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Design and Optimization of Pregabalin Fast Dissolving Tablets

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ABSTRACT: In the present work, oral dispersible tablets of Pregabalin were prepared by direct compression method with a view to enhance patient compliance. To formulate fast-dissolving tablets of Pregabalin for rapid dissolution of drug and absorption, which may produce rapid onset of action in the treatment of Epilepsy. Drug and excipientcompatibility studies were measured by using FTIR studies.Eight formulations having different concentrations of super disintegrates were prepared. The pure drug and formulation blend was examined for the angle of repose, bulk density, tapped density, Compressibility index, and Hauser's ratio. These tablets were evaluated for drug content, weight variation, friability, hardness, wetting time and in vitro disintegration time.Drug content was found to be in the range of 81.15to 89.38%. In vitro drug release was found to be93.35% for 60 min. The wetting time is an important criterion for understanding the capacity of disintegrates to swell in the presence of little amount of water were found to be in the range of144-159 sec. Among the formulations tablets of batch F8containing crospovidoneshowed superior organoleptic properties along with excellent in-vitro disintegration time and drug release as compared to other formulations. Hence Crospovidoneis recommended as suitable disintegrate for the preparation of direct compression fast-dissolving tablets of Pregabalin. It was concluded that the presence of a super disintegrate is desirable for or dispersion of tablets by direct compression method.

KEYWORDS: Pregabalin, superdisintegrants, FTIR studies, direct compression technique, in-vitro drug release studies, Drug release kinetics.

I. INTRODUCTION

Most of the drugs are administered in solid dosage forms orally as powders, capsules, pills, cachets and tablets. Oral route is the most preferred, Dosage form means converting the drug into more palatable, elegant and easily acceptable by of the patient. Main purpose of dosage form is to deliver the drug at site of action for maximum therapeutic effect and minimum adverse effects. FDT are solid unit dosage forms containing medicinal agent and are rapidly disintegrated when placed upon the tongue in a matter of seconds. In these Super disintegrants have the property of more amount of water absorbing and swelling of tablet causes rapid bursting and disintegration. These tablets possess dissolution, absorption and therapeutic effect was significantly more than conventional tablets. Widely used synonyms for FDT are oral dispersible tablets, oral disintegrating tablet, rapid melts, mouth dissolving tablets and melt in mouth tablets. Fast dissolving tablets are defined as per US FDA as "solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less.

II. METHODOLOGY

Preformulation study:

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a drug as well as stability in presence of other excipients. The primary objectives of this investigation are identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation. Preformulation studies were performed on the drug, which include melting point determination, solubility and compatibility studies.

a) Determination of melting point: melting point of Pregabalin was determined by capillary method.

b) Solubility: solubility of the Pregabalin was determine in 6.8 pH buffer, ethanol, methanol and chloroform.

Preparation of standard curve of Pregabalin

Pregabalin was analyzed using UV/visible spectrophotometer, using solution prepared in 6.8 pH buffer.

Preparation of 6.8-pH

28.80 gm of Disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in 1000 ml of water.

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Preparation of standard curve of Pregabalin in 6.8 pH

For the standard graph, Pregabalin10 mg was accurately weighed and dissolved in 10ml of 6.8 phosphate buffer. From the stock solution (1mg/ml), different concentration of Pregabalinviz, 10, 20,30, 40, 50 mcg/ml were prepared and made up to volume with 6.8 phosphate buffer.

Drug excipient compatibility

FT-IR spectroscopy FTIR spectra were obtained on Shimadzu FTIR Model 8400-S spectrometer. The spectra was recorded as a dispersion of the sample in Potassium Bromide in IR disk (2 mg sample in 200 mg KBr) with the scanning range of 400 to 4000 cm-1 and the resolution was 1 cm -1

Direct compression technique

Different tablet formulations were prepared by direct compression method. The formulations are composed of superdisintegrants. All powders were passed through 100-mesh sieve. The microcrystalline and the superdisintegrantswere mixed uniformly. Drug was added to the superdisintegrantsand blended for 20 min. The resulting powders were mixed with magnesium Stearate and talc in polyethylene bag for 10 min. The lubricated powders were compressed using 8mm punch (single punch tablet machine) in to tablets. The total weight of tablet was kept at 200 mg.

Table-1: Formulation table of Pregabalinfast dissolving tablets

S.No	Ingredient(mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Pregabalin	75	75	75	75	75	75	75	75
2	Sodium starch glycolate	5	10	15	20	-	-	-	-
3	Crospovidone	-	-	-	-	5	10	15	20
4	Lactose	113	103	98	93	113	103	98	93
5	Magnesium stearate	3	3	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2	2	2
7	Aspartame	2	2	2	2	2	2	2	2
8	Total. wt	200	200	200	200	200	200	200	200

Pre compression parameters

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Bulk density (Db): It is the ratio of total mass (M) of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume (V0) was noted

Db= M/V0 ----------

Where, M is the mass of powder, V0 is the bulk volume of the powder.

Tapped Density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the weighed powder to constant volume It is expressed in gm/ml and was calculated using equation

Dt= M/Vt ----------

M is the mass of powder, Vt is the tapped volume of the powder.

Carr's index/compressibility index: Carr's Index was calculated by using the values of the bulk density and tapped density by using the equation

Carr's index= tapped density-bulk density/tapped densityx100

Hausner's ratio: Based on the tapped density and bulk density, the hausner's ratio of the tablet blend was computed by using equation

Hausner's ratio (H) =tapped density / bulk density

Pre compression parameters

Drug content

Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The weight equivalent to 10 mg Pregabalin was weighed and dissolved in 5 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with phosphate buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 310 nm .

Friability test

Friability of the tablets was determined using Roche friabilator at 25 rpm/min for 4 min. 40 tablets were weighed and loss in weight (%) was calculated.

Friability = (W1 – W2)/W1 × 100

Weight of 40 Tablets = W1,

Weight of 40 Tablets after friability = W2

Wetting time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. The wetting times were measured.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

R = 100 × (Wa– Wb)/Wa

Where,

Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption.

In vitro disintegration test

In-vitro disintegration time: Disintegration time is the time taken by the tablet to break into smaller particles. The disintegration test was carried out in an apparatus containing a basket rack assembly with six glass tubes which consisted of a 10 mesh sieve, the basket was raised and lowered 28-32 times per minute in the medium of 900ml of 6.8 phosphate buffer, which is maintained at 37±2°C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet. Then, the times taken for disintegration of six FDTs were tabulated and average disintegration time was calculated

Dissolution studies

In vitro drug release Dissolution studies of pregabalin from all physical mixtures and solid dispersions were performed according to the method described in USP XXIV, using USP II apparatus (paddle method). The dissolution test was performed using 900 ml phosphate buffer pH 6.8, at 370 ± 0.50C and 50 rpm. Aliquots (5 ml) was removed from the dissolution medium at specific time intervals and was replenished immediately with same volume of fresh medium, the amount of released Pregabalin was determined by UV analysis at 310 nm.

Drug release kinetics

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

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Q0 ñ Qt = K0t
Rearrangement of equation yields:
Qt = Q0 + K0t
where
Qt is the amount of drug dissolved in time t,
Q0 is the initial amount of drug in the solution (most times, Q0 = 0)

First order model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:
dC n= nKc (5) dt
where K is first order rate constant expressed in units of time-1.
Equation (5) can be expressed as:
log C = log C0 ñ Kt / 2.303
where
C0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of nK/2.303.

Higuchi model

This model is based on the hypotheses that initial drug concentration in the matrix is much higher than drug solubility; drug diffusion takes place only in one dimension (edge effect must be negligible)drug particles are much smaller than system thickness; matrix swelling and dissolution are negligible; drug diffusivity is constant; and perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by the equation:
ft = Q = A √D(2C ñ Cs) Cs t
where Q is the amount of drug released in time t per unit area A,
C is the drug initial concentration,
Cs is the drug solubility in the matrix media and
D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

Korsmeyer-Peppas model

Korsmeyer derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in KorsmeyerPeppas model.

$$Mt / M\infty = Ktn$$

where Mt / M∞ is a fraction of drug released at time t,
k is the release rate constant and n is the release exponent.

Stability studies

The purpose of stability testing is to provide evidence of how the quality of an Active Pharmaceutical Ingredient (API) or Finished Pharmaceutical Product (FPP) varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product related factors that influence its quality.
The formulations stored in glass vials covered with aluminium foil were kept at room temperature and in refrigerator (4◦C) for a period of 90 days. Furthermore, the samples were also evaluated for particle size and percent retention of Pregabalin.

III. RESULTS & DISCUSSIONS

In the present study 8 formulations with variable concentration of polymer were prepared and evaluated for physico-chemical parameters, invitro release studies and stability studies.

Preformulation studies

a) Organoleptic evaluation

Table-2: Organoleptic properties of Pregabalin

Properties	Results
Description	Crystalline powder
Taste	tasteless
Odour	odourless
Colour	White

b) Determination of melting point

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Melting point of Pregabalin was found in the range of 239^{0}c, which complied with the standard, indicating purity of the drug sample.

c) Solubility

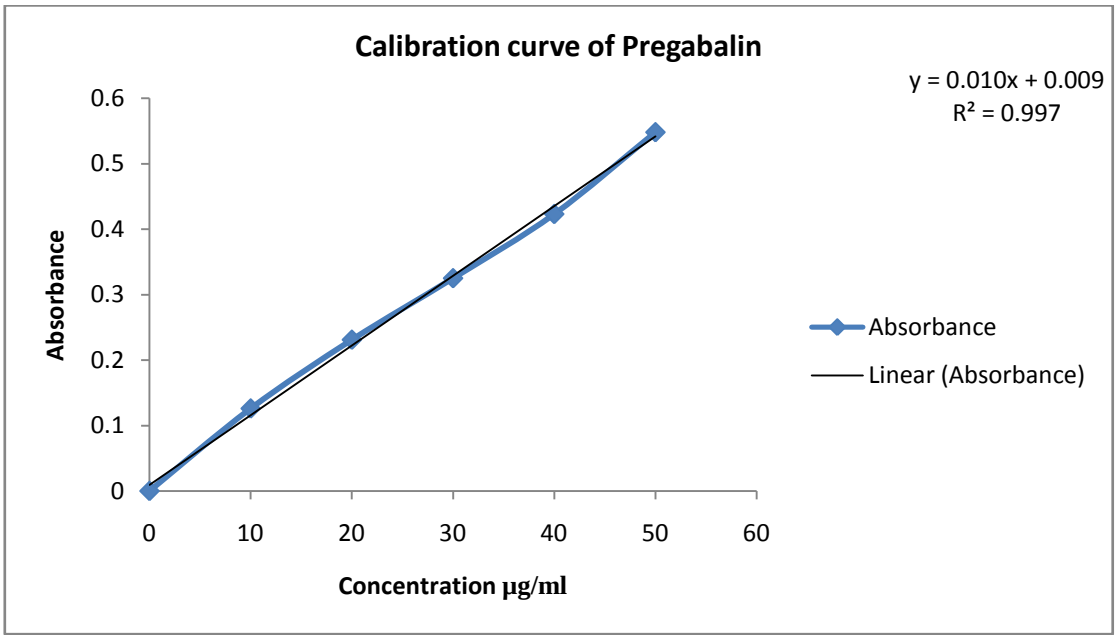
Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in acetone and in chloroform.

Preparation of standard curve of Pregabalin

Standard curve of Pregabalinwas determined by plotting absorbance V/s concentration at 310 nm. Using solution prepared in pH 6.8 at 310 nm. And it follows the Beer's law. The R^2 value is 0.997.

Table-3: Data for standard graph of Pregabalin Phosphate buffer pH 6.8

Concentration (µg/ml)	Absorbance in Ph 6.8 buffer
0	0
10	0.126
20	0.231
30	0.325
40	0.423
50	0.548



Fourier Transformation Infra-red (FTIR) analysis:

FT-IR Spectra of Pregabalinand F8 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Pregabalinand superdisintegrant. It also confirmed that the stability of drug during microencapsulation process.

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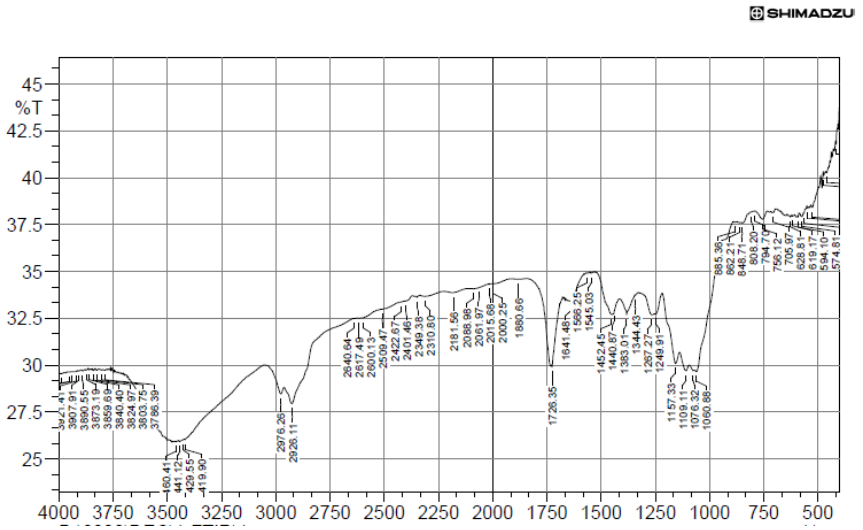

Fig-1: FTIR spectra of pure drug

Table-4: Characteristic Peaks of Pregabalin

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3873.19
2	OH Bending	3000-2500	2976.26
3	C-H stretching	2500-2000	2310.80
4	C=O stretching	1500-1000	1452.45

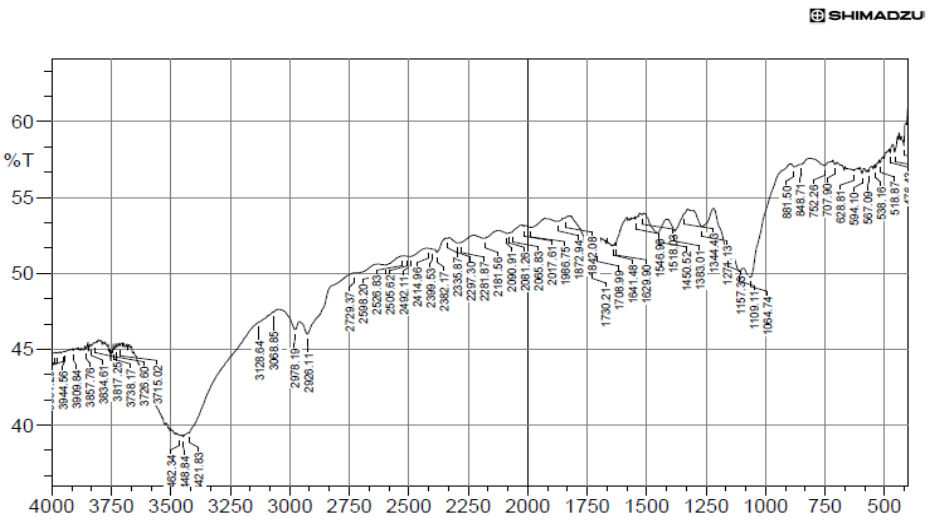

Fig-2: FTIR Spectra of physical mixture of drug and excipients

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Table-5: Characteristic Peaks and frequency of physical mixture of drug and excipients

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3857.76
2	OH Bending	3000-2500	2729.19
3	C-H stretching	2500-2000	2335.92
4	C=O stretching	1500-1000	1450.52

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

Evaluation studies

Pre compression parameters

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.500-0.516.

b) Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.600-0.618.

c) Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 28 to31^0

d) Compressibility index: Compressibility index was carried out, it found between 14% to 17.70 % indicating the powder blend have the required flow property for compression.

Characterization of Formulation

Table-6: Pre compression parameters of PregabalinFast dissolving tablets

S. no	Bulk density(gm/cc)	Tappeddensity(gm/cc)	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.506	0.603	16.08	1.19	31^0c
F2	0.511	0.615	16.91	1.20	28^0c
F3	0.502	0.610	17.70	1.21	30^0c
F4	0.499	0.600	16.83	1.20	28^0c
F5	0.516	0.618	16.50	1.19	29^0c
F6	0.510	0.614	17.63	1.20	30^0c
F7	0.500	0.600	16.90	1.21	28^0c
F8	0.509	0.609	16.68	1.20	30^0c

Post compression parameters

Weight variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness (n=3) were uniform in F1 to F8 formulations and were found to be in the range of 2.0 mm to 2.8 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 4.18 to 4.37kg/cm^2. This

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ensures good handling characteristics of all batches.

Friability:
The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:
The percentage of drug content for F1 to F8 was found to be between 81.15 % and 89.38 % of Pregabalin, it complies with official specifications.

Disintegration Time:
In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods. The shortest registered disintegration time was 45 s, while the longest greatly exceeded 40 sec.

Wetting Time:
The weight of the tablet before keeping in Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and re weighed (W_a) using the same. The shortest registered wetting time was 148 sec, while the longest greatly exceeded 158 sec.

Table-7: Evaluation parameters of PregabalinFast dissolving tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time(sec)	Wetting time (sec)
F1	199	2.3	4.22	0.35	85.39	56	144
F2	200	2.6	4.21	0.40	81.15	52	149
F3	199	2.7	4.37	0.43	85.35	48	158
F4	200	2.8	4.29	0.48	83.14	49	157
F5	199	2.2	4.45	0.43	88.93	53	149
F6	200	2.7	4.18	0.45	84.16	55	146
F7	200	2.2	4.28	0.47	83.29	46	154
F8	200	2.6	4.30	0.46	89.38	45	148

Dissolution studies
All the four formulation of PregabalinFast dissolving tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-8: Drug release studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	30.15	32.60	29.50	26.20	28.96	24.42	23.40	20.22
10	39.50	40.52	36.58	32.63	33.46	33.60	30.28	34.74
15	48.32	49.45	50.70	51.28	50.27	52.70	50.13	56.28
30	55.35	65.62	69.85	65.40	63.92	65.82	63.21	68.28
45	68.70	78.20	75.46	77.14	75.81	75.12	74.03	79.50
60	85.35	92.36	89.80	90.31	8976	91.80	89.40	93.35

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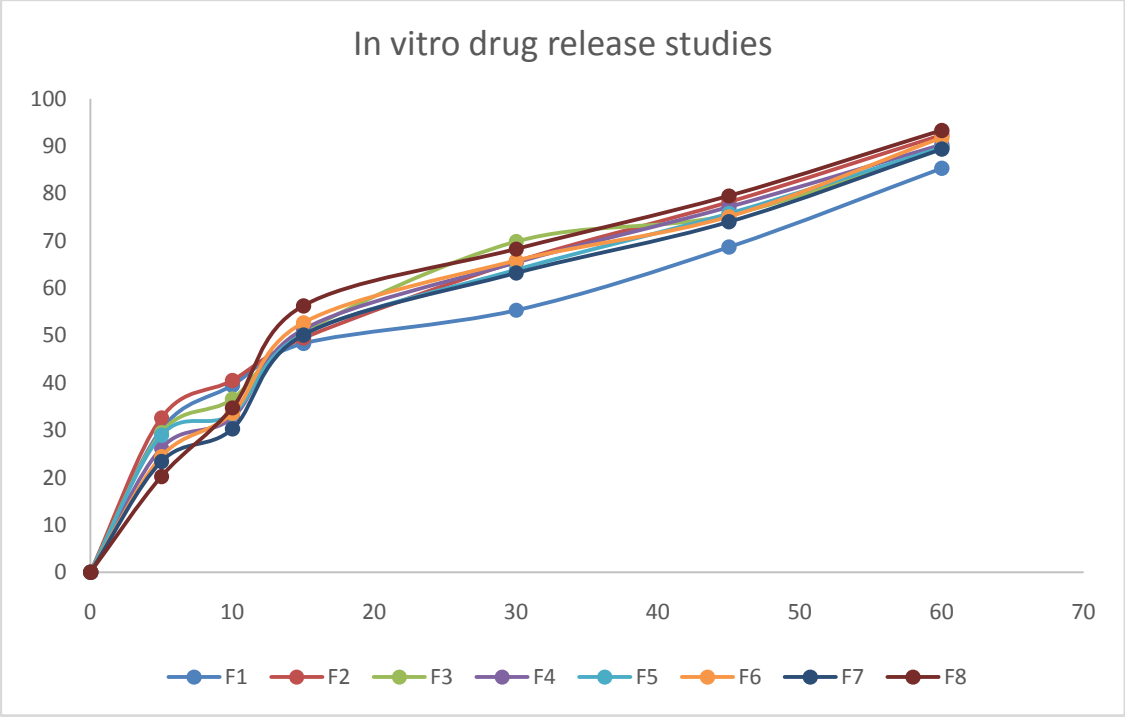

Fig-4: Dissolution Profile of F1 to F8 formulations

Drug release kinetics

Table-9: Drug Release Kinetics of Formulation F8

TIME	%CDR	SQUARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	0	0
5	23.22	2.236068	0.69897	1.062206	75.78	1.946747
10	34.74	3.162278	1	1.32531	65.26	1.896802
15	56.28	3.872983	1.176091	1.454692	43.72	1.854367
30	68.28	5.477226	1.477121	1.587711	31.72	1.78746
45	79.50	7.745967	1.778151	1.70105	20.50	1.681688
60	93.35	10.95445	2.079181	1.71391	6.65	1.673492

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Zero order kinetics

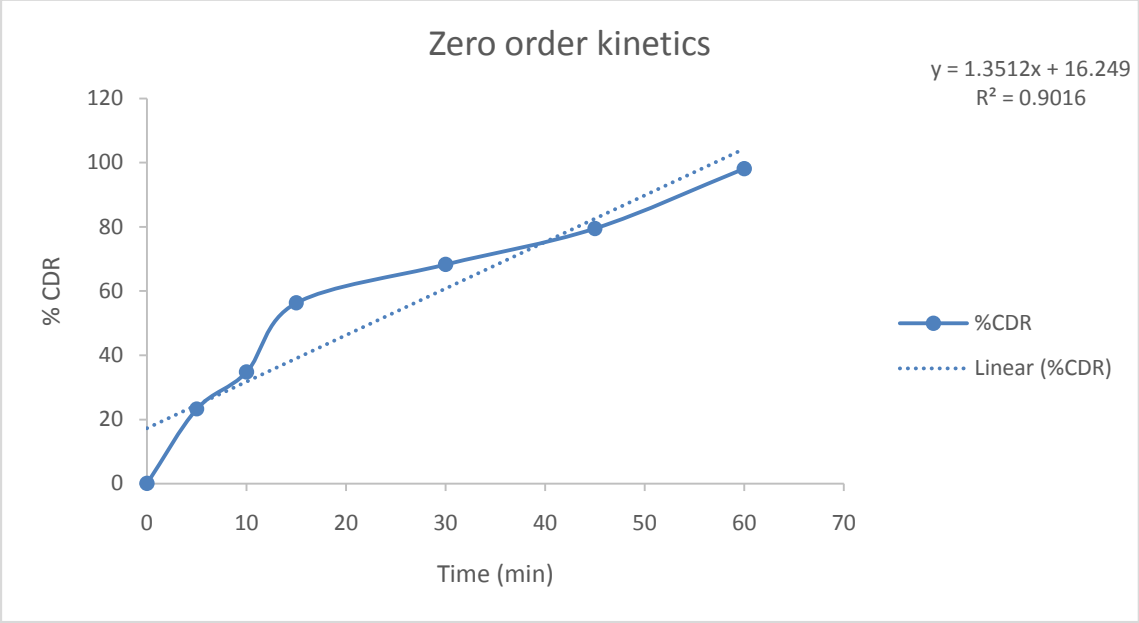

Fig-5: Zero order kinetics

First order kinetics

Fig-6: First order kinetics

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Higuchi model

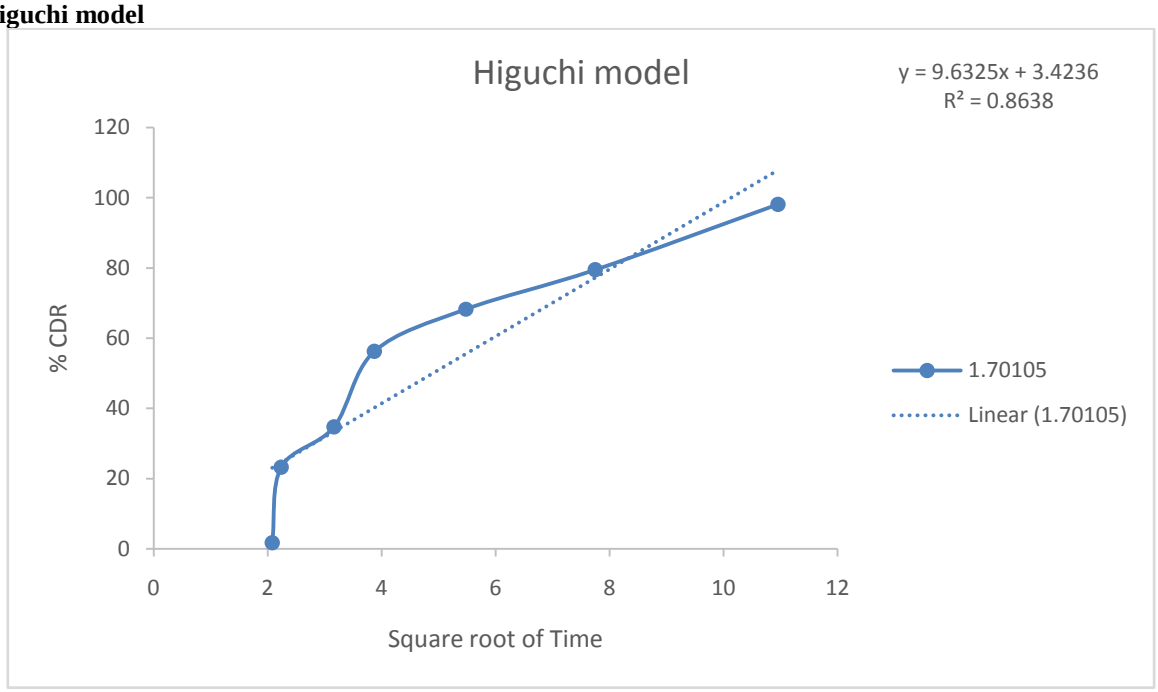

Fig-7: Higuchi model

Krosmayerpeppas

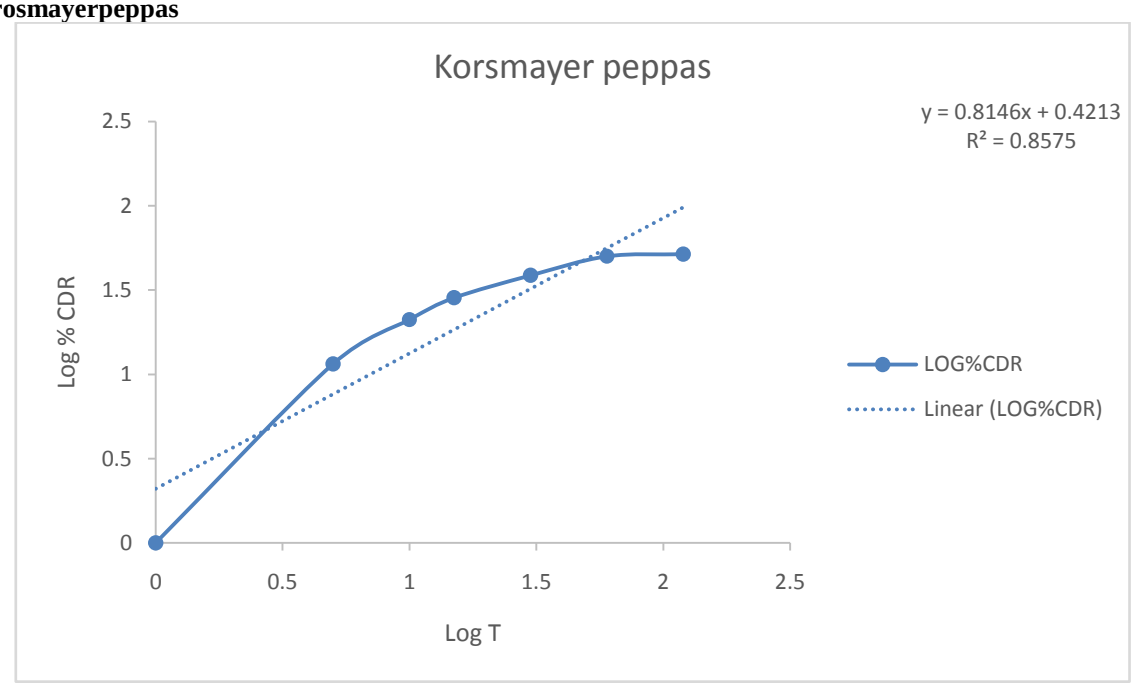

Fig-8: Krosmayerpeppas

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Stability studies

Table-10: Stability Studies of Optimized Formulation

S.NO	Time in days	Physical changes	Mean % drug release		
			Fast dissolving tablet		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	93.35	92.18	90.25
2.	30	No Change	93.35	92.32	90.14
3.	60	No Change	93.35	92.12	90.08
4.	90	No Change	93.35	92.35	90.17

There was no significant change in physical and chemical properties of the tablets of formulation F8 after 90 days, parameters like % drug release and assay values at various conditions(at 40^0C/ 75% RH) as per ICH guidelines quantified at various time intervals were shown in Table and dissolution profile.

IV. CONCLUSION

In the above studies F8formulation showed promising results. It was further supported by FTIR analysis which showed that F8 had no interaction with excipients. The stability studies were carried out for the optimized formulation for 3 months and it showed acceptable results. The kinetic studies of the formulations revealed that dissolution is the predominant mechanism of drug release.

So F8formulation was considered as the optimized formulation.

REFERENCES

[1]. Bhaskaran, S. and Narmada, G.V., Fast Dissolving drug delivery systems: A brief overview**,** Indian Pharmacist**,** 2002, 1 (2), 9-12.

[2]. Devrajan, P.V, Gore, S.P., Fast Dissolving Tablets: The Future Compaction, Express Pharma Pulse, 2000: 23, 7(1), 16.

[3]. Kuchekar, B.S., Badhan, A.C., Mahajan, H.S., Fast Dissolving drug delivery systems: A brief overview, Pharma Times, 2003, 35, 7-9.

[4]. Reddy, L. H., Ghose, B. and Rajneesh, Fast Dissolving drug delivery systems: A brief overview, Indian J. Pharm. Sci.**, 2002**, 64(4): 331- 336, Parakh, S.R. and Gothoskar, A.V., Fast Dissolving drug delivery systems: A brief overview, **Pharma. Tech.,** 2003, 92- 100.

[5]. Lalla, J.K. and Sharma, A H., **Indian Drugs,** 1994, 31(11), 503-508.

[6]. www. ElanNanoCrystal_Technology.htm.