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Original Article

Formulation and in-vitro evaluation of Tramadol HCl multi-particulate floating tablets

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ABSTRACT

The present study designed to prepare a gastro-retentive floating extended release tablets of tramadol were formulated, characterized and evaluated for in vitro performance. Tramadol Hydrochloride is a synthetic opioid analgesic drug used to treat moderate to severe pain. Tramadol is a highly soluble drug, half-life 6 hours and oral dose is 50 to 100 mg every 4 to 6 hours. The pellets were prepared by using various release retard polymers like HPMC K 15M, Kollidon SR, Carbopol 971 P in different ratios, and gas generate agent like sodium bicarbonate. The pellets are compressed in to tablets; the tablets are evaluated for physical parameters like weight variation, friability, hardness, disintegration test, dissolution test, buoyancy test, buoyancy lag time and total floating time. The release mechanism were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The drug release mechanism was found fickian type in most of the formulations. Formulation F12 selected as best formulations, drug release of 98.71% in a period of 24 h. Tablets followed zero order kinetics and non-fickian diffusion. The effervescent based floating tablet of Tramadol could be a promising approach to increase its gastric residence time up to 24 h.

Keywords: Tramadol Hydrochloride, Floating tablets, Pellets, Gastric retention and in vitro release.

INTRODUCTION

The oral extended drug delivery system is complicated by limited gastric residence time. Several difficulties are faced in designing extended release systems for better absorption and enhanced bioavailability. Rapid gastrointestinal transit can prevent complete drug release in the absorbance zone and reduce the efficacy of administered dose. The majority of drugs are absorbed in stomach or the upper part of small intestine [1,2]. One of the most feasible approaches for achieving a extended and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. floating drug delivery systems (FDDS) [3]. Floating drug delivery offers several applications for dugs having poor bioavailability because of narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and enhances bioavailability [4]. Floating drug delivery systems are classified into effervescent and non-effervescent system. The most common approach for effervescent floating tablets are prepared using mixture of hydrophilic polymer and gas generating agent like sodium bicarbonate in the formulation [5]. CO_2 gas generated when sodium bicarbonate reacts with acidic medium and it provides buoyancy to the dosage form by its entrapment within hydrophilic polymer network. However, the effectiveness of this type of system can be reduced by fluctuation in gastric pH due to factors like disease condition and presence of food [6]. Other non-effervescent approaches for improvement in floating pattern of matrix tablets are porosity enhancement, entrapment of swollen particles by super disintegrants in gel matrix, and addition of low-density excipients in formulation such as polyproline foam powder and aerosol [7, 8].

Tramadol is an opioid centrally acting analgesic with weak opioid agonist properties. It blocks pain through opioid receptor binding and inhibition of non-epinephrine and nerotonin reuptake. Tramadol is having short plasma half-life (6h), and has an absorption zone from the upper intestinal tract. Efficacy of administered drug 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 concentration. It is ideal for developing gastro retentive floating drug delivery

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system [9-12]. To address the above all issues, in the present study aimed to develop a newer floating drug delivery system of tramadol HCl as a model drug to prolong gastric retentive with low frequency administration for better patient compliance. The dosage forms are developed using different polymers like hydrophilic and hydrophobic release retard polymers.

MATERIALS AND METHODS

Materials: Tramadol was procured from Srini Pharmaceuticals Pvt. Ltd, Hyderabad. Kollidon SR, Carbopol 971 P and HPMC K 15M were procured from MSN Laboratories, Hyderabad. Other ingredients like Sodium biocarbonate, magnesium stearate were procured from S.D. Fine chemicals, Mumbai.

Preparation of floating extended release tablets:

Preparation of Pellets: Pellets were prepared by wet granulation followed by extrusion-spheronisation, using different grades of polymers with varying concentrations. The powder mixture were passed through sieve # 40 and granulated with solvent. Different proportions of water and Isopropyl Alcohol were used in the granulation liquid to prepare pellets of various porosities. The compositions of the pellets and preparation details are given in the Table. The powders were dry mixed for 5 min before adding the granulation liquid and for an additional 10 min with the liquid. After mixing, the wet mass was immediately extruded. Immediately after extrusion the extrudate was spheronised. The pellets were dried in a Hot air oven. The desired size fractions were separated by dry sieving with a set of standard sieves.

Coating of pellets: Reservoir pellets were prepared by conventional coating pan, with added Hydroxy Propyl methyl cellulose K 15M: sodium bicarbonate and coated at different percentages of weight build up.

Preparation of Tablets: After the sufficient coating of pellets, magnesium stearate were added and further mixed for additional 4 minutes. The tablets were compressed using 11 mm Flat bevel edged punch on a single stroke punching machine, the weight of tablets was kept constant for tablets of all batches. The compositions of all formulations are shown in Table 1.

Compatibility study by FT-IR: Drug was triturated with potassium bromide in 1:3 ratios and pelletalised at 5 tons pressure in a hydraulic press. The pure drug, physical mixtures and optimizedformulations 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 analyzed for drug polymer interactions.

Evaluation of Tablets:

Thickness: Twenty tablets were randomly taken and individual tablet thickness was measured by using Vernier calliperse. Average thickness and standard deviation values were calculated.

Hardness: Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test: From each batch, twenty tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows

$$\% \text{ Friability} = (W1 - W2) \times 100/W1$$

Where, W1 = Initial weight of the 20 tablets.

W2 = Final weight of the 20 tablets after testing.

Weight Variation Test: To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA), along with standard deviation was calculated. Percent weight variation was calculated as follows.

$$\% \text{ weight variation} = (WI - WA) \times 100/ WA$$

Drug Content (Assay): The drug content of the Pellets and tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the formulation. An accurately weighed portion of the powder equivalent to about 100 mg of Tramadol was transferred to a 100 mL volumetric flask containing 70mL of 0.1N HCl, shaken by mechanical means for 1h.Then it was filtered through a Whatman filter paper (No.1) and diluted to 100 mL with 0.1N HCl. From this resulted solution 1 mL was taken, diluted to 50 mL with 0.1NHCl and absorbance was measured against blank at 270 nm.

Disintegration Test: The disintegration time for all 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.

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 pellets from each formulation batch were placed in USP type II dissolution apparatus (Disso 2000, Labindia) containing 900 ml 0.1N 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.

In -Vitro Drug Release Characteristics: Drug release was assessed by dissolution test under the following conditions: n=3, USP type II dissolution apparatus (paddle method) at 75 rpm in 900 mL of 0.1 N HCl of pH 1.2, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 274 nm.

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], Higuchi [eq. 3] and Peppas (eq.4) .

$C = k0\ t$ [1]

$LogC = LogC_0 – K_1\ t / 2.303$ [2]

$Q = kH\ t1/2$ [3]

where Q∞ being the total amount of drug in the matrix, k0 the zero order kinetic constant, k1 the first order kinetic constant and kH representing the Higuchi rate constant.

$Mt / M\infty = kt^n$ (4)

Where Mt / M∞ = fraction of drug released, k = a kinetic constant, t = release time and n = the diffusional exponent for drug release.

Where Q∞ being the total amount of drug in the matrix, k0 the zero order kinetic constant, k1 the first order kinetic constant and kH representing the Higuchi rate constant.

RESULTS AND DISCUSSION

Pellets properties: The term pellet refers to spherical agglomerates prepared by extrusion-spheronisation, while reservoir pellet refers to those agglomerates that have been coated with a barrier to modify the drug release, *i.e.,* to prolong the release time. The strength of the pellets are sufficient to compress the tablets and did not show any deformation during manufacturing. The application of a coating to the drug pellets increases their strength, depending on the coating thickness. The intra granular porosity of the pellets was dependent on the granulation liquid. The average loaded drug percent in pellets was 96.3% (Table 2). The friability of the pellets was found to be 0.07% indicating sufficient physical strength for the prepared formulations. The measured bulk density for selected formulation was 0.612 g/mL and tapped density 0.695 g/mL. The angle of repose θ was 23.2° (lower than 25°) indicating good flow potential for pellets. The pellets are floated within 50 s after disintegration of tablets.

The sizes (n=20) of Tramadol pellets were measured with a digital slide caliper (Fisher brand) and results are 1.251 to 1.272 mm. The friability rate of the pellets of the prepared batches can be considered for stable formulation. Moisture content in percentage is below 2 % for all formulations. The residual moisture content was considerable for stable batches.

FTIR Studies: Compatibility studies were performed using FT-IR spectrophotometer. The FT-IR spectrum of pure drug (Fig. 1) and physical mixture of drug and polymer were studied. These FT-IR peaks representing the polymer were found to be unaffected by the presence of the drug in the formulations, also major peaks of the polymers were found to be undisturbed by the presence of the drug. Other peaks observed were due to excipient or the drug present in the formulation. From the F12 formulation FT-IR spectrum (Fig.2), it was concluded that no significant difference in peak pattern in IR spectrum of drug, polymer, excipients.

Characterization of 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 (4.23 ± 0.32 to 4.62 ± 0.21 mm) and hardness (5.3 to 5.9 kg/cm2). The friability (0.14 to 0.23 %) and weight variation (1.04 to 1.41%) of different batch of tablets were found within acceptable limits. The tablets showed disintegration time less than 2 min and the best formulation F12 concentration of Croscarmellose Sodium (Ac-Di-Sol) shown 50 s. the pellets are separated individually and floated on the surface of the media. The tablets showed disintegration time less than 2 min and the best formulation is 1 min 10 s. Drug content (98.89 to 99.92 %) was found

uniform within the batches of different tablets. The results of physico-chemical evaluation of tablets are given in Table 3.

Floating Test: The floating tests of tramadol floating tablets were studied and the pellets show good floating characteristics. There was no floating lag time for any formulation. Floating time of formulation F9-F12 was found to be more than 24 hours. The time required for the pellets from the tablet to rise to the surface for floating was determined as the buoyancy lag time. Sodium bicarbonate induce CO2 generates in the presence of hydrochloric acid. The optimized formulation F12 concentration of sodium bicarbonate was found to be 85 % of total weight pellets. The formulation F 12 had buoyancy lag time in the range of 45 to 50 s.

In-Vitro Release Profile: The tablets showed the immediate disintegration in presence of croscarmellose sodium 4 % w/w and pellets are separated. The pellets are floated on the dissolution media. The formulation F1-F3 comprising of Kollidon SR on intra granular release retardant excipient, formulations F4-F6 contains Carbopol 971P, F5-F6 contains both Kollidon SR and Carbopol and these pellets are coated with different concentrations of HPMC K 15M. From all the formulations release data, F8 formulation contains HPMC K 15M polymer, which results in strong gel strength that retard the drug release.

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 was increased, there was a reduction in the rate of drug release. Formulation containing higher HPMC K15M concentration i.e., F2, F5 showed slower release rates when compared to formulation with lower concentration HPMC (Table 4).

Formulation F1-F3 containing the Kollidon SR shown faster release when compare to Carbopol formulation F4-F6. The mixtures of Carbopol, Kollidon SR and HPMC combinations were shown lesser drug release. Thus higher concentration of Kollidon SR and Carbopol cannot be incorporate into such formulation for control the release. The formulation F12 contain Carbopol 971 P and HPMC K 15M (1:1 ratio) shown fine dissolution compare to all formulation (Fig. 3).

Release Kinetics: To investigate the mechanism of drug release from floating tablets, various kinetic models like Zero order, first order, Higuchi's and Krosmeyer-Peppas equation were applied to the in-vitro release data obtained from different formulations. When plotting F12 formulation data, Zero order Kinetics, the plots were shown more correlation coefficient value 0.997. First order plots were shown low correlation coefficient value 0.779 (Table 5). From the above results it concluded that the release was zero order. When the data plotted to Korsmeyer equation and the value of diffusion exponent 'n' (0.589) indicated that the drug release from the batch F12 shown non-fickian diffusion.

CONCLUSION

The approach of present study was to develop floating tablets of Tramadol and henceforth evaluate the release profiles of these formulations. The pellets containing Tramadol was successfully prepared and the pellets shown good floating ability (> 24 h). The tablets are compressed using pellets shown good physical parameters. Formulation F 12 containing 75 mg of HPMC K 15M was found to release a maximum of 99.32% at the 24 hour. The drug release from F12 was found to follow zero order kinetics. It was also found linear in Krosmeyer plot, which confirms that diffusion is one of the mechanisms of drug release. From results obtained, it was concluded that the formulation of floating tablet of Tramadol hydrochloride containing combination of Carbopol 971 P and HPMC K 15M was taken as ideal or optimized formulation for 24 h release as it fulfils all the requirement of extended release dosage form.

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Table 1: Composition of Different formulations of Tramadol Floating tablets:

Excipients Name (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Pellets Composition												
Tramadol HCl	115	115	115	115	115	115	115	115	115	115	115	115
Microcrystalline Cellulose PH 100	50	50	50	50	50	50	50	50	25	25	35	30
Kollidon SR	100	50	75				50	50				
Carbopol				75	50	100	50	50	75	75	75	75
PVP K-30	10	10	10	10	10	10	10	10	10	10	10	10
Pellets Coating Composition												
Hydroxypropyl Methyl Cellulose K 15M	50	100	75	75	100	50	50	50	75	75	75	75
Sodium Bicarbonate	20	20	20	20	20	20	20	20	50	40	30	30
Carcarmellose Sodium	10	10	10	10	10	10	10	10	10	10	10	15
Weight of Pellets	**355**	**355**	**355**	**355**	**355**	**355**	**355**	**355**	**360**	**350**	**350**	**350**
Tablets Composition												
Tramadol HCl Pellets (equivalent to Tramadol	370	370	365	370	370	365	370	375	370	370	370	365
Magnesium Sterate	5	5	5	5	5	5	5	5	5	5	5	5
Total Weight	**375**	**375**	**370**	**375**	**375**	**370**	**375**	**380**	**375**	**375**	**375**	**370**

Table 2: Characterization of Pellets:

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diameter of Pellets (mm)	1.252	1.254	1.270	1.265	1.260	1.263	1.265	1.254	1.272	1.263	1.253	1.270
Drug content of pellets (%w/w)	96.02	95.87	97.20	96.45	96.20	97.20	95.64	94.52	97.20	94.36	95.30	96.30

Table 3: Characterization of physicochemical parameters of tablet

	F3	F6	F8	F12
Thickness (mm)	4.23	4.52	4.60	4.61
Hardness (kg/cm^2)	5.3	5.6	5.4	5.6
Friability (%w/w)	0.14	0.23	0.17	0.19
Disintegration Time	1 min 5 sec	57 sec	55 sec	50 sec
Drug content (%w/w)	98.92	99.02	99.58	99.92
Floating Time	>24 Hr	>24 Hr	>24 Hr	>24 Hr

Table 4: Kinetics of in vitro release from floating tablet of Tramadol

	% of Cumulative drug release			
Time (hr)	**F3**	**F6**	**F8**	**F12**
1	18.2	14.3	17.2	14.30
2	26.3	21.1	21.3	22.59
4	45.2	29.3	29.2	29.51
6	57.5	39.6	37.3	36.43
9	69.5	45.2	49.6	46.81
12	83.6	60.2	63.2	57.19
16	92.6	84.2	75.2	71.03
20	97.5	93.4	86.3	84.87
24	98.0	97.5	96.87	98.71

Table 5: Fitting results of floating tablet of Tramadol formulations to different kinetic equations

	F3	F6	F8	F12
Zero Order (R^2)	0.865	0.968	0.973	0.997
First Order (R^2)	0.984	0.928	0.895	0.779
Higuchi (R^2)	0.979	0.967	0.983	0.977
Koresmeyer Plot (R^2)	0.980	0.984	0.981	0.988
Koresmeyer 'n' value	0.556	0.624	0.571	0.589

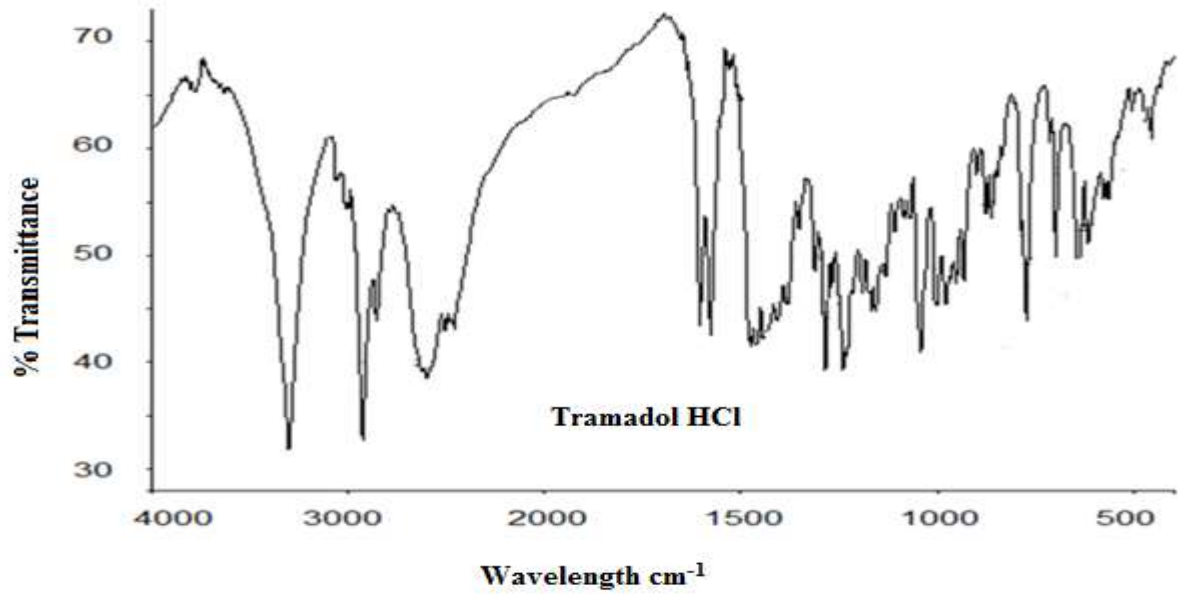

Fig. 1: FTIR Spectra of Tramadol Hydrochloride.

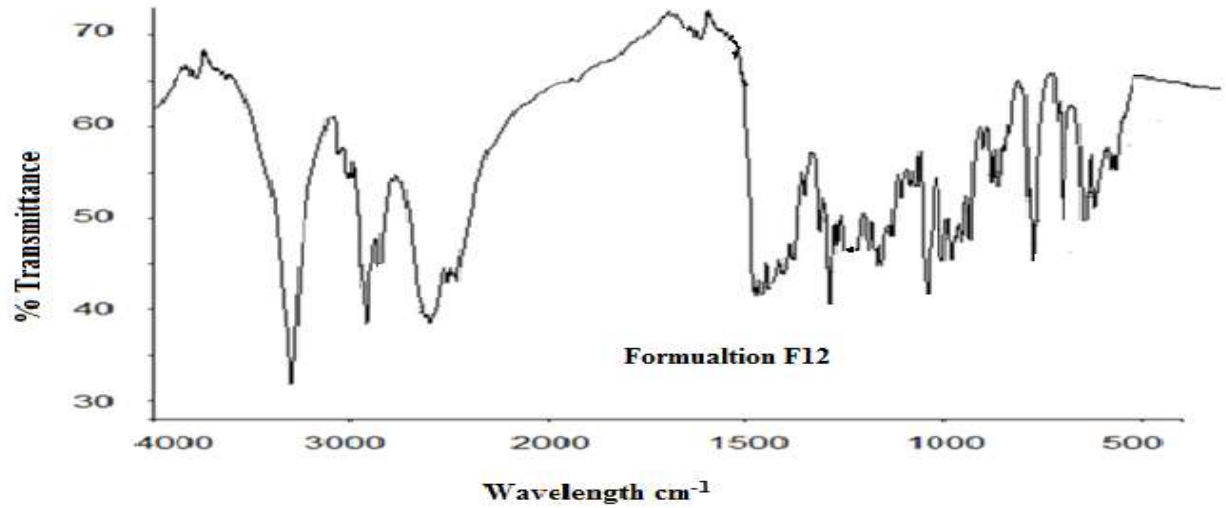

Fig. 2: FTIR Spectra of Tramadol Hydrochloride Tablets Formulation (F12).

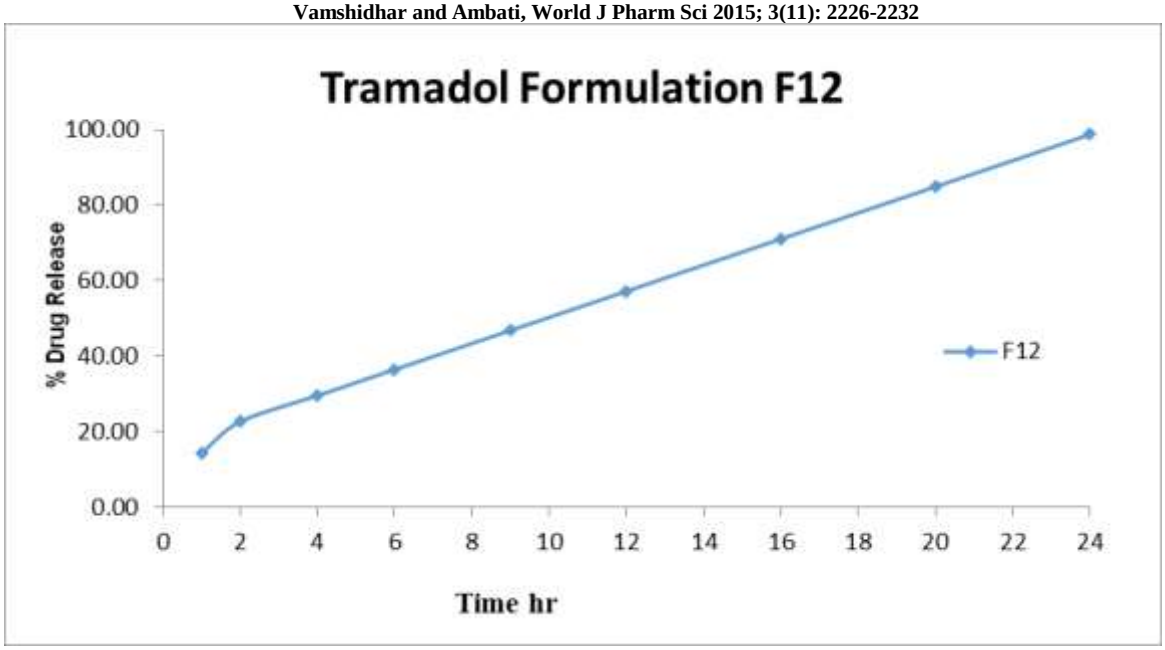

Fig. 3: Tramadol Hydrochloride Tablets (F12) Dissoluton Profile.

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