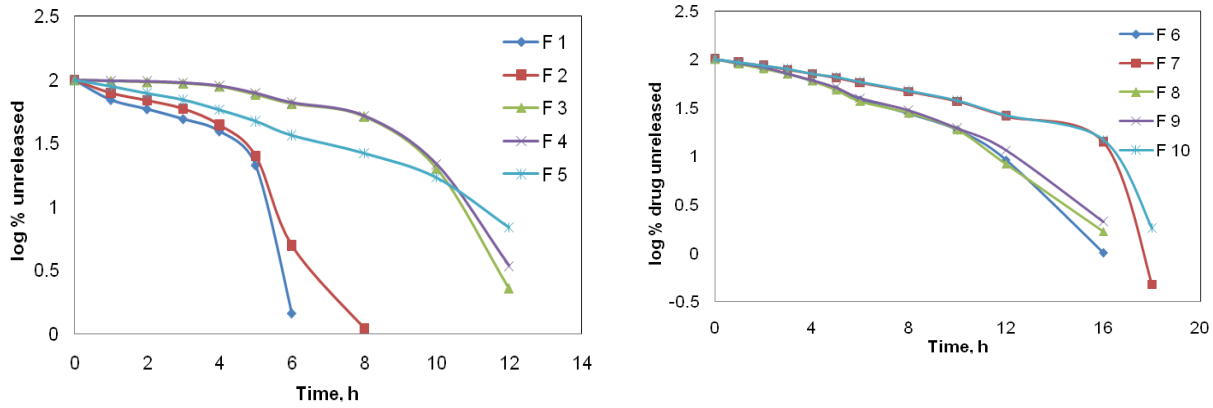

Fig 5: First order kinetic plots of Tapentadol floating matrix tablets (a) F1 to F5, (b) F6 to F10.

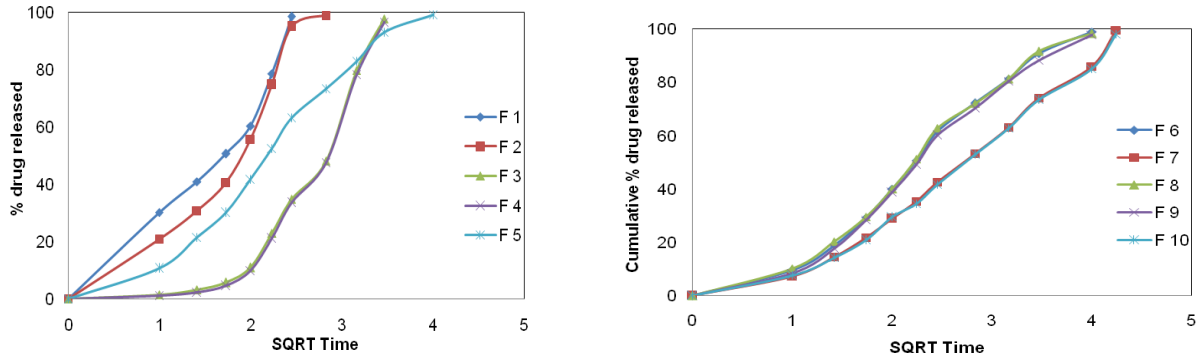

Fig 6: Higuchi diffusion plots of Tapentadol floating tablets (a) F1 to F5, (b) F6 to F10.

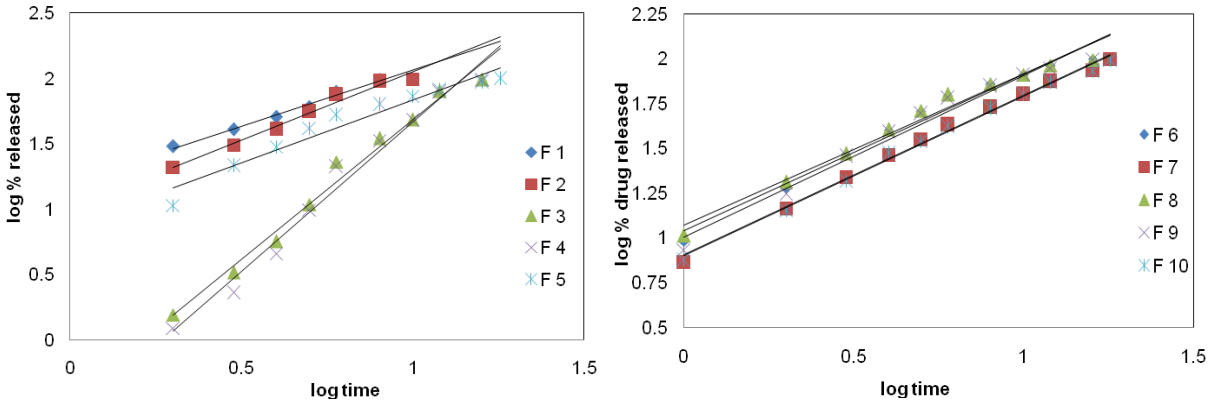

Fig 7: Erosion plots of Tapentadol floating tablets (a) F1 to F5, (b) F6 to F10.

CONCLUSION:

In the present study, gastro-retentive floating tablets of pramipexole were prepared successfully by direct compression method using HPMC K 100M and HPMC K 15M and Carbopol. Fabricated tablets showed acceptable weight variation, hardness, and uniformity of drug content. Thus with proper selection of the ratio of HPMC K 100M and HPMC K 15M, desired drug release was achievable. Extensive studies on similar formulations are essential to establish a successful formulation from the biopharmaceutical viewpoint.

REFERENCES:

1.Wade WE, Spruill WJ. Tapentadol hydrochloride: A centrally acting oral analgesic. Clin Ther. 2009;31:2804-2818.

2. Dewan Roshan Singh, Kusha Nag, Akshaya N. Shetti, and N. Krishnaveni. Tapentadol hydrochloride: A novel analgesic. Saudi J Anaesth. 2013; 7: 322–326.

3.Deepti Jain, Pawan Kumar Basniwal. Tapentadol, a novel analgesic: Review of recent trends in synthesis, related substances, analytical methods, pharmacodynamics and pharmacokinetics. Bulletin of Faculty of Pharmacy, Cairo University. Volume 51, 2013, 283–289.

4.Nalini Vadivelu, Alexander Timchenko, Yili Huang and Raymond Sinatra. Tapentadol extended-release for treatment of chronic pain: a review. J Pain Res. 2011; 4: 211–218 .

5.Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv Ther. 2011, 28(5):401-17.

6.Raghuram Reddy K., Srinivas Mutalik, Srinivas Reddy, Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation, AAPS Pharm Sci Tech 2003; 4 (4), 44–52.

7.Baumgartner S., Kristl J., Vrecer F., Vodopivec P., Zorko B. Optimization floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000; 195:125-135.

8.Brahma N., Singh K. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Con Rel. 2000; 63:235-259.

9.Lingam M., Bhasker K., Krishna Mohan C., Venkateswarlu V., Madhussudan Rao Y. Preparation of a matrix type multiple unit gastro retentive floating

drug delivery system for captopril based on gas formation technique: in vitro evaluation. AAPS Pharm Sci Tech. 2008; 9(2): 612-919.
10.Lingam M., Bhasker K., Naidu KVS., Chandra Mohan E., Suresh B., Venkateswarlu V., Madhussudan Rao Y. Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide. J Pharm Sci. 2009; 98(6): 21222132.
11.Park H., Kinan park. Gastroretentive drug delivery systems., crit. Reviews in Ther.Drug carrier systems. 1998; 15(3):243-284.
12.Prabakaran L., Bajpai M. Novel micropelletization technique: Highly improved dissolution, wettability and micromeritic behavior of domperidone. Curr Drug Deliv. 2006; 3:307-13.
13.Ramesh B., Naidu., Madhusudan Rao Y., Kishan V. Development and evaluation of gastroretentive norfloxacin floating tablets. Acta Pharm. 2009; 59:211–221.
14.Suresh B., Chandra Mohan E., Ashok T., Madhusudan Rao Y. Formulation of multiple tablets as a biphasic gastroretentive floating drug delivery system for fenoverine. Acta Pharm. 2010; 60:89-97.
15.Sathish D, Himabindu S, Shravan Kumar Y, Shayeda, Madhusudan Rao Y. Floating Drug Delivery Systems for Prolonging Gastric Residence Time: A Review. Curr Drug Deliv 2011;8(5):494-510.
16.Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive Dosage Forms: Overview and Special Case of Helicobacter Pylori. J Cont Rel 2006;111(1-2):1-18.
17.Adibkia K, Hamedeyazdan S, Javadzadeh Y. Drug Release Kinetics and Physicochemical Characteristics of Floating Drug Delivery Systems. Expert Opin Drug Deliv 2011;8(7):891-903.
18.Chawla G, Gupta P, Koradia V, Bansal Ak. Gastroretention a Means to Address Regional Variability in Intestinal Drug Absorption. Pharm Technol 2003;7:52-68.
19.Pawar Vk, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive Dosage Forms: A Review With Special Emphasis on Floating Drug Delivery Systems. Drug Deliv 2011;18(2):97-110.
20.Ali J, Arora S, Ahuja A, Babbar Ak, Sharma Rk, Khar Rk, et al. Formulation and Development of Hydrodynamically Balanced System for Metformin: In Vitro and In Vivo Evaluation. Eur J Pharm Biopharm 2007;67(1):196-201.
21.Baki G, Bajdik J, Pintye-Hodi K. Evaluation of Powder Mixtures and Hydrophilic Gastroretentive Drug Delivery Systems Containing Zinc Acetate and Sodium Bicarbonate. J Pharm Biomed Anal 2011;54(4):711-6.
22.Yao H, Xu L, Han F, Che X, Dong Y, Wei M, et al. A Novel Riboflavin Gastro-Mucoadhesive Delivery System Based on Ion Exchange Fiber. Int J Pharm 2008;364(1):21-6.
23.Purvi T. Bhatasana and Askok R. Parmal. Development and validation of RP-HPLC methodfor estimation of Tapentadol HCl in its tablet dosage form. Pelgia Research Library. 2012, 3(4): 422-426.
24.Y. Indira Muzib., Ravi Kumar Reddy. J., Chowdary. K. P. R and E. swathi. Development and validation of RP-HPLC method for estimation of Tapentadol HCl in bulk and tablet dos age forms., International journal of chemical and analytical science. 2013; 4:67-72.
25.Singh BM, Kim KH. Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery via Gastric Retention. J Cont Rel 2000;63:235-59.
26.Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Development of Sustained Release Gastroretentive Drug Delivery System for Ofloxacin: In Vitro and In Vivo Evaluation. Int J Pharm 2005;304:178-84.
27. El Gamal SS, Naggar VE, Allam AN. Optimization of Acyclovir Oral Tablets Based on Gastroretention Technology: Factorial Design Analysis and Physicochemical Characterization Studies. Drug Dev Ind Pharm 2011;37(7):855-67. age forms., International journal of chemical and analytical science. 2013; 4:67-72.