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Thermoplastic Granulation Approach to Retard Drug Release from Floating Tablets of Pregabalin

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ABSTRACT

The present work deals with the formulation and evaluation of floating tablets of Pregabalin using Thermoplastic granulation or Melt granulation technology[1]. Thermoplastic granulation is a process by which granules are obtained through the addition of a meltable binder which melts during the process. This technology is used to modify or control drug release of highly water soluble drugs using hydrophobic meltable binders as done in this present work. Pregabalin is a primary medication for epilepsy, neuropathic pain, and fibromyalgia was selected for this work. The primary objective was to formulate and evaluate floating tablets of the Pregabalin by using different meltable binders like stearic acid, bees wax, carnauba wax along with other excipients such as HPMC K4M (3000cps), ethyl cellulose, sodium bicarbonate in various proportions by employing thermoplastic granulation method Pregabalin has absorption window in the upper region of small intestine hence it is suitable candidate for floating systems. FTIR spectroscopic studies suggested that the drug is compatible with all excipients used in this formulation. The formulations were evaluated for the pre-compressional and post-compressional parameters. The floating tablets were evaluated for the floating ability and also percentage drug release by using 0.1 N HCl as dissolution medium. The formulation F10 with stearic acid as the meltable binder along with ethyl cellulose had floating ability of not less than 12 hours with a good drug release profile. The optimized formulation followed Higuchi mechanism which shows both diffusion and erosion.

Keywords: Pregabalin, Stearic acid, bees wax, carnauba wax, sodium bicarbonate and HPMC K4M (3000cps).

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INTRODUCTION

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as reduced dosing frequency, patient compliance and flexibility in formulation[4]. The primary aim of oral controlled drug delivery system is to achieve better bioavailability and release of drug from the system. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine. This can be overcome by altering the physiological state and designing the formulations, by which gastric retention of drug can be extended from 12-24 hours. Prolonged gastric retention increases bioavailability, decreases dose of drugs, increases solubility of drugs, which are less soluble in alkaline pH. Gastric retention can be achieved by muco-adhesion or bio adhesion systems, expansion systems, high density systems, magnetic systems, super porous hydrogels, raft forming systems, low density systems, and floating ion exchange resins. Floating drug delivery systems (FDDS)[5,6] have density less than gastric fluids, so remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased GRT and a better control over the fluctuations in plasma drug concentration.

Pregabalin[2,3](3S)-3-(amino methyl)-5-methylhexanoic acid, is a structural analogues of γ-amino butyric acid (GABA) which constitutes an important group of compounds that are used in the treatment of epilepsy and neuropathic pain. The half-life of Pregabalin is 5-6 hrs which makes it suitable candidate for sustained or controlled release formulation, moreover it reduces side effects, decreases dosing frequency and improves patient compliance. Hence the present work was aimed to develop floating tablets of Pregabalin using Thermoplastic granulation technique by which granules are obtained by addition of meltable binder which melts during the process. This process is also called melt agglomeration or melt granulation or thermoplastic granulation. In the present study meltable binders like stearic acid, bees wax, and carnauba wax were used in different concentrations along with Sodium bicarbonate was used to prepare these controlled release floating tablets.

MATERIALS AND METHOD

Pregabalin was gift sample from Orchid pharmaceuticals Chennai, Hydroxyl propyl methyl cellulose (HPMC K4M 3000 cps), Stearic acid, Bees wax, Carnauba wax, Ethyl cellulose, Poly vinyl pyrrolidone (PVP-K30), Magnesium stearate, Sodium Bicarbonate, Microcrystalline cellulose and Aerosil were obtained from SDFCL pharmaceuticals Mumbai.

Formulation of Pregabalin floating tablets by melt granulation method:

Meltable binder (stearic acid) was melted at 60º C and required quantity of drug was added to this melted mass. Then the mass was cooled to room temperature and subjected to air drying. Then obtained dry mass was passed through # 80 sieve. To this blend remaining ingredients were added after passing through # 60 sieve. Finally this blend was compressed by using tablet compression machine using 12 mm punch. The Pregabalin floating tablets were evaluated for Hardness, Friability, Weight variation, Thickness, Diameter, Drug content uniformity, Floating ability, and *In-vitro* drug release studies.

Table 2: Formulation table of Pregabalin floating tablets (350mg)

Ingredients (mg)	F1	F2	F3	F4	F5(a)	F5(b)	F6	F7	F8	F19	F10
Pregabalin	75	75	75	75	75	75	75	75	75	75	75
Steraic acid	15	0	0	0	15	15	15	37.5	15	15	15
Bees wax	0	15	0	0	0	0	0	0	0	0	0
Carnauba Wax	0	0	15	0	0	0	0	0	0	0	0
HPMC 3000CPS	140	140	140	140	140	0	140	140	175	140	140
Ethyl Cellulose	0	0	0	0	0	0	0	0	0	17.5	35
PVP K30	14	14	14	14	14	14	14	14	14	14	14
Sodium Bicarbonate	17.5	17.5	17.5	17.5	0	0	8.75	17.5	17.5	17.5	17.5
MCC	83.25	83.25	83.25	98.25	100.75	240.75	92	60.75	48.25	65.75	48.25
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Aerosil	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75

F5 (a) ----- Without Sodium Bicarbonate

F5 (b) ----- without HPMC and Sodium Bicarbonate

Friability:

For each formulation, the friability of 20 tablets was determined using the Roche friabilator. This test subjects a number of tablets to combined effect of shock and abrasion by utilizing a plastic chamber which revolve at a speed of 25 rpm, dropping the tablets to distance of 6 inches in each revolution. A sample of preweighed 20 tablets were placed in Roche friabilator, which were then operated for 100 revolutions for 4 minutes. The tablets were then de-dusted and reweighed. A loss of less than 1% in weight is generally considered acceptable. Percent friability (% F) was calculated.

Weight Variation Test:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness, Thickness, and Diameter:

Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users. Manufacturing processes such as coating, packaging and printing can involve considerable stress, which the tablet must be able to withstand. For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured. Diameter and hardness was determined using Vernier calipers and Hardness tester. Thicknesses of the prepared tablets were measured by screw gauge. Average of three readings were taken and the results were tabulated (n = 3).

Uniformity of drug content:

The drug content was performed to check the dose uniformity in the formulation. Randomly 10 tablets were weighed and powdered. A quantity equivalent to 100 mg of drug was added in to a 100 ml volumetric flask and dissolved in 0.1N HCl. After making suitable dilutions the drug content was estimated by UV- Visible Spectrophotometer at 210 nm against blank.

Floating lag time:

The buoyancy of tablets was studied at 37 ± 0.5 ^{0}C, in 100 ml of 0.1N HCl. A glass beaker containing 100 ml of 0.1N HCl was taken in which a tablet was placed for observation. The duration of time taken by the tablet to float was observed visually. Average of three readings were taken and tabulated (n = 3) in table 5.

***In vitro* drug release studies:**

Pregabalin floating tablets were placed in 900 ml of 0.1N HCl in USP-II apparatus (Paddle method). The medium was allowed to equilibrate to the temperature of 37^{0}C±0.5 ^{0}C. A tablet was placed in the vessel and the apparatus was operated up to 12 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn, filtered and again replaced with 5 ml of fresh medium to maintain sink conditions and analyzed spectrophotometrically at λmax 210 nm using a UV-Visible spectrophotometer.

Kinetics of *In-vitro* drug release :[7,8,9,10]

To analyze the mechanism of drug release and release kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi and Korsemeyer- Peppas. From this by comparing the R^2-values obtained, the best-fit model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disintegrate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation

$$\mathbf{Qt = Q_0 + K_0 t}$$

Where Qt = amount of drug dissolved in time t,

Q_0 =initial amount of drug in the solution and

$K_{0=}$ zero order release constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order kinetics:

To study the first order release rate kinetics, the drug release data was fitted to the following equation.

$\text{Log } Q_t = \log Q_0 + K_1 t / 2.303$

Where

$Q_{t=}$ amount of drug released in time t,

$Q_{0=}$initial amount of drug in the solution and

$K_{1=}$ first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids or solid matrices. Mathematical expressions were obtained for drug particle dispersed in uniform matrix that behaves as the diffusion media, and the equation is

$Qt = K_H . T^{1/2}$

Where

Qt= amount of drug release in time t,

K_H = Higuchi dissolution constant.

Korsmeyer and Peppas release model:

To study this model the drug release rate data was fitted to the following equation

$M^t / M^\infty = K.t^n$

Where

M t/ M∞ = the fraction of drug release,

K = release constant,

t = release time and

n = Diffusional exponent for the drug release that is dependent on the shape of matrix dosage form.

Stability studies:

Stability studies of pharmaceutical dosage forms were done as per ICH guide lines. These studies were designed to increase the rate of chemical or physical degradation of the drug

substance or product by using exaggerated storage conditions. Optimized formulation was stored at elevated temperatures such as 40^0C±2 ^{0}C/75%RH±5%RH for 90 days. The samples were tested for physical changes, hardness, friability, and drug content, floating lag time and percentage drug release at an interval of 30 days.

RESULTS AND DISCUSSION

Calibration curve of Pregabalin:

The absorbance of the solution was measured at 210 nm, using UV- Visible spectrophotometer with 0.1N HCl as blank. The values are shown below Table 1. A graph was plotted by taking concentration on X-axis and absorbance on Y-axis as shown in Figure1 which indicates the compliance with Beer's Lambert law within the concentration range.

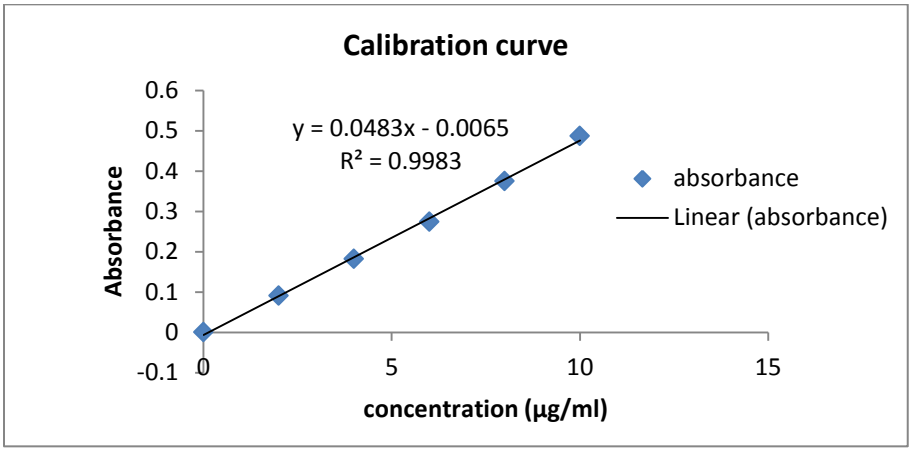

Figure 1: Standard calibration curve for Pregabalin

Table 1: Calibration curve data of Pregabalin

Concentration (µg / ml)	Absorbance
0	0
2	0.091
4	0.182
6	0.274
8	0.375
10	0.487

Compatibility studies:

FT-IR method: Pregabalin and excipients were subjected to FT-IR spectral analysis. The drug was compatible with excipients used in formulation, since no significant changes were observed in intensity and position of the peaks in the spectra which were in the Figure 2,3,4,5 and 6.

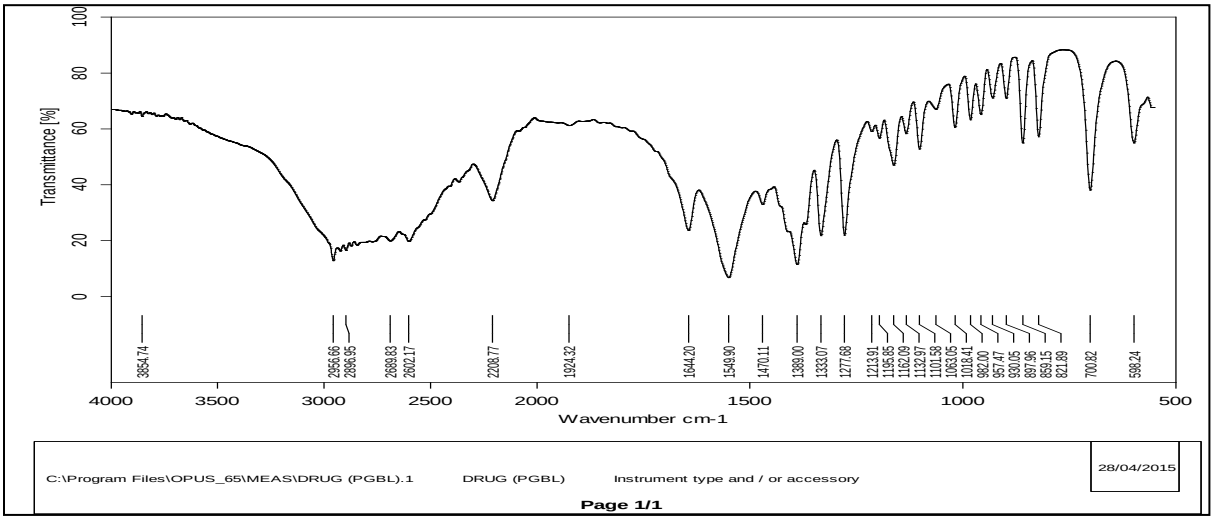

Figure 2: FTIR spectra of Pregabalin pure drug

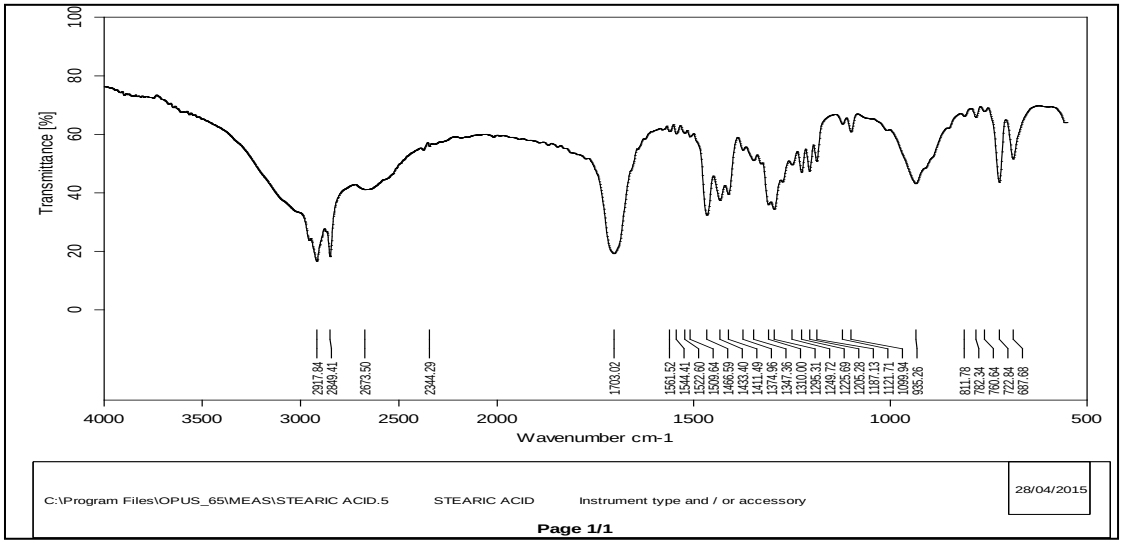

Figure 3: FTIR spectra of Pregabalin and Stearic acid

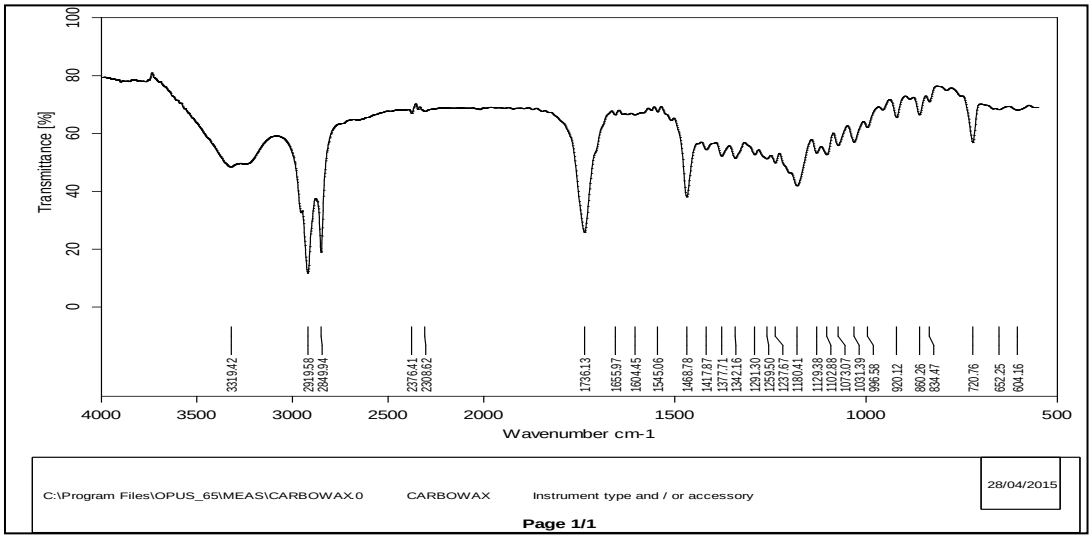

Figure 4: FTIR spectra of Pregabalin and carnauba wax

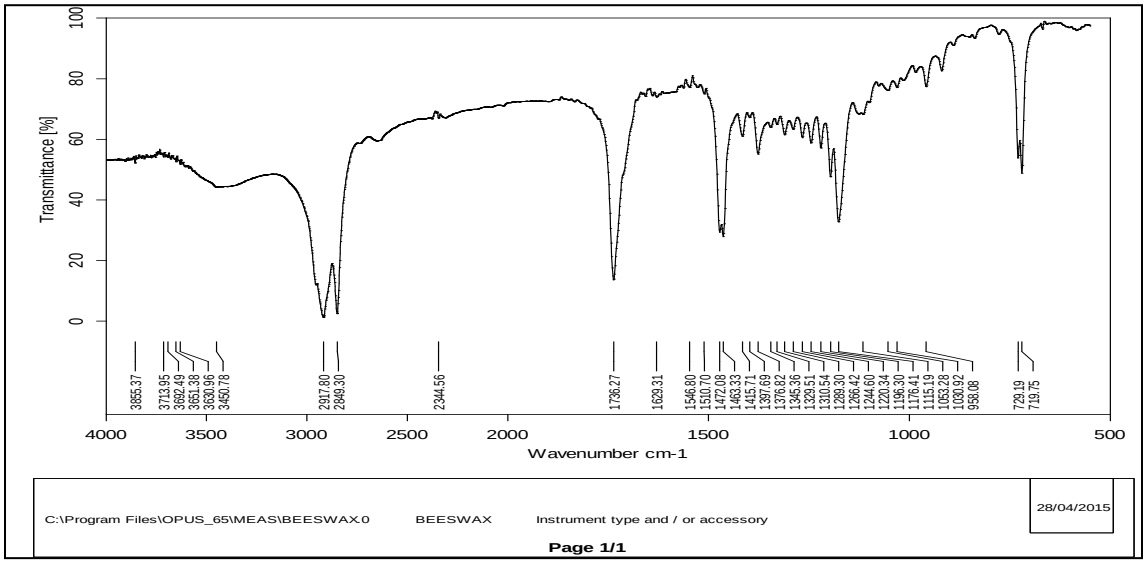

Figure 5: FTIR spectra of Pregabalin and Bee's wax

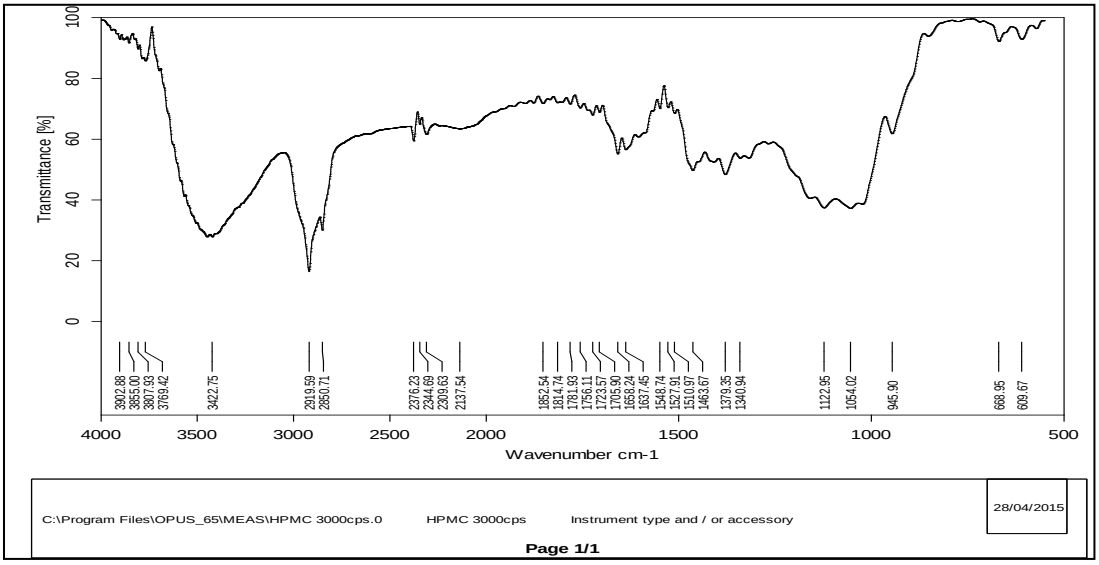

Figure 6: FTIR spectra of Pregabalin and HPMC 3000cps

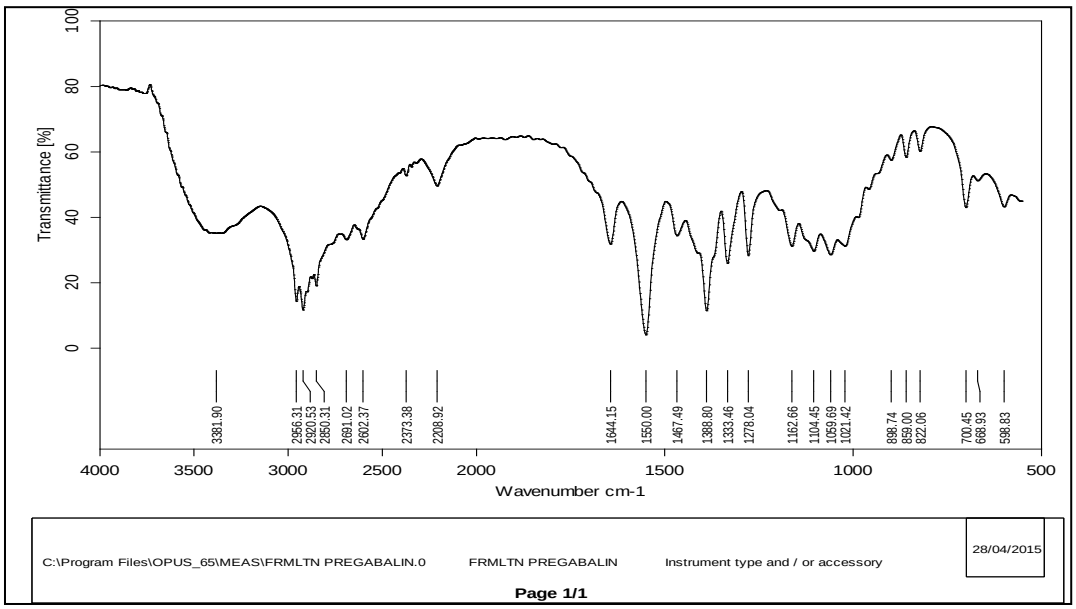

Figure 7: FTIR spectra of Pregabalin optimized formulation F (10)

Pre-compressional parameters:

The bulk density and tapped density for all formulations varied in between 0.264 gm/ml - 0.389 gm/ml and 0.292 gm/ml - 0.461gm/ml respectively. Carr's compressibility index for all formulations lies between 9.58%- 24.28%. All the formulations showed good compressibility. Hausner's ratio was found between 1.10- 1.25 which showed that all formulations have good compressibility. The angle of repose values were found to be in the range of 24º to 34º indicating good flow which were shown in the Table 3.

Table 3: Pre-compression parameters of Pregabalin tablet powder blends

Formulations	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's compressibility index	Angle of Repose (Ɵ)
F1	0.389±0.03	0.461±0.03	1.18	15.61	27º31"
F2	0.359±0.001	0.447±0.05	1.24	19.68	30°18"
F3	0.316±0.01	0.389±0.02	1.23	18.76	29°25"
F4	0.349±0.002	0.441±0.03	1.25	19.83	28°56"
F5a	0.313±0.005	0.389±0.01	1.24	24.28	34°22"
F5b	0.290±0.015	0.391±0.02	1.21	17.37	31°26"
F6	0.318±0.017	0.391±0.02	1.22	18.67	30°06"
F7	0.289±0.013	0.348±0.02	1.2	16.95	33°12"
F8	0.319±0.017	0.393±0.02	1.23	18.82	24°48"
F9	0.300±0.032	0.348±0.07	1.16	13.79	33°03"
F10	0.264±0.021	0.292±0.01	1.1	9.58	27°15"

Post compressional parameters:

All formulations were tested for physical parameters like hardness, thickness, weight variation, friability, floating lag time and drug content were tabulated in the Table 4 and were found to be within Pharmacopoeial limits. The percentage weight variation for all the formulations were found to be within the pharmacopoeial limits ±5%. Hardness was maintained between 3.41 kg/cm^2 to 5.03 kg/cm^2. The hardness for all the formulations was almost uniform and possess good mechanical strength with sufficient hardness. Thickness for all the formulations were found in a range of 3.23 to 3.93mm.The drug content values for all the formulations were found to be within the range of 96.6 to 99.8%.

Table 4: Post compression parameters of Pregabalin tablets F1 – F10

Formulation	Weight variation(mg)	Friability (%)	Hardness (kg/cm2)	Thickness (mm)	Drug content (%)
F1	349.6±0.58	0.97	3.76±0.05	3.26±0.25	98.2±0.10
F2	350.1±1.25	0.98	5.02±0.11	3.23±0.27	98.3±1.06
F3	348.3±0.55	0.96	4.4±0.1	3.2±0.2	97.2±0.92
F4	349.8±0.76	0.97	4.38±0.12	3.43±0.11	99±0.23
F5a	348.3±0.67	0.97	3.41±0.10	3.5±0.5	96.7±0.31
F5b	348.5±0.5	0.96	5.03 ± 0.05	3.83±0.28	98.9±0.61
F6	350.1±0.76	0.96	4.33± 0.05	3.4±0.52	97.8±0.50
F7	349.3±0.57	0.96	4.71 ± 0.10	3.33±0.57	98.1±0.63
F8	349 ±0.76	0.97	3.65±0.08	3.93±0.11	97.5±1.27
F9	349.6±0.56	0.98	4.26 ± 0.20	3.86±0.11	96.6±0.48
F10	349.5±0.28	0.98	4.81±0.11	3.8±0.2	99.8±0.46

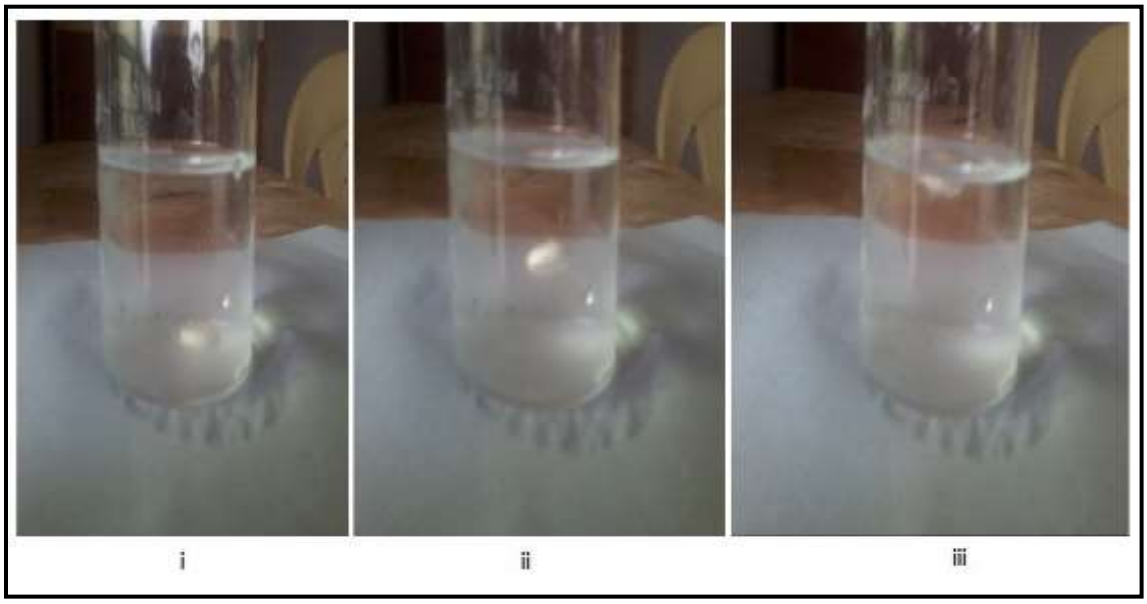

Figure 8: Figures of *in-vitro* floating studies of Pregabalin optimized formulation F10

Table 5: *In vitro* Buoyancy Studies of Pregabalin floating tablets

Formulation code	Floating lag time
F1	12 sec
F2	20 sec
F3	20 sec
F4	10 sec
F5a (Without NaHCO3)	-
F5b (Without HPMC & NaHCO3)	-
F6	20 sec
F7	15 min
F8	15 sec
F9	15 sec
F10	15 sec

***In-vitro* dissolution studies:**

F1 to F10 formulations were prepared by direct compression method and the dissolution studies for all the formulations of the Pregabalin were carried out using 0.1N HCl for 12 hours with sampling points 0.5, 1, 2, 4, 8 and 12hours. The samples were analyzed at 210 nm and *in-vitro* drug release from the respective formulations was calculated and shown in the Table 6.

Table 6: *In vitro* cumulative percentage drug release profile of Pregabalin floating tablets, formulations F1 –F10

Time (hr)	Cumulative % Drug Released									
	F1	F2	F3	F4	F5 (a)	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
0.5	22.42	36.74	33.68	46.41	24.64	26.43	16.72	18.37	21.75	13.23
1	46.64	51.57	46.73	72.38	37.83	44.53	32.54	34.62	45.63	34.67
2	61.36	72.65	64.96	95.64	58.29	54.72	44.62	48.85	58.47	51.32
4	88.58	97.86	94.54	--	--	84.39	58.34	66.64	69.27	64.75
8	93.77	--	--	--	--	91.25	71.45	78.42	82.32	86.42
12	--	--	--	--	--	--	--	--	97.58	99.32

For F5 (b) formulation dissolution study was not carried out as the formulation is not having both HPMC K4M (3000 cps) and Sodium bicarbonate, tablets were not having sufficient hardness and integrity. The tablet was broken into small pieces after placing in dissolution medium.

The formulations F1 to F3 were developed with 20% of meltable binders such as stearic acid, bee's wax and carnauba wax respectively. From the *in-vitro* studies we observed that even though all the three formulations had shown initial burst release, the formulation F1 with stearic acid as meltable binder shown release upto 8 hours. So, the stearic acid was selected as meltable binder for the further experimentation.F4 formulation was developed without the meltable binder to check the

effect of polymer (HPMC K4M 3000cps). From the *in-vitro* results it was observed that polymer alone doesn't have enough capability in controlling drug release.

The formulation F5 (a) was developed without floating agent and high percentage of polymer and F5 (b) was developed without polymer and floating agent. Formulation F5 (b) doesn't have good integrity when placed in dissolution medium. The formulation F5 (a) tablets showed very poor floating ability even though more polymer concentration was used it could not sufficient for the tablet to float.

The F6 formulation was developed with 2.5% of floating agent. *In-vitro* results of these tablets shown a drug release of 91.25% for 8 hours without control in the initial burst release. So, in-order to increase the floating time for more than 8 hours, the concentration of floating agent was increased to 5%.

Two trials were performed by altering the concentrations of stearic acid to 30% and HPMC K4M (3000cps) concentration to 50% in F7 and F8. *In-vitro* results revealed that drug release was more controlled than required.

Finally 20% stearic acid, 40% HPMC and 5% floating agent were considered as the optimized concentrations and ethyl cellulose was introduced in two different concentrations 5% and 10% in F9 and F10 formulations to control the initial burst release.

The formulation F10 with 10% ethyl cellulose had given the promising release of 99.32% for 12 hours with floating lag time10min when compared to F9.

Stability studies on formulation F10 showed no significant change in physical appearance, hardness, drug content uniformity and cumulative percentage drug release in the tests conducted after 90 days.

Table 7: Comparative data of regression and slope values of different kinetic studies.

Formula	Zero order	First order	Higuchi plot	Korsemeyer Peppa's plot	n values
	R^2 values				
F1	0.7427	0.9292	0.9332	0.9054	0.505
F2	0.873	0.9696	0.9982	0.999	0.473
F3	0.9035	0.9746	0.9995	0.9746	0.494
F4	0.8924	0.99	0.9959	0.998	0.522
F5	0.9408	0.9872	0.9949	0.9995	0.596
F6	0.7688	0.9372	0.9511	0.9517	0.45
F7	0.8068	0.9277	0.9704	0.9403	0.503
F8	0.8033	0.9378	0.9677	0.9462	0.513
F9	0.7693	0.9429	0.941	0.9014	0.417
F10	0.8513	0.9278	0.9749	0.9114	0.577

Table 8: Stability studies of optimized formulation F10

Time (days)	$40^0C \pm 2^0C$/ 75%RH±5%RH		
	Hardness (kg/cm2)	Drug content (%)	% Drug Release
30	4.81	99.8	99.32
60	4.81	99.4	98.96
90	4.75	98.7	97.88

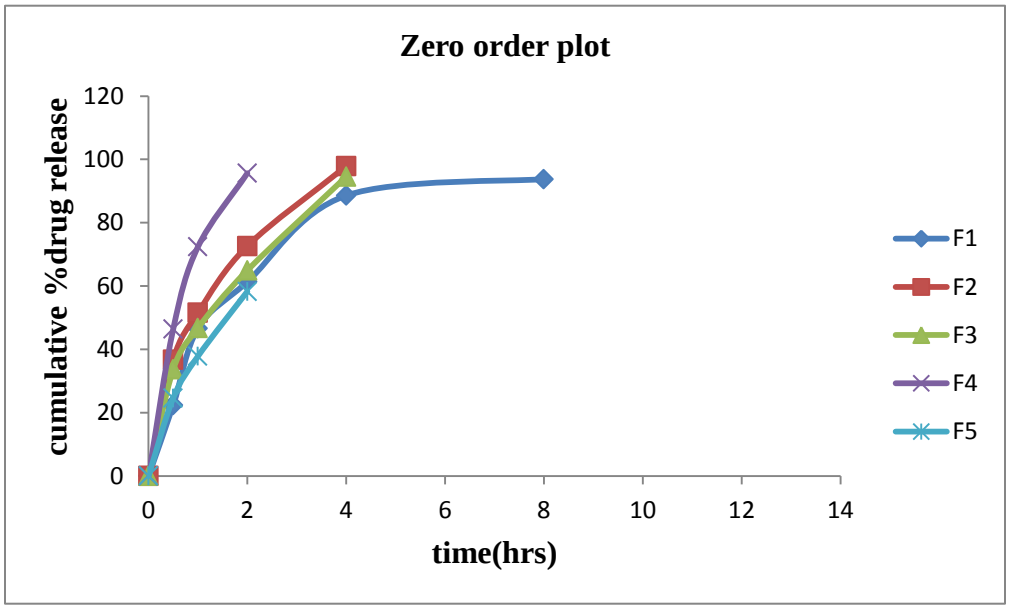

Figure 9: Zero order drug release plots for formulations F1-F5

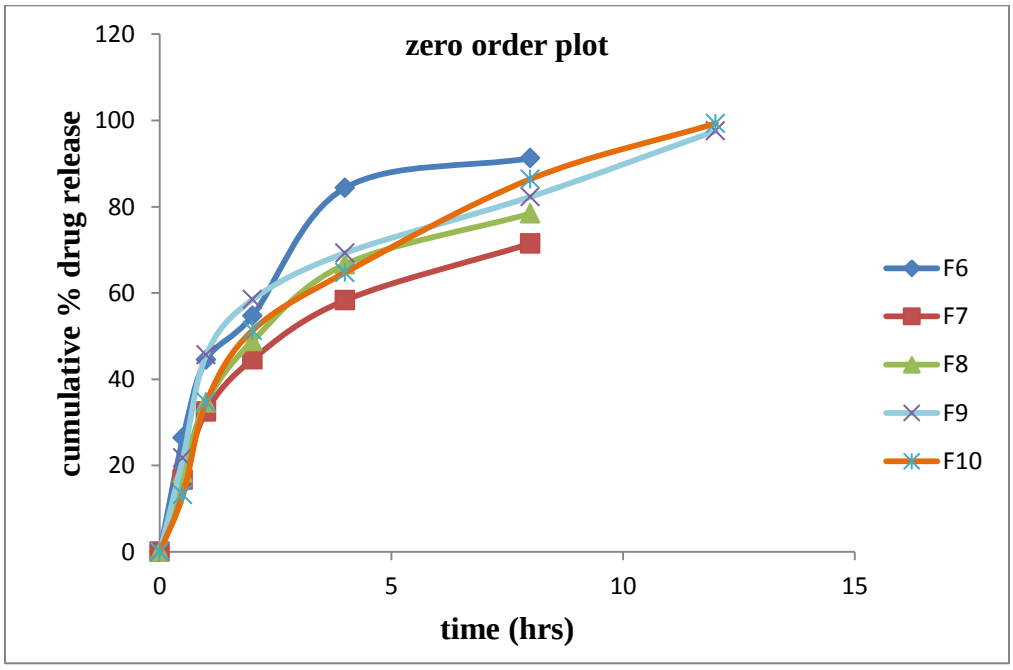

Figure 10: Zero order drug release plots for formulations F6-F10

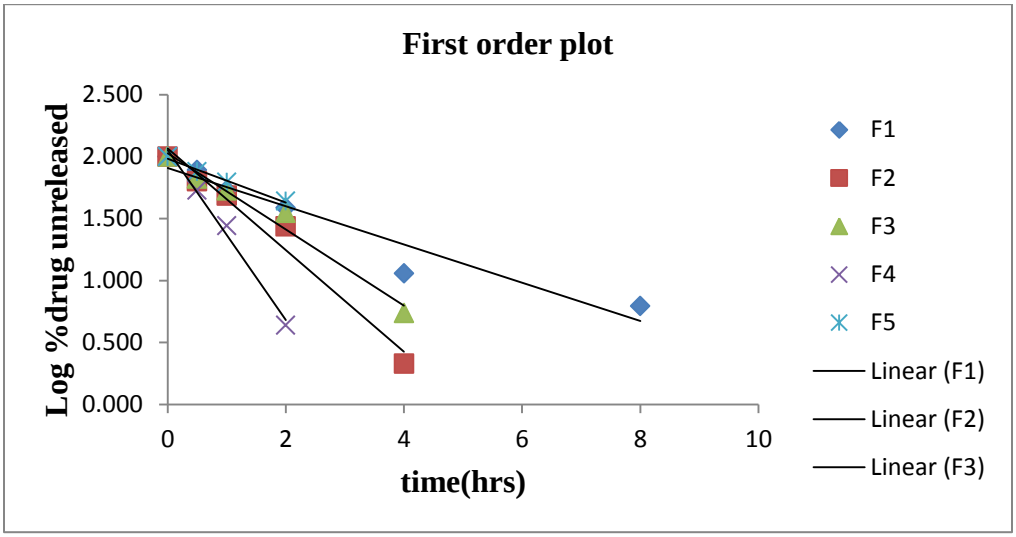

Figure 11: First order drug release plots for formulations F1-F5

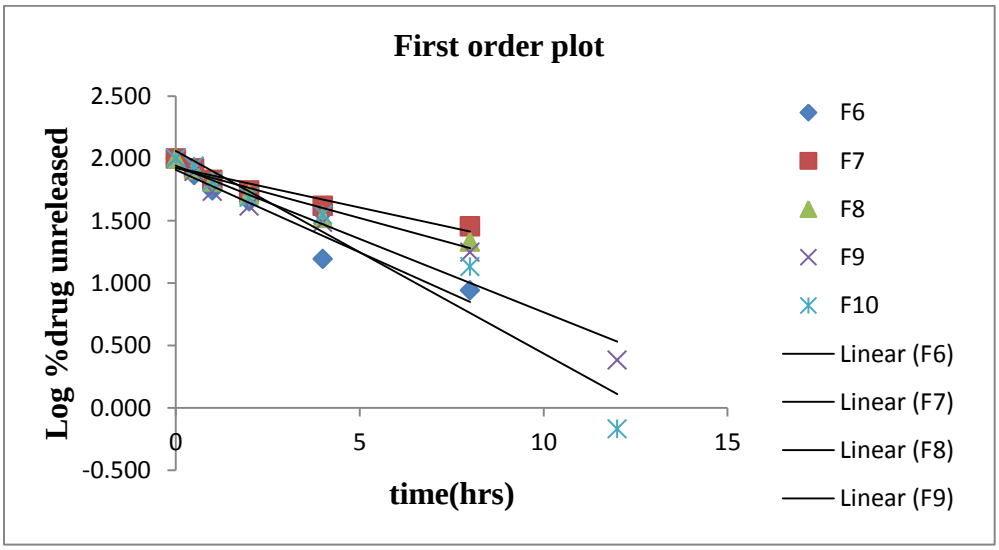

Figure 12: First order drug release plots for formulations F6-F10

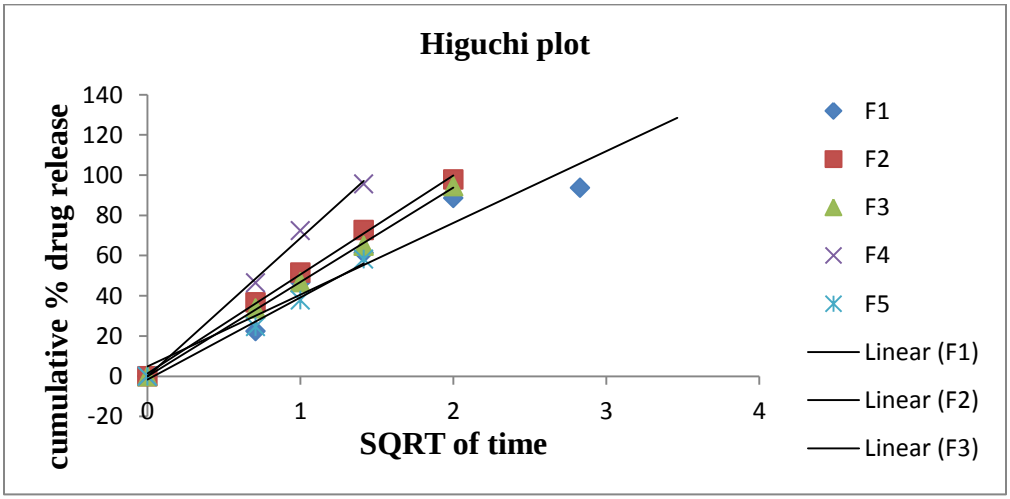

Figure 13: Higuchi plots for the formulations F1-F5

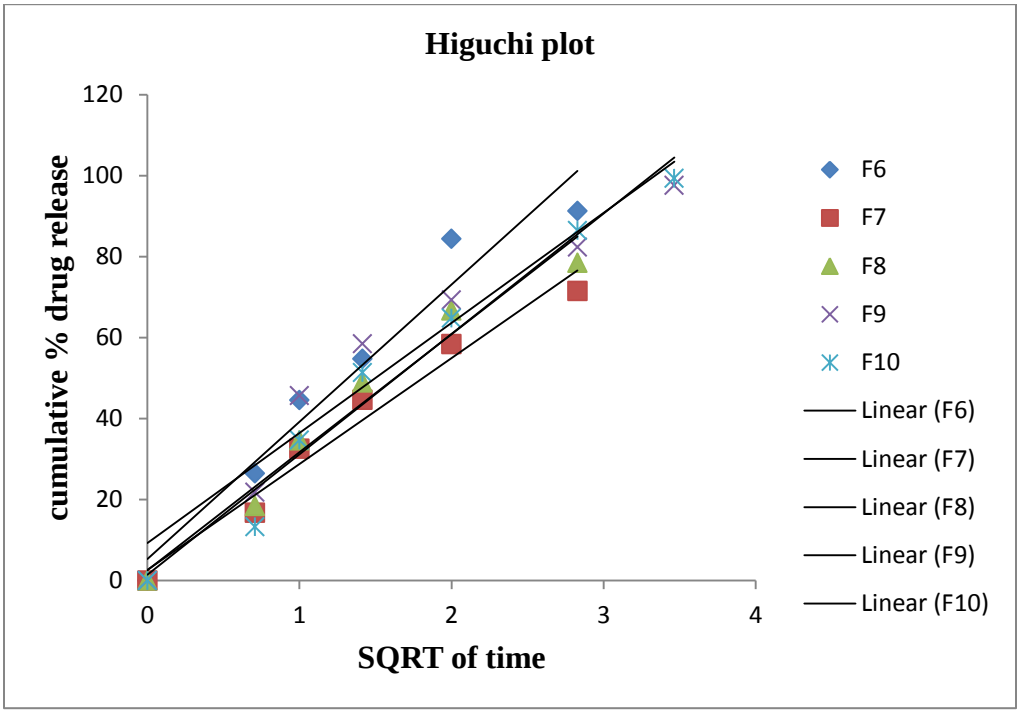

Figure 14: Higuchi plots for the formulations F6-F10

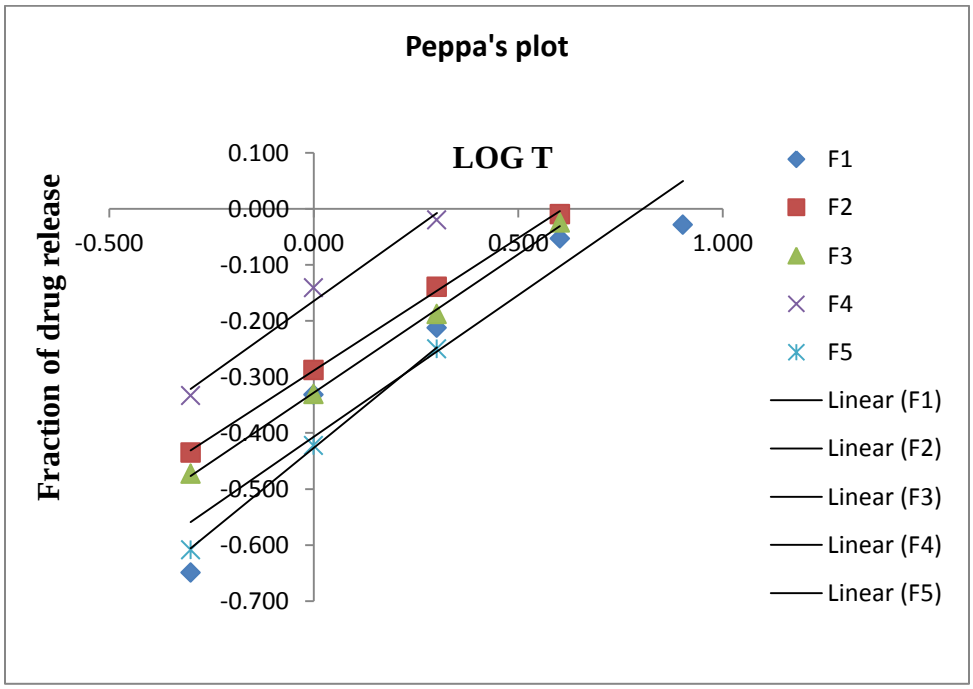

Figure 15: Korsemeyer Peppa's Plots for formulations F1-F5

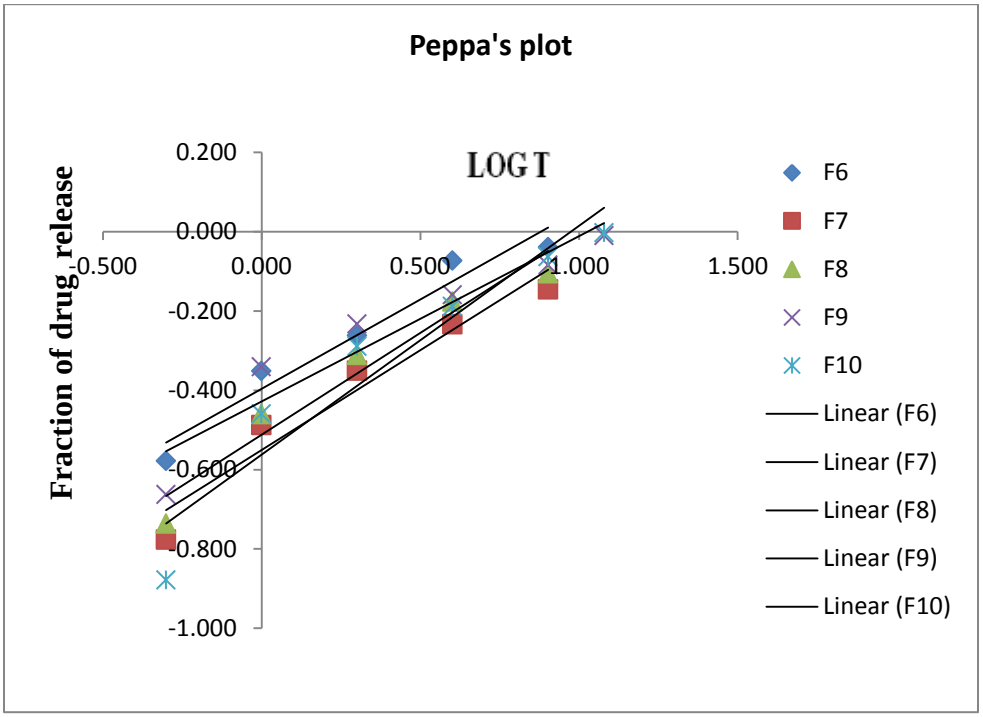

Figure 16: Korsemeyer Peppa's Plots for formulations F6-F10

CONCLUSION

The objective of present study was to develop floating tablets of Pregabalin by using Thermoplastic granulation technique. Floating Tablets of Pregabalin were formulated to increase gastric residence time and there by provides controlled release of drug and improves its therapeutic efficacy. Here hydrophobic meltable binders were used to sustain the release of Pregabalin which is BCS class 1 drug having high solubility and high permeability. Among all the formulations F10 was considered as the optimized formulation which showed more than 95% drug release in 12 hours with good control over the initial release and floating time of more than 14 hours.

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