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Design, Prepare and *In Vitro* Evaluation of Tramadol Floating Bilayered Tablets

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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 direct compression method using release retarding polymers like hydroxypropyl methyl cellulose grades (HPMC K4M and HPMC K15M) eudragit 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. Eight 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 (3.27 to 3.40 mm) and hardness (4.1 to 4.10 kg/cm^2). The friability (0.52 to 0.68%), weight variation (398-400) and Drug content (91.56 to 97.8%) of different batch of tablets were found within prescribed limits. Formulation F5 selected as best formulation, shown buoyancy lag time of 52 sec and drug release of 96.90% in a period of 60min. 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.

Keywords
Tramadol hydrochloride, HPMC grades, Eudragit, Sodium bicarbonate, FTIR Studies, In vitro drug release studies.

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1.INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. The gastro retentive dosage form will release the drug over an extended period in stomach and upper GI tract thus enhancing opportunity for absorption.[1,2] 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. [3] 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.[4,5] Conventional sustained release formulation of Tramadol hydrochloride is not adequate because of lack of initial bolus dose. This drawback can be overcome by combining immediate release layer and sustained release layer in a single bilayer tablet.[6] In developing a sustained release dosage form for Tramadol, it is important to have a fast release fraction which would allow for sufficient concentration of the drug in the blood stream to produce quick analgesic effect and a slow release fraction which would maintain that effect.[7]

2. MATERIALS AND METHOD

2.1 MATERIALS

Tramadol was collected as a gift sample from Hetero labs, Hyderabad, HPMC grades, eudragit and other excipients were purchased from AR chemicals.

2.2 METHODODOLOGY [8,9,10]

Drug-Excipient Compatibility Studies by FT-IR Analysis

Infrared spectrum of any compound or drug gives information about the groups present in that particular compound. The IR absorption spectra of the pure drug and physical admixtures of drug with various excipients were taken in the range of 4000-400 cm-1 using KBr disc method and observed for characteristic peaks of drug.

Formulation Development

Formulation of floating Bilayer Tablet

The floating Bilayer tablet was prepared by direct compression method.

Steps involved in Bilayer Tablet Preparation

1. Filling of immediate release layer of Tramadol drug particles in to dies
2. Slightly compressed the immediate release layer of tramadol drug
3. Ejection of upper punch
4. Addition of floating sustained release layer of tramadol powder over the immediate release particles
5. Increasing the compression force and compressed both the layer
6. Ejection of floating Bilayer tablet.

A. Preparation of Floating Tramadol Sustained Release (SR)

1. Drug + Polymer
2. Gas generating agents (Sodium bicarbonate + citric acid)
3. Dry granules were passed through a mesh no: 44
4. Mixed with magnesium stearate, talc
5. Compression

B. Preparation of Tramadol Immediate Release (IR)]

1. Drug (Tramadol) + Povidone
2. Dry granules were passed through a mesh no: 44
3. Mixed with magnesium stearate, talc
4. Compression

Formulation development

Table-1: Formulation development of Tramadol (IR)

Ingredients	F 1	F2	F3	F 4	F 5	F 6	F 7	F 8
Tramadol	20	20	20	20	20	20	20	20
Sodium starch glycolate	50	-	25	10	20	30	40	5
Cross caramellose	-	50	25	40	30	20	10	45
Sodium bi carbonate	10	10	10	10	10	10	10	10
Sodium starch glycolate	2.5	5	7.5	10	-	-	-	-
Cross caramellose	-	-	-	-	2.5	5	7.5	10
Citric acid	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3
Lactose	7.5	5	2.5	-	7.5	5	2.5	-
Talc	2	2	2	2	2	2	2	2
Total wt	100	100	100	100	100	100	100	100

Table-2: Formulation development of Tramadol (SR)

Ingredients	F 1	F2	F3	F 4	F 5	F 6	F 7	F 8
Tramadol	100	100	100	100	100	100	100	100
HPMC K 4M	100	-	-	-	50	-	-	50
HPMC K 100M	-	100	-	-	50	50	-	-
Eudragit	-	-	100	-	-	50	50	-
Sodium carboxy methyl cellulose				100	-		50	50
Sodium bi carbonate	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5
Micro crystalline cellulose	70	70	70	70	70	70	70	70
Magnesium stearate	3	3	3	3	3	3	3	3
Lactose	10	10	10	10	10	10	10	10
Talc	2	2	2	2	2	2	2	2
Total wt	300	300	300	300	300	300	300	300

The powder Sustain layer powder were blended for 20 min. to obtain uniform distribution of the drug in formulation. 300mg of the powder mix was accurately weighed and fed into the die of single punch tablet press and compressed at 1.5 N compression force using 10-mm concave punches. The Immediate layer mix was blended for 20 min to obtain uniform distribution of the drug in formulation. 100 mg of the powder mix was accurately weighed and manually fed into the die on controlled release layer and compressed at a compression pressure using 10-mm concave punches.

Formulation Trial Batch of Tramadol Immediate Release (IR) Tablet[11,12]

The trial batch of Tramadol IR tablet containing drug Tramadol with disintegrant was prepared according to the following formula. Different percentage of disintegrant has been used in trial batch and to study the immediate release effect of Tramadol.

Formulation of Floating Bilayer tablet of Tramadol HCl SR

From the trial formulations of Floating Tramadol SR and Tramadol IR, the Bilayer floating tablet of Tramadol SR and Tramadol IR are formulated by varying the percentage of polymers.

Formulation of Bilayered tablet

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 drug were poured in the die, containing initially compressed sustained release layer and compressed to form bilayer tablet with hardness of 6 kg/cm2. The hardness was kept constant for all formulations and was measured using Pfizer hardness tester.

EVALUATION PARAMETER[13,14,15]

Trial batches of different formulations of individual tablets (sustained and immediate) and Bilayer tablets were prepared and evaluated for the following parameters.

Evaluation parameters

Angle of repose

The angle of repose is defined as the maximum angle possible between the surface of a pile powder and the horizontal plane. The tangent of the angle is equal to the coefficient of friction between the particles.

$\tan\theta = h/r$

$\theta = \tan^{-1} h/r$

Where, h = height of the pile

r = radius of the pile.

Bulk Density and Tapped Density

A measured quantity of granules was transferred to a measuring cylinder measuring its initial volume [V0] and tapped mechanically either manually or using some tapping device till a constant volume [Vf] and it includes the true volume of the granules and void space between them. The bulk density and tapped density was calculated by the following formulae. Bulk density is the ratio between a mass of granules and its bulk volume (Vo). It is expressed by g/cc.

Bulk Density = Mass of Powder

Bulk Volume of Powder (Vo)

Tapped density is the ratio between mass of granules and volume of the granules after tapping (VF). It is expressed by gm/cc.

Compressibility Index and Hausner's Ratio

The compressibility index and Hausner's ratio are measures the flow property of a powder to be compressed. As such, they measure the relative

importance as interparticulate Interactions. In a free flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in values. For poorer flowing materials, inter particulate Interactions will be greater and greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio. The compressibility index and Hausner's ratio are calculated by measuring the values for bulk density (ρ bulk) and Tapped Density (ρ tapped) as follows, and official limits are shown in the table.

Compressibility Index =Mass of Powder/Tapped Volume of Powder (VF)

Tapped density=Tapped density – Bulk density X 100

Physical Evaluation of Tablet

Weight variation

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

Hardness

The tablet-crushing load is the force required to break a tablet by compression. Hardness was measured by using hardness tester (Pfizer hardness tester). For each batch, six tablets were selected randomly and evaluated. Hardness of about 4-6 kg/cm^2 is considered to be minimum for uncoated tablets and for mechanical stability.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. Preweighed sample of ten tablets were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions, the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

Percentage Friability =

$$\frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \times 100$$

Floating Lag Time

The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Content uniformity

Twenty tablets from each batch were weighed and powdered. Powder equivalent to 4mg of Tramadol was accurately weighed and transferred into 100ml volumetric flask and dissolve in acetronitrile until clear solution is obtained. The resulting solutions was made to 100ml with 0.1N HCl and shake for 10 mins. The 10ml of the above solution was diluted up to 100ml with 0.1N HCl and filtered through 0.45µ membrane filter analysed by Shimadzu UV/VIS double beam spectrometer at 270 nm.

Percentage purity of Drug content = Amount of drug/ Label claim

***In-Vitro Drug* Dissolution Test**

The *in-vitro* dissolution study of Floating Tramadol SR tablet, Tramadol IR tablet and optimized Bilayer Floating tablet of Tramadol SR and Tramadol IR were performed according to USP apparatus II (Paddle type).

Drug release kinetics[16]

Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time't' or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models. These models are used to characterize drug dissolution/release profiles.

(i) Zero Order Kinetics

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. The following equation is used to express the model:

Qt = Qo + Kot

Where,

Qt is the amount of drug dissolved in time t

Qo is the initial amount of drug in the solution

Ko is the zero-order release constant

For practical purposes the equation is rearranged

Percent drug released = Kt

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

(ii) First Order Kinetics

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior; in such a way that amount of drug released by unit time diminish. The following equation is used to express the model:

log Qt = log Qo + Kt/2.303

Where,

Qt is the amount of drug dissolved in time t

Qo is the initial amount of drug in the solution

K is the first order release constant

For practical purposes the equation is rearranged:

Log % of drug unreleased = Kt/2.303

This model is applicable to dosage forms such as those containing water soluble drugs in porous matrices.

(iii) Higuchi Model

Higuchi describes drug release as a diffusion process based in Fick's law, square root dependent. The following equation is used to express the model:

Qt = Kht1/2

Where, Qt is the amount of drug dissolved in time t

Kh is the first order release constant

For practical purposes the equation is rearranged:

Percent drug released = Kt1/2

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs.

(iv) Peppas-Korsmeyer Model

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved

The following equation is used to express the model

Qt/Q∞ = Ktn

Where, Qt is the amount of drug dissolved in time t

Q∞ is the amount of drug dissolved in infinite time

n is the release exponent indicative of drug release mechanism

K is the kinetic constant

For practical purposes the equation is rearranged:

Log percent drug released = log k +n log t

Peppas used n value in order to characterize different release mechanism concluding for values of n = 0.5 for Fickian diffusion and values of n, between 0.5 to 1.0 for anomalous transport (corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics) and higher values of n, n=1 or n>1 for case-II transport (corresponds to erosion and relaxation of swollen polymer layer).

Stability Study[17]

Stability is officially defined as the time lapse during which the drug product retains the same properties and characteristics that is possessed at the time of manufactures. This process begins at early development phases. Instabilities in modern formulation are often detected only after considerable storage periods under normal conditions. To reduce their time required to obtain information's, various tests that involve storage of products under condition that accelerate decomposition have been introduced.

3.RESULTS & DISCUSSION

Fourier Transformation Infra-red (FTIR) analysis:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan). The instrument was calibrated by using polystyrene film.

Fourier Transformation Infra-red (FTIR) analysis of Tramadol:

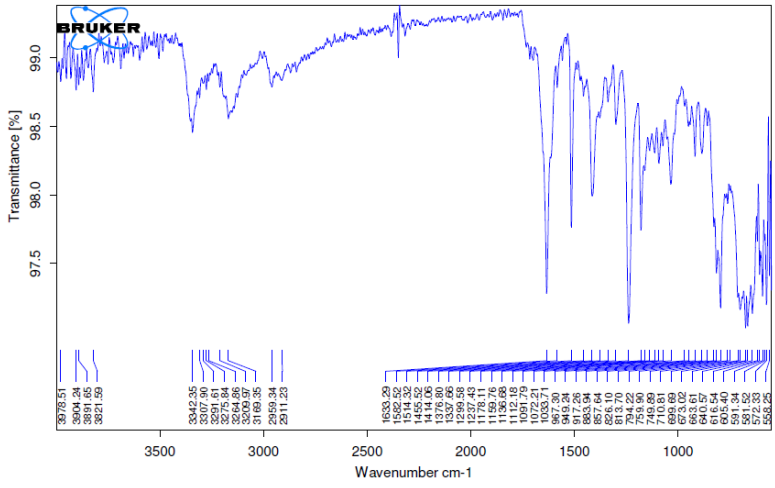

Fig- 1: FT-IR graph for Tramadol Pure drug

The presence of N-H primary and secondary stretching and charecteristic C-N stertching confirms Tramadol drug.

Fourier Transformation Infra-red (FTIR) analysis of Optimaized formulation:

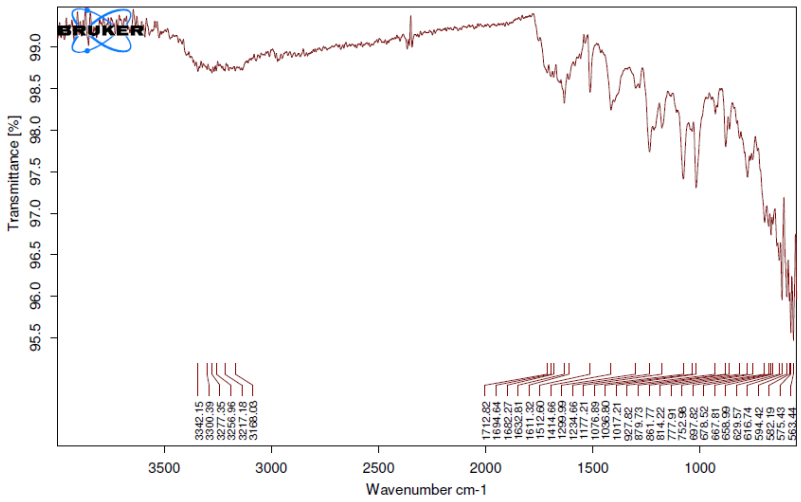

Fig-2 : FT-IR graph for Tramadol Pure drug

The presence of N-H primary and secondary stretching and charecteristic C-N stertching confirms tramadol drug. The IR spectrum of Tramadol and Drug Excipients mixture was shown in figure number respectively. In the present study, it has been observed that there is no chemical interaction between Tramadol, and the polymers used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Table-3: Evaluation of the Tramadol tablets for physical parameters

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation	400	399	400	401	400	399	398	400
Thickness (mm)	3.29	3.40	3.28	3.30	3.27	3.31	3.38	3.32
Hardness (kg/cm^2)	4.7	4.6	4.2	4.1	4.4	4.8	4.7	4.10
Friability (%)	0.65	0.68	0.62	0.61	0.59	0.55	0.54	0.52
Content uniformity	96.26	95.86	94.89	93.90	97.85	94.25	95.22	91.56
Floating lag time(sec)	42	51	46	48	52	49	47	60

- **Uniformity of weight**
  All the prepared tablets of Tramadol were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ± 5%.
- **Hardness and friability:**
  The hardness of the tablet formulations was found to be in the range of 4.1 to 4.10 kg/cm^2. The friability values were found to be in the range of 0.52 to 0. 68%.
- **Uniformity of drug content:**
  The low values of standard deviation indicate uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 94.25 to 97.85 percent (which was within the acceptable limits of ±5%.).

***In vitro* Dissolution studies:**

The dissolution conditions used for studying the drug release from bilayered tablet:

Table-4: In-vitro dissolution Profiles for Tramadol Immediate layer and Tramadol sustained release layerat 270 nm in 0.1N HCl

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	18.9	21.5	30.8	35.5	42.8	38.25	42.58	28.39
10	32.3	38.2	43.8	49.5	58.6	49.5	57.25	47.85
15	40.5	45.5	50.10	58.6	60.9	53.65	60.10	52.68
20	47.1	64.8	62.55	67.3	73.29	65.32	73.19	65.3
30	78.5	75.10	77.62	71.55	85.21	70.26	88.0	79.2
45	85.0	89.8	86.35	87.2	92.58	83.99	91.25	81.25
60	89.1	91.5	92.66	94.65	96.90	91.25	95.30	90.26

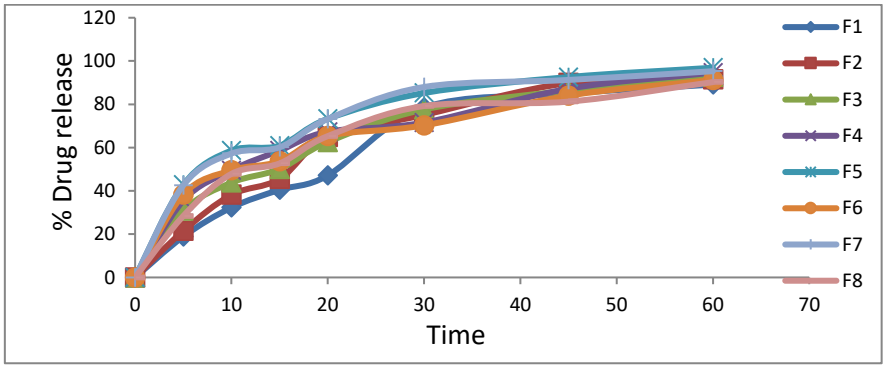

Fig-3: **In-vitro dissolution Profiles for bilayered tablets**

Among all formulations, F5 shows better drug release when compared with all other formulations.

Kinetic studies for optimized formulation

Table-5: Kinetic studies for optimized formulation

S.NO	TIME	LOG T	SQUARE ROOT OF TIME	%CR	ARA	Square root of T	LOG %CR	LOG% ARA
1	0	0	0	0	0	0	0	0
2	5	0.69897	2.236068	42.8	52	2.23	1.681241	1.716003
3	10	1	3.162278	58.6	20.5	3.16	1.900367	1.311754
4	15	1.176091	3.872983	60.9	16	3.87	1.924279	1.20412
5	20	1.30103	4.472136	73.29	4.7	4.47	1.979093	0.672098
6	30	1.39794	5.477226	85.21	0.8	5.47	1.996512	-0.09691
7	45	1.477121	6.708204	92.58	-	6.70	-	-
8	60	1.653213	7.745967	96.90	-	7.74	-	-

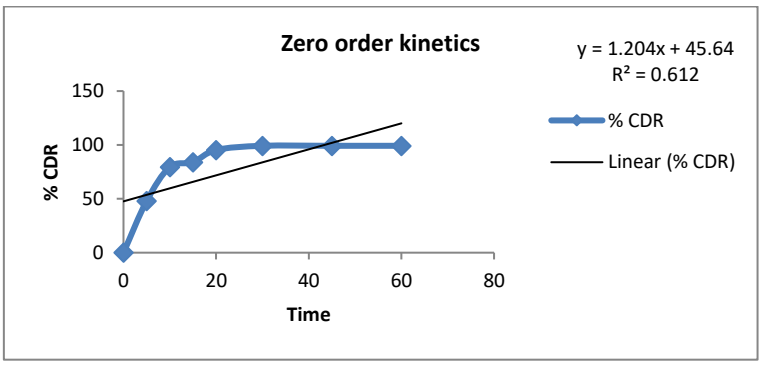

Fig-4: Zero order plot for optimised formulation

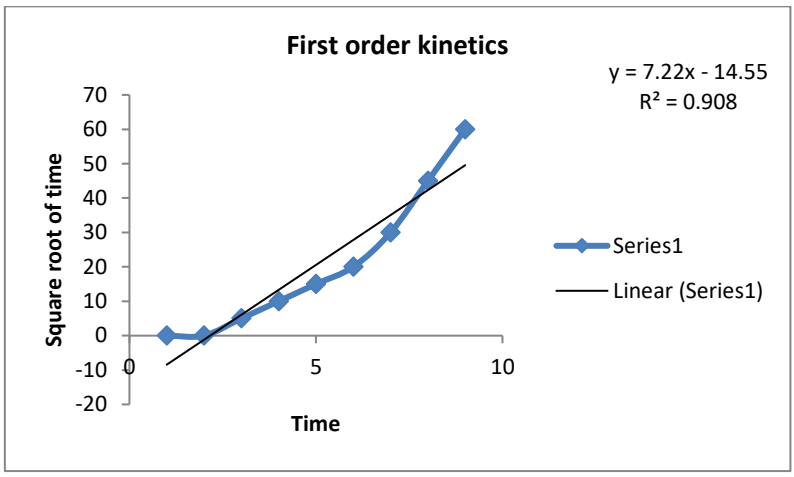

Fig-5: First order plot for optimised formulation

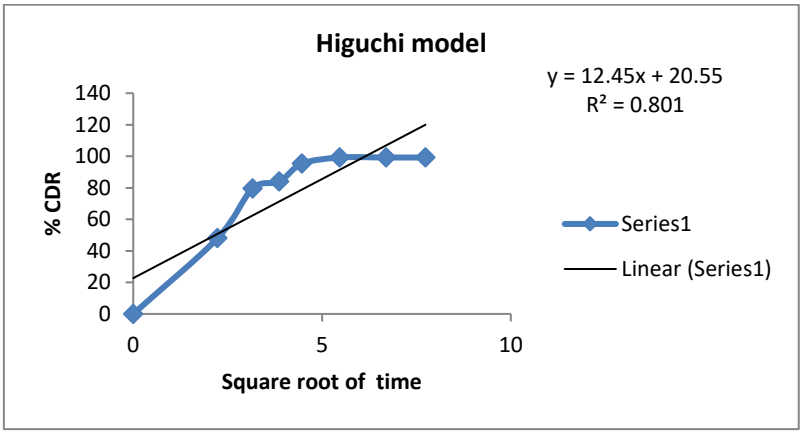

Fig-6: Higuchi plot for optimised formulation

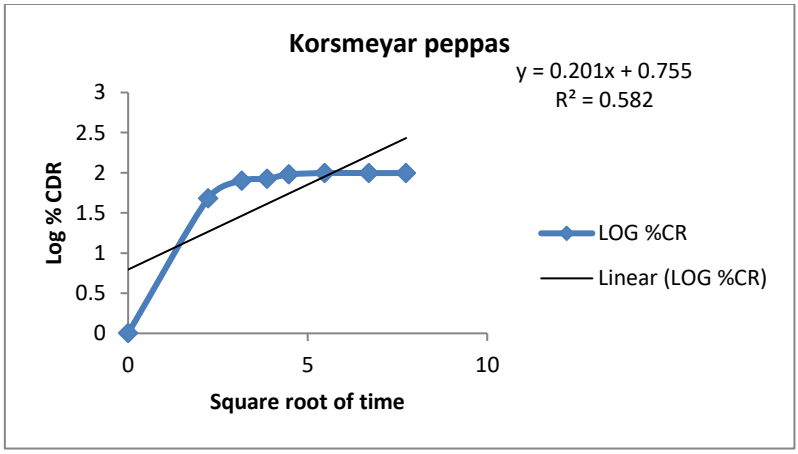

Fig-7: Kors mayer peppas plot for optimised formulation

Stability studies:

Table-6: Stability Studies of Optimized Formulation

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	**25^{0}C/60%RH % Release**	96.90	96.88	96.87	96.84	**Not less than 85 %**
F-5	**30^{0}C/75% RH % Release**	96.90	96.89	96.87	96.83	**Not less than 85 %**

F-5	**40^{0}C/75% RH % Release**	96.90	96.87	96.85	96.82	**Not less than 85 %**

There was no significant change in physical and chemical properties of the tablets of formulation F5 after 3 Months, parameters like % drug release and assay values at various conditions (at 40^{0}C/ 75% RH) as per ICH guidelines quantified at various time intervals.

4.CONCLUSION

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

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