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Formulation and In-Vitro Evaluation of Bilayer Floating tablets of Tramadol Hydrochloride

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Abstract

The present investigation concerns the development of bilayer floating tablets of Tramadol hydrochloride (TH) for prolongation of gastric residence time. TH is a synthetic opioid analgesic used to treat moderate to severe pain. An attempt was made to prepare bilayered floating tablets of TH by wet granulation method using release retarding polymers like hydroxypropyl methyl cellulose grades (HPMC K4M, K15M, K100M), PEO, Sodium alginate and sodium bicarbonate as gas generating agent, with a view to deliver the drug at sustained or controlled manner in gastrointestinal tract and consequently in to systemic circulation. Five formulations were prepared and evaluated for compatibility study, buoyancy lag time, total floating time, swelling study, in-vitro disintegration and in-vitro dissolution studies. Formulations were found uniform with respect to thickness (5.04 to 5.07 mm) and hardness (6.3 to 6.6 kg/cm^2). The friability (0.29 to 0.37%), weight variation (1.44 to 1.71%) and Drug content (98.73 to 99.23%) of different batch of tablets were found within prescribed limits. Formulation F3 selected as best formulation, shown buoyancy lag time of 39 sec, total floating time of 36 hrs and drug release of 95.90% in a period of 24 hrs. Tablets followed diffusion controlled first order kinetics and non-fickian transport of the drug. FTIR study revealed the absence of any chemical interaction between drug and polymers used.

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Tramadol hydrochloride, bilayer floating tablets, wet granulation method, in-vitro release, swelling index, buoyancy.

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INTRODUCTION

The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the

gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time. Indeed, gastric drug retention has received significant interest in the past few decades. Most of the conventional oral delivery systems have shown some limitations related to fast gastric-emptying time [1].

One of the novel approaches in the area of oral sustained release drug delivery is gastroretentive drug delivery system (GRDDS). Drugs those are having a narrow absorption window and having more solubility in gastric region are suitable candidates for GRDDS. GRDDS prolongs the retention time of dosage forms in the stomach or upper gastrointestinal tract, as to improve solubility, bioavailability and the therapeutic efficacy of the drugs. Several techniques have been proposed to increases the gastric residence time of dosage forms such as buoyancy or floating system, hydrodynamically balanced system, expanding or swelling system, bio/mucoadhesive system, sedimentation or high density system, geometry or modified shape system may also use to increase gastric residence time [2]. The biphasic system is used mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of drug. Coronary vasodilator, antihypertensive, antihistaminic, analgesic, antipyretics and antiallergenic agents are mainly used for this system The biphasic system may contain one or two drugs for immediate release and sustained release layer [3]. Tramadol is a centrally acting analgesic with a low affinity for opioid receptors. Tramadol is a synthetic codeine analogue that is a weak m-opioid receptor agonist. Part of its analgesic effect is produced by inhibition of uptake of norepinephrine and 5-hydroxytryptamine. In the treatment of mild-to-moderate pain, tramadol is as effective as morphine or meperidine. The half life of the drug is about 4-5 hrs and the approximate equianalgesic dose is 50-100 mg for every 4-6 hrs. Hence to reduce the frequency of administration and to improve the patient compliance, the sustained release preparation of Tramadol hydrochloride is preferred over the conventional formulation. Tramadol hydrochloride is freely soluble in water; hence release retarding polymers such as HPMC K4M, K15M, K100M, PEO, Sodium alginate plays an important role in controlling the release of Tramadol hydrochloride from the formulation [4].

MATERIALS AND METHODS

Tramadol hydrochloride obtained as a gift sample from East West Pharma. Roorkee, HPMC K4M, K15M, K100M was gifted from Colorcon Ltd. Goa, Croscarmellose sodium was gifted from S.Zaveri Pharma Ken Ltd. Mumbai, PEO, Sodium alginate, Sodium bicarbonate, Citric acid, Microcrystalline cellulose and Poly vinyl pyrrolidine K30 was purchased from S.D Fine Chemicals, Mumbai. All the chemicals and reagents required for the present experimental work are of analytical grade.

Preparation of bilayer floating tablets:

Bilayer floating tablet contains two layers i.e. immediate release layer and floating sustained release layer.

Formulation of the immediate release (IR) layer

The immediate release granules were prepared by blending the drug with different concentration of super disintegrant (Croscarmellose sodium as 3, 4 and 5%) and other excipients like spray dried mannitol, microcrystalline cellulose. The granules so obtained were used to obtain IR layer of drug in bilayer floating tablet. For preliminary studies to optimize the IR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 10 station Rimek compression machine to get IR tablets. These prepared granules were lubricated with magnesium stearate and talc. Three formulation batches were made in order to achieve desired disintegration time and drug release. Formulation compositions of different immediate release batches are given in the Table 1.

Formulation of the floating sustained release (SR) layer

The floating sustained release granules were prepared by wet granulation technique. Required quantity of drug, and polymers (HPMC K4M, HPMC K15M, HPMC K100M, PEO and Sodium alginate), alkalizing agent (sodium bicarbonate), and acidifying agent (citric acid) were weighed and passed through sieve with mesh #40 and were mixed homogeneously in a poly-bag for about 5-10 min and was taken in a mortar. To the mortar 5% PVP K30 in isopropyl alcohol was used as granulating agent. The wet mass was passed through mesh #14 and dried in hot air oven at 50°C for 30 min and dried granules were sieved through mesh #16. Finally well formed granules were lubricated with magnesium stearate and talc. Formulation compositions of all batches are given in the Table 2.

Bilayer floating tablets were prepared by direct compression method using 12 mm flat faced punch of 10 station Rimek compression machine. First the granules of floating sustained release layer were poured in the die cavity and the granules were compressed. After the compression, the upper punch was then lifted and the immediate release granules of drug were poured in the die, containing initially compressed sustained release layer and compressed to form bilayer tablet with hardness of 6 kg/cm^2. The hardness was kept constant for all formulations and was measured using Pfizer hardness tester.

Table 1: Formulation of Tramadol hydrochloride immediate release tablets

S. No.	Ingredients (mg)	Formulation code		
		IR1	IR2	IR3
1	TH	50	50	50
4	CCS	**3**	**4**	**5**
5	MCC	20	20	20
6	Spray dried mannitol	24	23	22
7	Magnesium stearate	2	2	2
8	Talc	1	1	1
	Total	**100**	**100**	**100**

Table 2: Formulation of Tramadol hydrochloride bilayer floating tablets

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5
1	IR3	100	100	100	100	100
2	TH	140	140	140	140	140
3	HPMC K4M	150	--	--	--	--
4	HPMC K15M	--	150	--	--	--
5	HPMC K100M	--	--	150	--	--
6	PEO	--	--	--	150	--
7	Sodium alginate	--	--	--	--	150
8	Sodium bicarbonate	125	125	125	125	125
9	Citric acid	25	25	25	25	25
10	PVP K30	25	25	25	25	25
11	MCC	20	20	20	20	20
12	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
13	Mg. stearate	10	10	10	10	10
14	Talc	5	5	5	5	5
	Total	**600**	**600**	**600**	**600**	**600**

Preformulation studies:

Angle of repose [5]

Angle of repose was determined using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The height (h) and radius (r) of the powder cone was measured and angle of repose was calculated by following formula:

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

Apparent bulk density [6]

Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is. Bulk density was determined by using following formula.

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Volume}}$$

Tapped density

Weighed sample of powder mixture was transferred to a graduated cylinder and was tapped for a fixed time or for a fixed number of taps (100). The tapped density was determined by using the following formula.

$$\text{Tapped density} = \frac{\text{Weight of powder taken}}{\text{Tapped volume}}$$

Compressibility index [7]

Based on the apparent bulk density and the tapped density, the percentage compressibility of the powder mixture was determined by the following formula.

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

Hausner's ratio

Hausner ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of Tramadol hydrochloride bilayer floating tablets:

General appearance

Morphological characters like shape, colour and texture were determined visually.

Thickness [8]

Thickness of prepared tablets was tested using verniercalipers. The test was done in triplicate and average was determined.

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2. Test was done in triplicate.

Weight variation

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of 324 mg is ± 5%.

$$\text{Percent Division} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability [9]

Friability of the tablets was determined using Roche friabilator. This device subjects 10 tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets were placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) was calculated by the following formula.

$$F = (1 - W_o / W) \times 100$$

Where, W_o is the weight of the tablets before the test and W is the weight of the tablet after the test.

Drug Content

The drug content was carried out by weighing 10 tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to 190 mg of Tramadol hydrochloride and dissolved in a 100 ml volumetric flask containing 50 ml of 0.1N HCl and volume was made up to 100 ml with same solvent. The volumetric flask was shaken using sonicator for 1 hr and after suitable dilution with 0.1N HCl, the drug content was determined using UV-Visible Spectrophotometer at 271 nm.

Swelling studies [10]

The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was weighed and kept in petri dish containing 50 ml of 0.1N HCl buffer solution. At the end of specified time intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed. The % of weight gained by the tablet was calculated by using following formula:

$$\text{Swelling index (\%)} = \frac{M_t - M_0}{M_0} \times 100$$

Where, M_t – weight of tablets at time't'; M_o – weight of tablets at time 'o'

Buoyancy lag time determination and Total floating time [11]

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total floating time of all tablets was determined by visual observation.

***In-vitro* disintegration time** [12]

The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted. Average of three determinations was taken.

***In-vitro* dissolution study**

In vitro drug release studies for the prepared immediate release tablets were conducted for a period of 10 min and bilayer floating tablets were conducted for a period of 24 hrs using USP XXIV type-II (Paddle) dissolution apparatus at 37±0.5°C at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed for Tramadol hydrochloride by UV spectrophotometer at 271 nm.

Kinetic study [13]

In order to analyze the release mechanism, several release models were tested such as:

Zero order: $Q_t = Q_o + K_o t$ ----------1

Where Q_t is the amount of drug released at time *t*, Ko is the apparent dissolution rate constant or zero order release constant and Qo is the initial concentration of the drug in the solution resulting from a burst effect; in this case the drug release runs as a constant rate.

First order: $\ln Q_t = \ln Q_o + K_1 t$ ----------2

Where K_1 is the first order release constant; in this case the drug released at each time is proportional to the residual drug inside the dosage form.

Higuchi: $Q_t = K_H \sqrt{t}$ ----------3

Where Q_t is the amount of drug released at time *t* and K_H is the higuchi release rate constant; this is the most widely used model to describe drug release from pharmaceutical matrices.

Korsmeyer-Peppas: $Q_t/Q_\infty = K_k t^n$ ----------4

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism.

The value of n for a tablet, n = 0.45 for Fickian (Case I) release, >0.45 but <0.89 for non-Fickian (Anomalous) release and 0.89 for Case II (Zero order) release and >0.89 for super case II type of release. Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain and anomalous transport (Non Fickian) refers to the summation of both diffusion and dissolution controlled release.

Fourier Transform Infrared Spectroscopy (FTIR) studies

The pure drug, physical mixtures and optimized formulations were subjected for FTIR analysis. The samples were prepared on KBr-press (Startech Lab, India). The samples were scanned over a range of 4000-400 cm^{-1} using fourier transformer infrared spectrophotometer. Spectra were analysed for drug polymer interactions.

RESULTS AND DISCUSSION

Micromeritic properties of precompressional granules

In the present study, wet granulation method was adopted for tableting. Hence the granules of drug and polymers should possess good flow and compaction properties. Plain Tramadol hydrochloride exhibited angle of repose value of 33.82±0.36° indicating poor flow property. It was further supported by high compressibility index value (24.62±0.19%) and Hausner's ratio (1.33±0.02). The drug is mixed with flow promoters like diluents and lubricants to increase flow property. All the formulations exhibited the angle of repose value between 21.70-27.64°, which was further supported by good compressibility index value of 13.72-18.51% and Hausner's ratio of 1.15-1.22, thus indicating the suitability of precompressional granules for compression into tablets. The results are shown in Table 3.

Table 3: Micromeritic properties of precompressional granules of Tramadol hydrochloride bilayer floating tablets.

Formulation Code	Angle of repose* (θ)	Bulk density* (g/cm³)	Tapped density* (g/cm³)	Carr's Index* (%)	Hausner's ratio*
Pure drug	33.82±0.36	0.49±0.14	0.65±0.24	24.62±0.19	1.33±0.02
F1	25.72±0.15	0.48±0.15	0.56±0.13	14.83±0.41	1.16±0.01
F2	24.53±0.16	0.44±0.11	0.51±0.30	13.72±0.18	1.15±0.02
F3	21.70±0.09	0.48±0.17	0.56±0.14	14.28±0.12	1.16±0.04
F4	27.64±0.34	0.51±0.15	0.63±0.16	18.51±0.28	1.22 ±0.02
F5	26.56±0.26	0.55±0.19	0.66±0.06	16.66±0.52	1.20± 0.05

*Average of 3 determinations ± SD.

Physico-chemical evaluation of bilayer floating tablets.

The prepared tablets were evaluated for their various physico-chemical properties. The tablets were white, circular in shape and were found to be uniform with respect to thickness (5.04 to 5.07 mm) and hardness (6.3 to 6.6 kg/cm²). The friability (0.29 to 0.37 %) and weight variation (1.44 to 1.71%) of different batch of tablets were found within acceptable limits. Drug content (98.73 to 99.23 %) was found uniform within the batches of different tablets. The results of physico-chemical evaluation of tablets are given in Table 4.

Table 4: Physico-chemical evaluation of Tramadol hydrochloride bilayer floating tablets.

Formulation Code	Thickness† (mm)	Hardness† (kg/cm²)	Weight variation* (%)	Friability† (%)	Drug content† (%)
F1	5.05±0.04	6.3±0.31	1.44±0.65	0.36±0.08	98.73±0.58
F2	5.04±0.03	6.6±0.42	1.58±0.19	0.37±0.07	99.18±0.72
F3	5.07±0.04	6.3±0.40	1.71±0.36	0.29±0.05	99.13±0.68
F4	5.05±0.02	6.4±0.35	1.63±0.28	0.32±0.06	98.97±0.81
F5	5.06±0.05	6.6±0.37	1.55±0.37	0.35±0.05	99.23±0.62

All values are expressed as mean ± SD †n=10, *n=20.

Swelling study of Tramadol hydrochloride bilayer floating tablets.

Investigation of polymer swelling and erosion is a valuable exercise to better understand the mechanism of release and the relative importance of participating parameters. Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of network

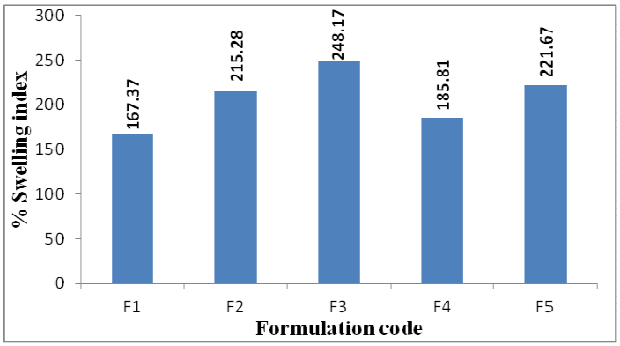
structure, hydrophilicity and ionization of functional group. Swelling study was performed on all the batches of floating tablet for 24 hrs. The results of swelling index are given in Table 5, while the plot of % swelling index against time (hrs) is depicted in Fig. 1. All the bilayer floating tablets swelled but remained intact without breaking throughout the period of swelling (16-24 hrs) in 0.1N HCl. The order of swelling index observed with different polymers was HPMC K100M (F3) > Sodium alginate (F5) > HPMC K15M (F2) > PEO (F4) > HPMC K4M (F1)

Table 5: % Swelling index of Tramadol hydrochloride bilayer floating tablets.

Time (hrs)	Swelling Index (%)*				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	46.27	56.40	58.32	53.11	57.49
2	65.84	79.81	82.52	73.04	81.70
3	76.50	92.14	98.07	85.62	95.57
4	88.75	103.77	112.61	97.28	106.22
6	101.03	116.27	129.14	110.15	119.84
8	118.17	135.53	147.38	123.44	139.08
10	134.22	146.34	164.71	135.73	148.63
12	148.83	162.51	181.24	153.84	166.99
16	167.37	186.02	204.48	174.52	191.05
20	---	202.67	227.94	185.81	208.51
24	---	215.28	248.17	---	221.67

*Average of 3 determinations

Fig. 1: % Swelling index of Tramadol hydrochloride bilayer floating tablets.



Buoyancy lag time and Total floating time

Gastro retentive buoyant tablets need to possess certain characteristics. Therefore experiments were conducted for buoyancy lag time as well as flotation period. Buoyancy lag time indicates how much time a tablet would take, under *in vitro* simulated conditions to float over the gastric fluid. The tablets were placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time. Sodium bicarbonate induces CO_2 generation in the presence of hydrochloric acid. The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml and the tablet becomes buoyant. The optimized concentration of sodium bicarbonate was found to be 25% of total tablet weight and it was maintained constant in all the floating tablets prepared. All floating tablets had buoyancy lag time in the range of 37 (F4) to 39 sec (F2, F3). The total floating time was found to be in the range of 24 (F1) to 36 hrs (F3), indicating a stable gel layer formation by all polymers and sodium bicarbonate that persists for a longer time. The results of the buoyancy lag time (BLT) and total floating time (TFT) for the different floating tablet formulations are given in Table 6.

Table 6: Buoyancy lag time and Total floating time of Tramadol hydrochloride bilayer floating tablets.

Formulation Code	Floating lag time (sec)*	Total floating time (hrs)*
F1	38	24
F2	39	30
F3	39	36
F4	37	28
F5	38	32

*Average of 3 determinations

In-vitro disintegration study

The most important parameter that is needed to optimize during the development of immediate release tablets is disintegration time. Disintegration time is very important for an IR tablet which is desired to be less than 60 sec. In the present study three formulations IR1-IR3 containing CCS disintegrated in 29, 25 and 20 sec respectively. CCS when it comes in contact with water quickly wicks water into the tablet through capillary action to

create internal pressure that disintegrates tablet. The results are given in Table 7.

Table 7: In-vitro disintegration time of Tramadol hydrochloride IR tablets in 0.1N HCl.

Formulation code	Disintegration time (sec)*
IR7	29
IR8	25
IR9	20

*Average of 3 determinations

In-vitro release profile of Tramadol hydrochloride immediate release tablets in 0.1N HCl.

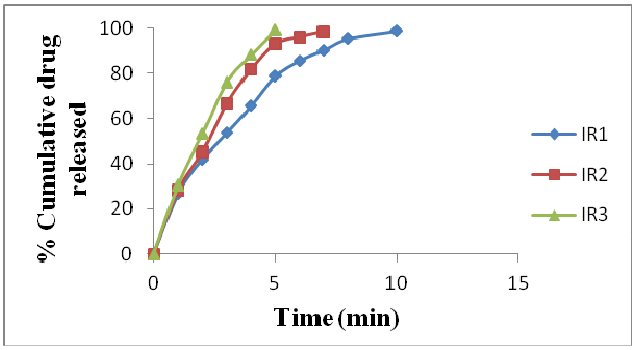
The dissolution was carried out in 900 ml of 0.1N HCl at 37±0.5˚C at 50 rpm using USP XXIV type-II (Paddle) dissolution apparatus for a period of 20 min. The IR tablets composed of croscarmellose sodium as superdisintegrant (IR1-IR3) with different concentrations like 3, 4 and 5% showed drug release of about 98.65, 98.40 and 99.08% at the end of 10, 7 and 5 min respectively. The rapid increase in the drug release with increase in CCS may be due to rapid wicking and disintegration of the tablet into primary particles. Among all the formulations IR3 consisting of 5% CCS as superdisintegrant showed 99.08% of drug release at the end of 5 min and was considered as best formulation. IR3 was further used in the preparation of all the bilayer floating tablets. The results of *in-vitro* drug release of all IR tablets are given in Table 8 and depicted in Fig. 2.

Table 8: Comparative In-vitro % drug release profiles of Tramadol hydrochloride IR formulations**.**

Time (min)	% Cumulative drug released*		
	IR1	IR2	IR3
0	0	0	0
1	26.72	28.09	30.54
2	41.87	45.15	53.35
3	53.56	66.40	76.01
4	65.43	81.61	88.26
5	78.65	92.99	99.08
6	85.61	96.14	---
7	90.35	98.40	---
8	95.33	---	---
10	98.65	---	---

*Average of 3 determinations

Fig. 2: Comparative in-vitro % drug release profile of Tramadol hydrochloride IR formulations.



In-vitro release profile of Tramadol hydrochloride bilayer floating tablets in 0.1N HCl.

IR layer of all bilayer floating tablets showed the burst release (50 mg) of Tramadol hydrochloride within 5-7 min. Presence of super disintegrant (Croscarmellose sodium 5% w/w) in immediate release layer showed faster disintegration of the layer. This can be attributed to the extent of water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration.

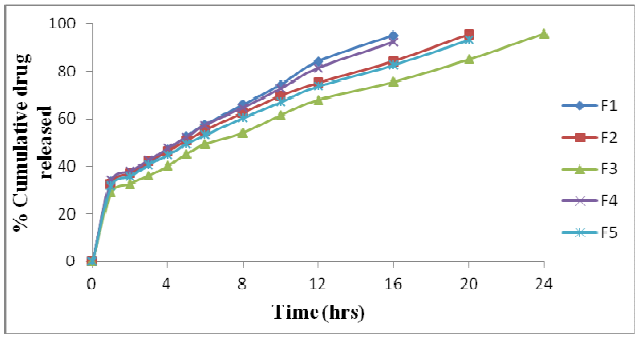
In case of sustained release formulations F1-F5 comprising of different grades of HPMC, PEO and Sodium alginate showed drug release between 92.22-95.90% at the end of 16-24 hrs respectively. The effect of polymer on release was studied by observing the release profile of sustained release formulations. In case of formulation (F3) containing HPMC K100M showed maximum drug release upto 24 hrs is due to highly viscous nature of HPMC K100M polymer, which results in strong gel strength that retards the drug release. In case of formulations composed of HPMC K4M, HPMC K15M, PEO and Sodium alginate the drug release drastically retarded below 24 hrs from the prepared bilayer floating tablets. This is due to the low viscous nature of polymers compared to HPMC K100M. The results of in-vitro drug release of all bilayer floating tablets are given in Table 9 and depicted in Fig. 3.

Table 9: Comparative In-vitro % drug release profiles of Tramadol hydrochloride bilayer floating tablets.

Time (hrs)	Cumulative release data (%)*				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	33.457	32.587	29.035	34.180	31.932
2	36.452	37.237	32.727	38.045	35.785
3	41.339	42.272	36.222	42.652	40.740
4	46.901	46.469	40.169	47.644	44.856
5	52.781	50.831	45.363	52.373	49.570
6	57.683	55.288	49.430	57.416	53.299
8	65.929	62.511	54.240	64.651	60.367
10	74.364	69.556	61.528	72.645	67.039
12	84.214	75.122	67.990	81.331	73.746
16	95.127	84.181	75.567	92.228	82.654
20	---	95.453	84.989	---	93.196
24	---	---	95.904	---	---

*Average of 3 determinations

Fig. 3: Comparative In-vitro % drug release profiles of Tramadol hydrochloride bilayer floating tablets.



Drug release kinetics:

To investigate the mechanism of drug release from bilayer floating tablets, various kinetic models like zero order, first order, Higuchi's and Korsmeyer-Peppas equations were applied to the *in-vitro* release data obtained from different formulations.

When the data was plotted as per zero order kinetics, plots were obtained with low correlation coefficient values ranging from 0.869-0.901. First order plots showed high correlation coefficient values ranging from 0.918-0.961. From the observations it was concluded that the order of release was as per first order equation, indicating that the dissolution rate of drug was dependent of the amount of drug available for dissolution. When the drug release data was fitted to Higuchi equation, linear plots were obtained with high correlation coefficient values ranging from 0.974-0.987. The drug release was proportional to square root of time indicating that the drug release from all the bilayer floating tablets was diffusion controlled. The release data obtained were also put in Korsemayer-Peppas model in order to find out n values, which describe the drug release mechanism. The n values of different selected bilayer floating tablet formulations were found in the range of 0.808-0.956, indicating non-fickian super case II type transport mechanism. Hence the above observations led us to conclude that, all the bilayer floating tablets followed diffusion controlled first order kinetics. The results of kinetic study are shown in Table 10.

Table 10: Data showing drug release kinetics of Tramadol hydrochloride bilayer floating tablets.

Formulation Code	Zero order		First order		Higuchi		Korsmeyer-peppas	
	n	r^2	n	r^2	n	r^2	n	r^2
F1	5.057	0.898	-0.071	0.942	21.74	0.974	0.956	0.520
F2	3.854	0.869	-0.055	0.939	19.89	0.987	0.859	0.511
F3	3.242	0.901	-0.046	0.918	17.55	0.981	0.808	0.544
F4	4.772	0.878	-0.060	0.961	21.72	0.985	0.935	0.502
F5	3.787	0.875	-0.049	0.960	19.49	0.987	0.857	0.514

FT-IR studies

IR spectra of the drug and its formulations were used to establish the physical characterization. The drug and its formulations exhibited characteristic absorption bands in the corresponding IR regions. The difference in the values of characteristic absorption bands indicating the positions of functional groups and bonds present in the drug

molecule is negligible and is well within the permissible range. Thus it is clear from the FT-IR spectras that the drug and formulations are almost identical suggesting that the drug remains in the same normal form before and after its use in the preparation of formulations. Hence it can be taken into the consideration that the drug has not changed its identity and characteristic properties both in the free state and in its formulations. From the above discussion it can be concluded that no interaction is observed between the drug and various types of polymers used for the preparation of different formulations. The results of FT-IR studies are shown in Fig. 4-9.

Fig. 4: FT-IR spectra of Tramadol hydrochloride pure drug.

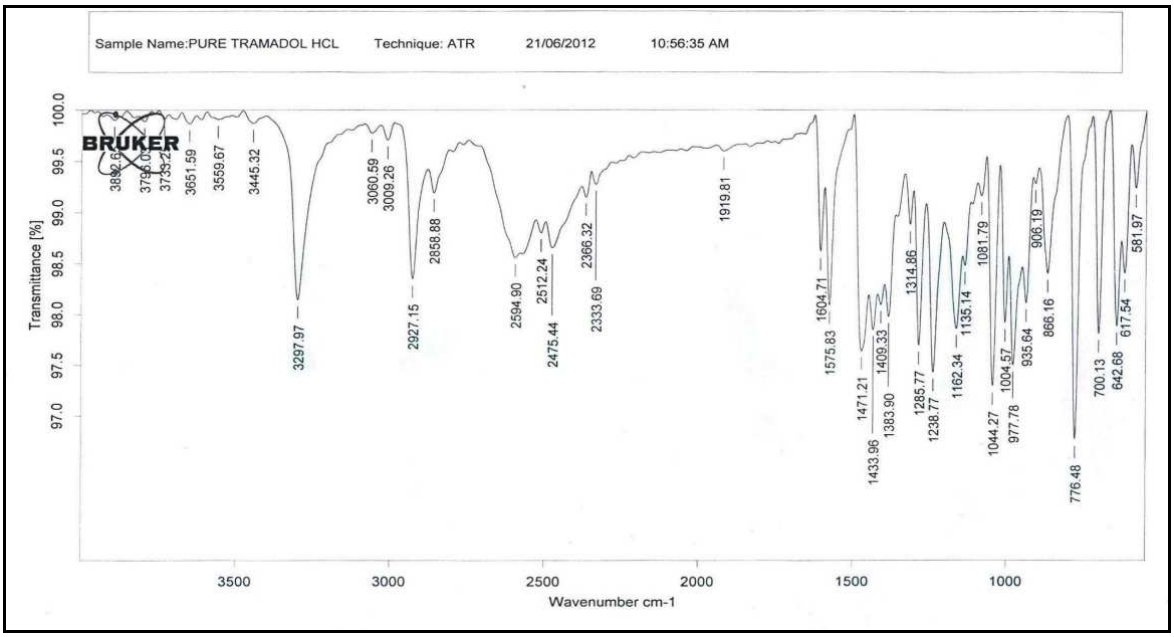


Fig. 5: FT-IR spectra of Tramadol hydrochloride bilayer floating tablet F1 (HPMC K4M).

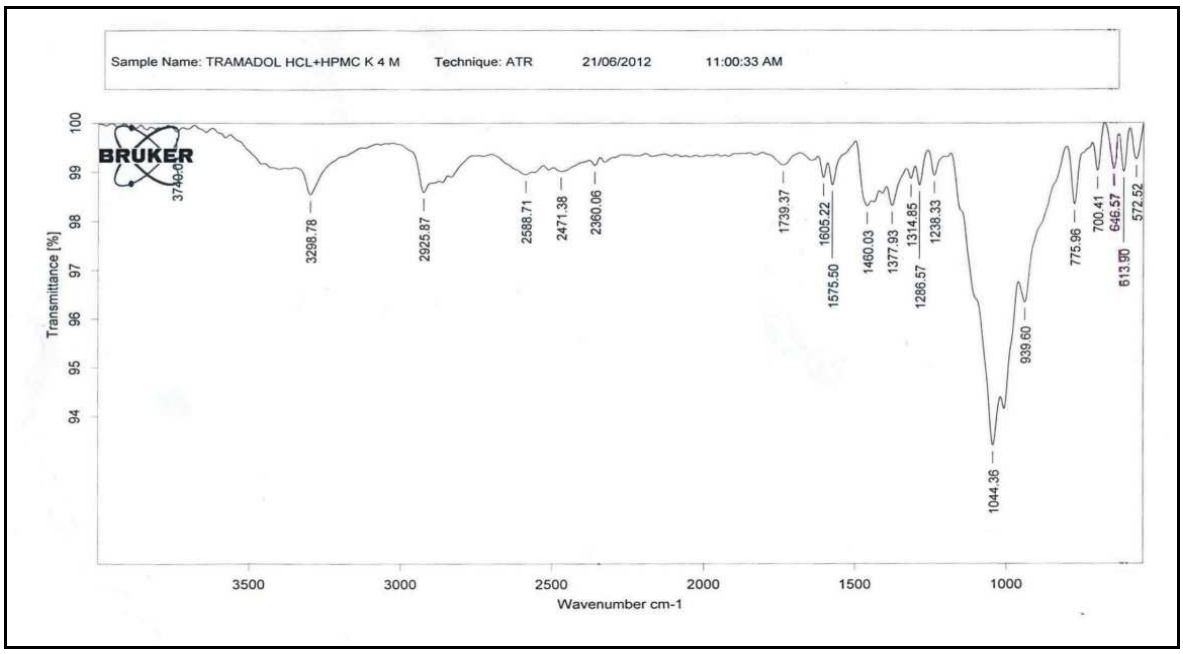


Fig. 6: FT-IR spectra of Tramadol hydrochloride bilayer floating tablet F2 (HPMC K15M).

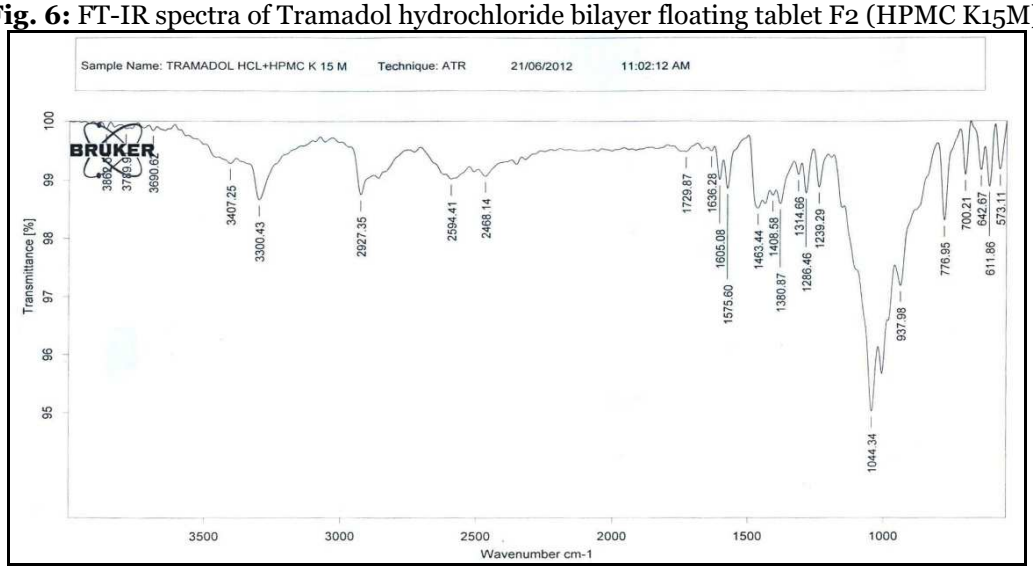


Fig. 7: FT-IR spectra of Tramadol hydrochloride bilayer floating tablet F3 (HPMC K100M).

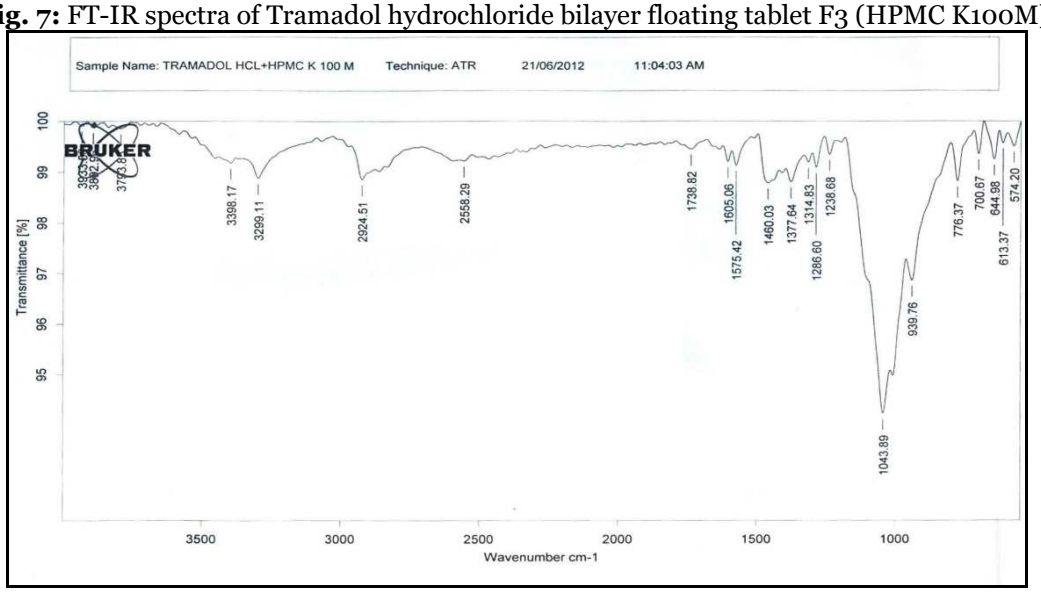


Fig. 8: FT-IR spectra of Tramadol hydrochloride bilayer floating tablet F4 (PEO).

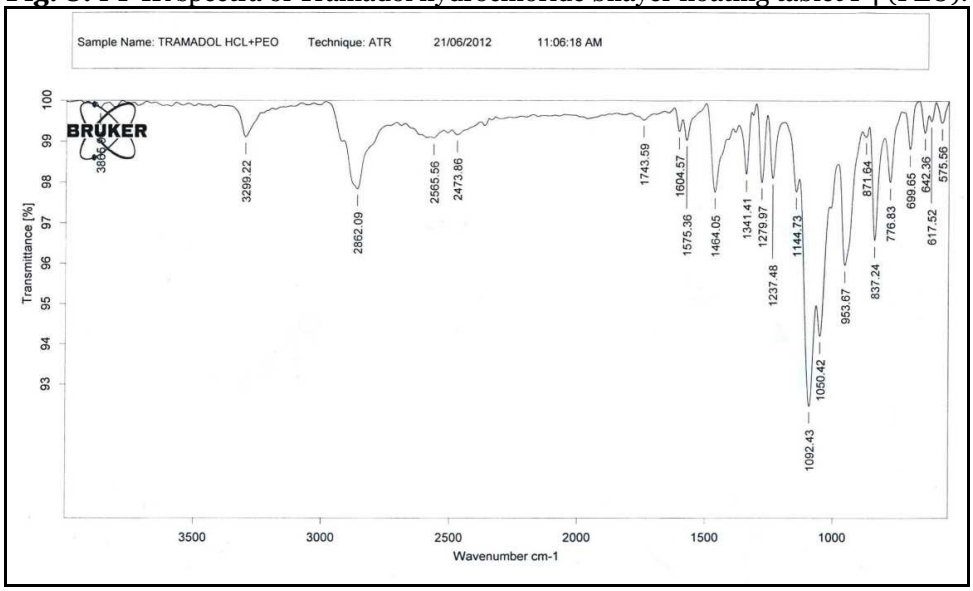
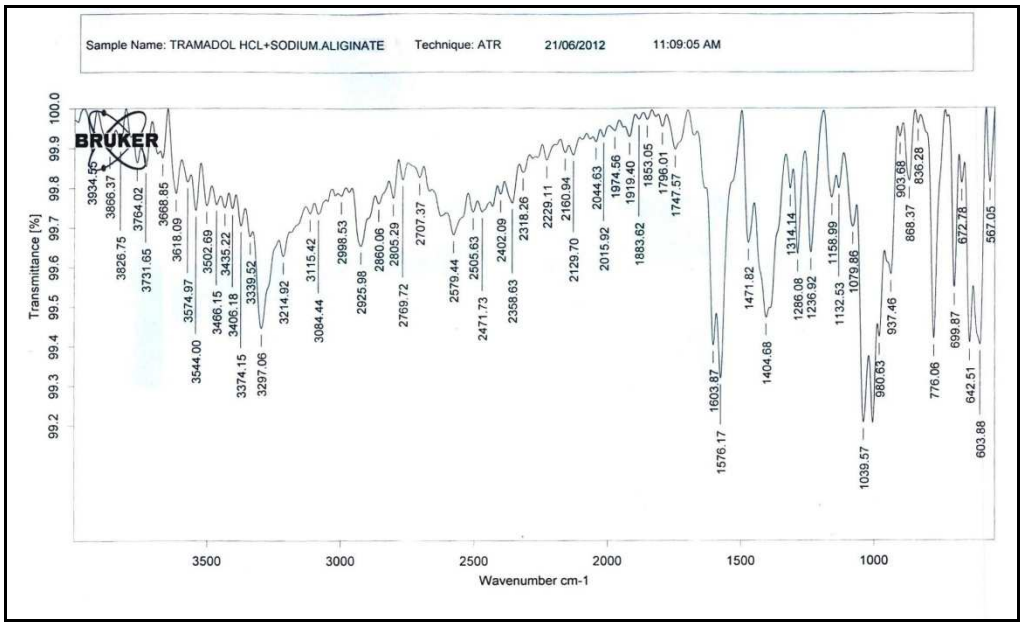


Fig. 9: FT-IR spectra of Tramadol hydrochloride bilayer floating tablet F5 (Sodium alginate).



CONCLUSION

The research was undertaken with the aim to formulate and evaluate the bilayer floating tablets of Tramadol hydrochloride using HPMC K4M, K15M, K100M, PEO and Sodium alginate as polymers. From results obtained, it was concluded that the formulation of bilayer floating tablet of Tramadol hydrochloride containing HPMC K100M as polymer was taken as ideal or optimized formulation for 24 hrs release as it fulfils all the requirement of sustained release dosage form.

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