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Influence of Natural, Synthetic Polymers and Fillers on sustained release matrix tablets of Pregabalin

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Abstract:
The objective of the present study was to develop sustained release matrix tablets of Pregabalin for the treatment of neuropathic pain and epilepsy. The tablets were prepared by wet granulation and formulated using drug with Hydrophilic, hydrophobic, synthetic, natural polymers and 4 different fillers were used. The effect of Polymer concentration, combination and fillers on drug release rate was analyzed for the formulations F-1 to F-17. The tablets were subjected to physicochemical studies, *in-vitro* drug release, kinetic studies and stability studies. The physicochemical properties of tablets were found within the limits. The prepared tablets were analyzed by using FTIR, DSC, SEM and stability studies. Between drug and polymer no interaction were detected from the FTIR and DSC studies. Gel formation and pores formation increased in diameter with time observed from Scanning electron microscope study (SEM). The mechanism of drug release from formulation F-15 was Anomalous (non-Fickian) diffusion. Optimized formulation F-15 was stable after stability studies in accelerated temperature and humidity.

Keywords: Pregabalin, HPMC K100, Locust bean gum, Matrix tablets, Sustained release.

Introduction:

When compared with other route of administration oral route is most generally used route since it is simplest, pain less, safest, cost-effective route of drug administration. [1] Matrix tablet preparation method is uncomplicated approach in designing of sustained release system. Carbopol are synthetic high-molecular-weight polymers of acrylic acid cross-linked with either allylsucroseor allyl ethers of pentaerythritol. Due to existence of carboxylic acid groups in the polymer chain, the Ph of their aqueous solution (1%) ranges from 2.5 to 3.07.An augmented attention has been shown by researchers in the application of Carbopol as matrix formers in oral controlled release dosage forms. [2-4]

Ethyl cellulose is an inert, hydrophobic polymer and is essentially tasteless, odorless, colorless, noncaloric, and physiologically inert. It has been expansively used as a pharmaceutical vehicle in a number of dosage forms .In sustained-release dosage forms. It is used as matrix-forming material. [5-11] Xanthan gum is a high-molecular-weight extracellular polysaccharide produced by fermentation process of gram negative bacterium *Xanthomonas campestris.* Xanthan gum is biodegradable and biocompatible and forms gel in water hence, appears to be gaining appreciation for the fabrication of matrices with controlled drug release characteristics. [12-15]

LBG is extracted from the seeds of the carob tree (Ceratonia siliqua), which is very abundant in the Mediterranean region although its localization also extends to different regions of North Africa, South America, and Asia. The polysaccharide is also referred in the literature by several other synonyms, such as carob bean gum, carob seed gum, carob flour, or even Ceratonia.[16] Hydroxypropylmethylcellulose (HPMC) is hydrophilic cellulose ether commonly used as a pH-independent gelling agent in controlled release preparation [17].

Decrease in drug release was observed from the matrix tablets of hpmck10 0 with Lbg. This might be due to quick hydration on the outer layer of tablet and gelatinous layer formation character of Hpmck100, Hydration, and swelling and gelatinous layer formation nature of Tamarind Seed Polysaccharide. The involvement of synergism between LBG and xanthan gum is also the reason for the decrease in drug release. Tamarind Seed Polysaccharide (TSP) is a galactoxyloglucan (a monomer of mainly three sugars- galactose, xylose and glucose- in a molar ratio of 1:2:3) isolated from seed kernel of Tamarindus indica. TSP is a non toxic, biocompatible and cheap agro-based material which could be safely used for controlled drug delivery systems. Sahoo et al. [18-20] Plastic polymers, e.g., ethyl cellulose and acrylate, which are capable of forming insoluble or skeleton matrices, have been widely used for controlled release of drugs due to their inertness and drug embedding ability. Liquid penetration into the matrix is the rate controlling step in such systems, unless channeling agents are used. [21]

Powder forms, Eudragit RL PO and RS PO have free flowing and direct compressible properties unlike other forms. [22] MCC shows a slower release due to its low solubility in water. Starch 1500 as a filler excipient, in HPMC matrices may bring about retardation effect resulting from interactions between HPMC and starch 1500 that can affect the properties of the gel layer around the tablet, hence showing the slowest drug release in comparison. This slow release may be due to slower penetration of water front towards the center core of the matrix as well as the property of starch to hydrate and form a gel layer barrier due to intramolecular hydrogen bonds in the highly branched amylopectin. [23] Are Insoluble and non swelling filler. The effect of hydrophilic, hydrophobic, synthetic, natural polymers like Hydroxypropyl methylcellulose (HPMC), Ethyl Cellulose(EC), carbopol, eudragit RSPO, eudragit RLPO, locust bean gum, tamarind seed polysaccharide, Xanthan Gum(XG) , fillers like microcrystalline cellulose, starch 1500, dibasic calcium phosphate, on *in-vitro* drug release of Pregabalin were analyzed from the present study.

MATERIALS AND METHODS:

Methods:

Preparation of tablets:

The granules for tablet preparation were prepared according to the formula given in the table no. 1, 2. Granulation is the key process in the production of many dosage forms involving the sustained release of drug from coated or matrix-type particles. A granule is an aggregation of component particles that is held together by presence of bonds of finite strength.

Matrix tablet containing Pregabalin can be prepared successfully by using wet granulation method, using tamarind polysaccharide, HPMC K 100, carbopol 934, xanthan gum, locust bean gum and ethyl cellulose and eudragit RSPO, RLPO polymers as retardant and, microcrystalline

cellulose, starch 1500 and dibasic calcium phosphate as fillers. Essential quantities of drug and polymer were mixed thoroughly, and a sufficient volume of granulating agent (PVP K30) was added slowly. After adequate cohesiveness was obtained, the mass was sieved through 22 mesh. The granules were dried at 50°C for 45minuts and were mixed with talc and magnesium stearate. The tablets were compressed using Mini Press tablet compression machine (Clit jemkey Eng Pvt. Ltd).

Extraction of Tamarind Seed Polysaccharide [24]:

To 20 g of tamarind kernel powder, 200 ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800 ml of boiling distilled water. The solution was boiled for 20 mints under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged at 5000 rpm for 20 minutes. The supernatant was separated and poured into twice the volume of absolute ethanol by continuous stirring. The precipitate was washed with absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60° C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range. The particle size range of 150-75 microns was used for preparation of tablets.

Evaluation of Granules:

Evaluation of physical properties of matrix tablets

The matrix tablets which prepared were evaluated for uniformity of weight and drug content, as per I.P. Friability was determined using Electro lab friabilator. Hardness was measured by using Pfizer hardness tester. Diameter and thickness were measured by Vernier caliper. [25] The result was shown in table no: 3, 4.

Angle of Repose:

The angle of repose of granules was determined by the funnel method. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The diameter of the powder cone was measured the angle of repose was then calculated using the formula,

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

Where, θ = angle of repose

h = height of pile

r = radius of the base of the pile.

Bulk Density:

Bulk density is measured by dropping cylinder (containing powder) on to a wooden surface 3 times from a height of 1 inch at 2 second intervals. The loose bulk density (LBD) and tapped bulk density (TBD) were determined. The tapping was continued until no additional change in volume was noted. LBD and TBD were calculated using the following formula

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index. [26]

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Drug content:

Tablets were individually finely ground in a mortar. Accurately weighed quantity of the powder tablet equivalent to 100mg of the drug was transferred to 100ml volumetric flask dissolve in 100 ml 0.1 N HCL . Aliquots were filtered and assayed spectrophotometrically (UV-Spectrophotometer, Labindia-25UV/VIS

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spectrometer, Mumbai) at 207 nm for Pregabalin content.

Hardness and Friability:

5 tablets from each formulation were subjected to Hardness and Friability which determined by using Monsanto tablet hardness tester. Diameter and thickness were measured by Vernier caliper (5). Friability was determined using Riche Rich Pharm tablet friability test apparatus. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Where, F = Percentage friability

W initial = Initial weight before friability test.

W final = Final weight after friability test.

Weight Variation Test:

Randomly selected ten tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit

$$PD = \frac{W_{avg} - W_{initial}}{W_{avg}} \times 100$$

Where, PD = Percentage deviation,

Wavg = Average weight of tablet, W initial = individual weight of tablet.

***In Vitro* Release Studies:**

In vitro release studies were carried out for all the formulations as per USP-II tablet dissolution tester employing rotating paddle at 50 rpm using 900 ml of Hcl pH 1.2 and phosphate buffer of pH 6.8 as dissolution medium. A 5ml aliquot of sample was withdrawn at 60 minutes. Further samples were collected at 1 h interval up to 12 h. They were filtered and estimated for Pregabalin released using UV-visible spectrophotometer at 207nm and 210 nm. At each time of withdrawal, 5ml of fresh medium was replaced into the dissolution flask. The concentrations were calculated using the standard curve prepared using 0.1N Hydrochloric acid as solvent. The cumulative percentage of Pregabalin released was also calculated.

Seventeen different formulas having different polymers like hydroxyl propyl methylcellulose, tamarind seed polysaccharide, locust bean gum, xanthan gum, ethyl cellulose, eudragit RSPO, RLPO and 4 different fillers were developed to study the effect of combination, concentration of polymer and fillers on drug release.

FT-IR Spectroscopy:

Compatibility between the drug and excipients assessed with an Agilent Technologies, Cary 630 FTIR by using KBR pellet to hold the sample.

Thermal analysis:

Thermal analysis was carried out with a differential scanning calorimeter (DSC, Perkin-Elmer, and Pyris-1). Scanning was performed at a temperature ranging from to 280^{0}C at a heating rate of 10 ^{0}C/min under an atmosphere of nitrogen. The sample weight was 2 - 4 mg and it was sealed in a perforated aluminum pan.

Scanning electron microscopy (SEM)

The surface morphology of the matrix tablets was examined with a scanning electron microscope (JEOL-JSM-840A, Japan).

6.9.4. Stability studies

Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to increase the rate of chemical or

physical degradation of the drug substance or product by using exaggerated storage conditions. Selected formulations were stored at different storage conditions at elevated temperatures such as 25°C± 2°C / 60% ± 5% RH, 30°C ± 2°C / 65% ±5% RH and 40°C ± 2°C / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes.

Results:

When cumulative % drug release plotted versus time it was observed that, for three of the polymers used, an increase in polymer concentration induce a decrease in the release rate. The drug release rate from xanthan gum matrix was found to be less as compared to HPMC K100M. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. Whereas formulation containing ethyl cellulose(F-4 to F-6) gave higher drug release as compared to formulation containing HPMC K100M (F-1 to F-3) and xanthan gum (F-7 to F-9), which may be due to quick hydration of polymer matrix within 1 to 3 hours, after which matrix might get started to erode. It is expected that the developed formulation should have the following theoretical drug release profile, *i.e.*, 96.45% for 10hrs. Formulations F-1 to F-2 and F-4 to F-9 failed to meet the needed theoretical drug release profile. Formulation F3 met the needed theoretical drug release profile and has the sustain action i.e. retarding the drug release so the release is for a long time and thus more bioavailability; for these reasons, it was considered the best formulation among all the nine formulations of this series.

Tablets F-1 to F-17 released 12.00% to % of drug at the end of 1 hour; 98.27%,99.11%, 98.60%, 99.533%,99.077%,98.62%, 99.13%, 99.58%, 99.09%, 99.93%, 99.53%, 99.89%, 99.09%, 98.22%, 99.06%, 98.4% and 98.9% drug at the end of 8 hours,9 hours,10hors, 9 hours,10 hours,11 hours, 9hours,10hours,11hours, 10 hours,11hours,12hours,11hours,11hours,12hours, 12hours,12hours respectively. Incorporation of HPMC K100 along with locust bean gum better retarded the release rate of drug compared to other granulating agents. Optimized formulation F-15 shown superior capacity to control the drug release from the matrix tablets.

The formulated granules are evaluated for angle of repose, compressibility index and drug content. The results of angle of repose and compressibility index (%) ranged from 26.12 ± 1.73 to 32.35 ± 1.81, and8.94 ± 0.61 to 14.11 ± 0.16 respectively. The drug content in a weighed amount of granules of all formulations ranged from 99.99.33 ± 0.11 to 98.10 ± 0.13 %. The average percentage deviation of 20 tablets of each formula was less than ±5%. The hardness and percentage friability of the tablets of all batches ranged from 5.9 ± 0.34 to 6.83 ± 0.35 kg/cm 2 and 0.23 ± 0.4 to 0.37 ± 0.21%, respectively.

Table 1: Tablet composition of different formulations (F-1 to F-12) of Pregabalin sustained release matrix tablets (mg/tablet).

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
DRUG	100	100	100	100	100	100	100	100	100	100	100	100
Locust Bean Gum	-	-	-	100	150	200	-	-	-	-	-	-
Xanthan Gum	-	-	-	100	150	200	-	-	-	-	-	-
TSP	-	-	-	-	-	-	100	150	200	-	-	-
Eudragit RSPO	-	-	-	-	-	-	-	-	-	100	150	200
Eudragit RLPO	-	-	-	-	-	-	-	-	-	100	150	200
Ethyl cellulose	100	100	200	-	-	-	-	-	-	-	-	-
Carbopol 934	100	100	200	-	-	-	-	-	-	-	-	-
HPMC K 100	-	-	-	-	-	-	100	150	200	-	-	-
PVP K30	30	30	30	30	30	30	30	30	30	30	30	30
DCP	-	-	-	-	-	-	-	-	-	-	-	-
MCC	252	152	52	252	152	52	252	152	52	252	52	152

* Quantities were taken in milligrams

Table 2: Tablet composition of different formulations (F-13 to F-17) of Pregabalin sustained release matrix tablets (mg/tablet)

FORMULATION CODE	F13	F14	F15	F16	F17
Drug	100	100	100	100	100
Locust Bean Gum	100	150	200	200	200
Xanthan Gum	-	-	-	-	-
TSP	-	-	-	-	-
Eudragit RSPO	-	-	-	-	-
Eudragit RLPO	-	-	-	-	-
Ethyl cellulose	-	-	-	-	-
Carbopol 934	-	-	-	-	-
HPMC K 100	100	150	200	200	200
PVP K30	30	30	30	30	30
DCP	-	-	-	52	-
MCC	252	152	52	-	-
Starch 1500	-	-	-	-	52
Magnesium stearate	12	12	12	12	12
Talc	6	6	6	6	6

* Quantities were taken in milligrams

Table 3: Tablet properties of formulations F-1 to F-10

Parameters	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Thickness (mm)	4.54 ± 0.023	4.05 ± 0.03	4.18 ± 0.16	4.00±0.02	4.20±0.023	4.28±0.043	3.88±0.36	4.18±0.03	3.61±0.16	4.23 ± 0.03
Hardness (kg/cm^2)	6.0 ± 0.3	6.4 ± 0.2	6.3 ± 0.25	6.4±0.02	6.1 ± 0.25	5.9±0.34	6.1±0.25	6.6±0.12	6.83±0.35	6.1 ± 0.1
Friability (%)	0.26 ± 0.31	0.35 ± 0.31	0.3 ± 0.21	0.24±0.2	0.34 ± 0.41	0.28±0.61	0.32±0.41	0.29±0.12	0.28±0.35	0.30 ± 0.1
Drug content (%)	98.96 ± 0.11	99.09 ± 0.12	98.10 ± 0.134	99.99±0.11	99.01±0.172	98.76±0.14	99.11±0.172	99.49±0.154	98.89±0.214	99.54 ± 0.04

Table 4: Tablet properties of formulations F-11to F-17

Parameters	Formulation code						
	F11	F12	F13	F14	F15	F16	F17
Thickness (mm)	4.42 ± 0.012	3.98 ± 0.024	4.33 ± 0.016	3.56 ± 0.12	3.41 ± 0.14	3.89 ± 0.025	4.0 ± 0.03
Hardness (kg/cm^2)	6.0 ± 0.06	6 ± 0.02	6.6 ± 0.02	6.5 ± 0.34	6.5 ± 0.13	6.3 ± 0.04	6.4 ± 0.05
Friability (%)	0.24 ± 0.1	0.28 ± 0.2	0.25 ± 0.21	0.33 ± 0.61	0.37 ± 0.21	0.23 ± 0.4	0.32 ± 0.21
Drug content (%)	99.50 ± 0.31	99.69 ± 0.131	99.91 ± 0.241	98.62 ± 0.14	99.01 ± 0.241	98.2 ± 0.13	98.45 ± 0.122

Table 5: Friability and Hardness of optimized formulation after stability studies

No. of Days	Formulation F-15					
	Friability (%)			Hardness (Kg/cm²)		
	25⁰C /60% RH	30⁰C /65% RH	40⁰C /75% RH	25⁰C / 60% RH	30⁰C /65% RH	40⁰C / 75% RH
0	0.32	0.39	0.31	6.5	6.5	6.6
15	0.41	0.34	0.41	6.5	6.4	6.5
30	0.47	0.39	0.47	6.4	6.5	6.5
45	0.31	0.47	0.40	6.5	6.6	6.7
60	0.40	0.33	0.38	6.6	6.4	6.5
75	0.35	0.45	0.46	6.4	6.5	6.5
90	0.42	0.38	0.51	6.5	6.4	6.6

Table 6: % Drug release and Drug content of optimized formulation after stability studies

No. of Days	Formulation F-15					
	% Drug release			Drug content (%)		
	25⁰C /60% RH	30⁰C /65% RH	40⁰C /75% RH	25⁰C / 60% RH	30⁰C /65% RH	40⁰C / 75% RH
0	99.06	99.06	99.06	99.30	99.30	99.30
15	99.00	98.98	98.96	99.26	99.24	99.20
30	98.92	98.88	98.80	99.18	99.12	99.04
45	98.72	98.68	98.64	99.10	99.04	99.00
60	98.69	98.56	98.53	98.90	98.84	98.80
75	98.58	98.52	98.48	98.70	98.64	98.60
90	98.40	98.32	98.28	98.50	98.46	98.40

Table 7: Kinetics of drug release from Pregabalin sustained release matrix tablets

FORMULATION	ZERO ORDER R^2	FIRST ORDER R^2	HIGUCHI R^2	PEPPAS	
				R^2	n value
F1	0.996	0.763	0.971	0.998	0.843
F2	0.992	0.752	0.973	0.990	0.841
F3	0.998	0.905	0.939	0.974	0.891
F4	0.992	0.722	0.982	0.992	0.790
F5	0.990	0.903	0.942	0.985	0.840
F6	0.982	0.900	0.922	0.958	0.877
F7	0.973	0.813	0.997	0.991	0.792
F8	0.99	0.750	0.987	0.995	0.834
F9	0.993	0.699	0.955	0.985	0.798
F10	0.995	0.575	0.995	0.977	0.832
F11	0.989	0.690	0.939	0.954	0.753
F12	0.992	0.536	0.976	0.983	0.804
F13	0.992	0.754	0.986	0.998	0.777
F14	0.994	0.763	0.98	0.994	0.818
F15	0.984	0.732	0.940	0.977	0.85
F16	0.978	0.732	0.924	0.970	0.845
F17	0.980	0.771	0.94	0.976	0.856

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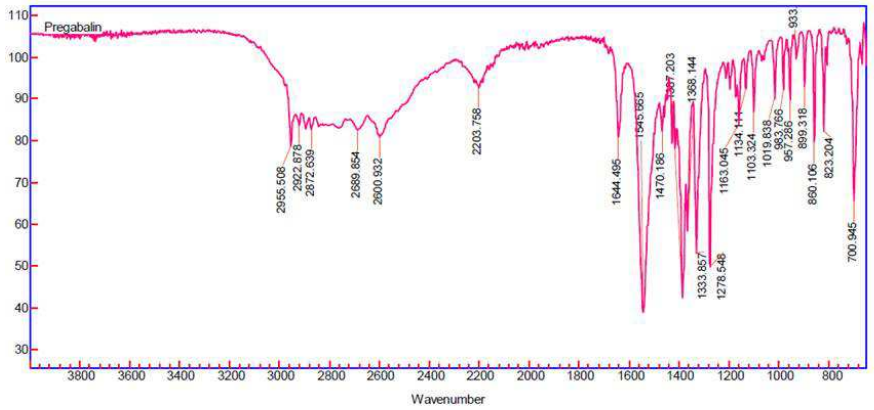


FIG 1: FTIR Spectroscopy of pure drug (Pregabalin)

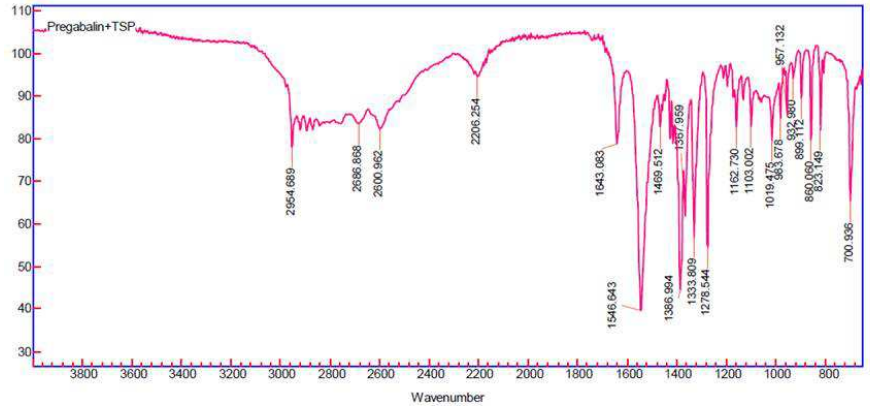


FIG: 2. FTIR spectroscopy of pure tamarind poly saccharide (Tsp) + Pregabalin

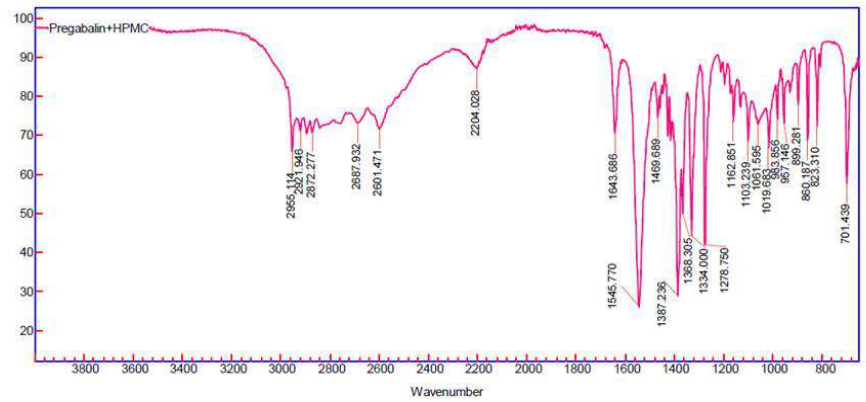


FIG: 3. FTIR Spectroscopy of Hpmc K 100+ Pregabalin

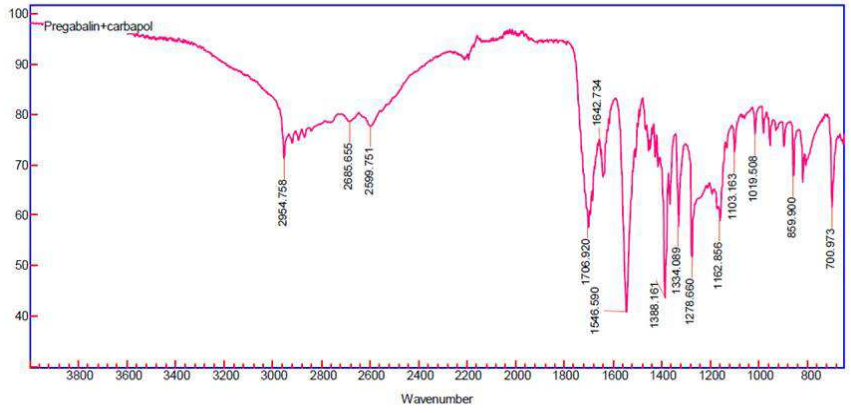


FIG 4: FTIR Spectroscopy of carbopol + Pregabalin

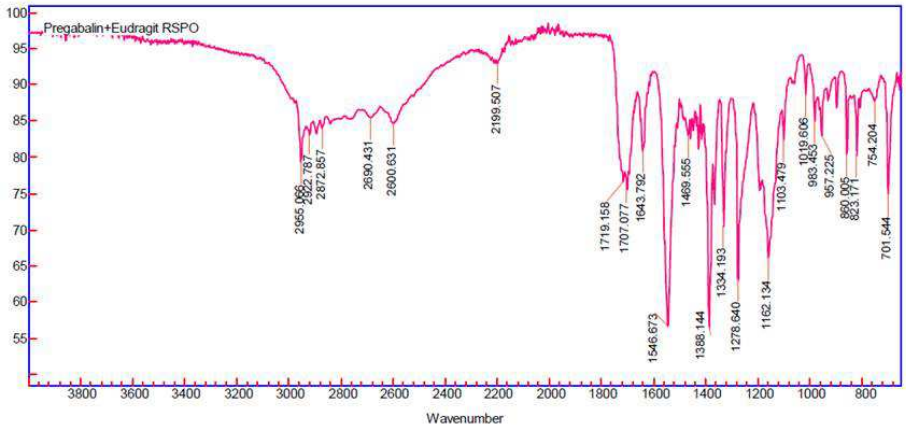


FIG: 5. FTIR Spectroscopy of Eudragit RSPO+ Pregabalin

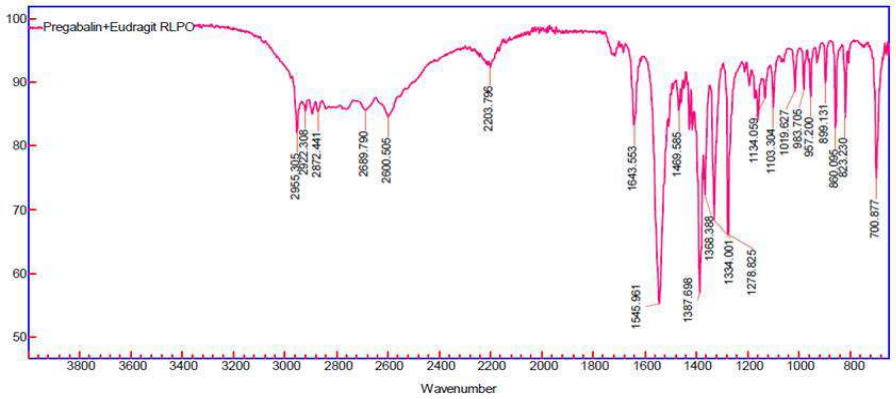


FIG 6: FTIR Spectroscopy of Eudragit RLPO+ Pregabalin

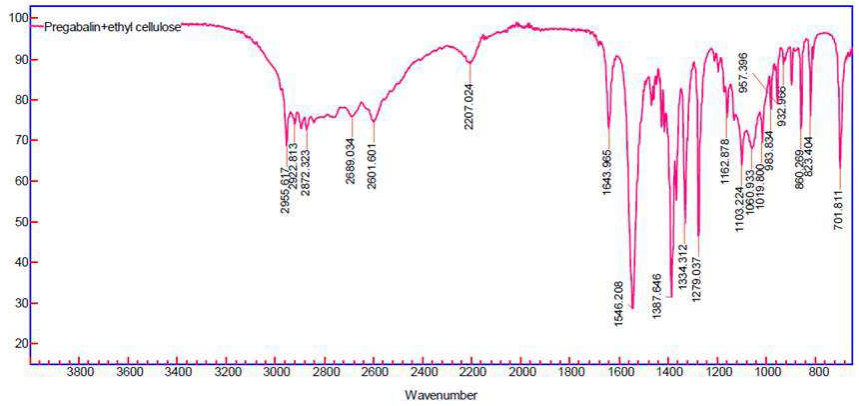


FIG 7: FTIR Spectroscopy of ethyl cellulose + Pregabalin

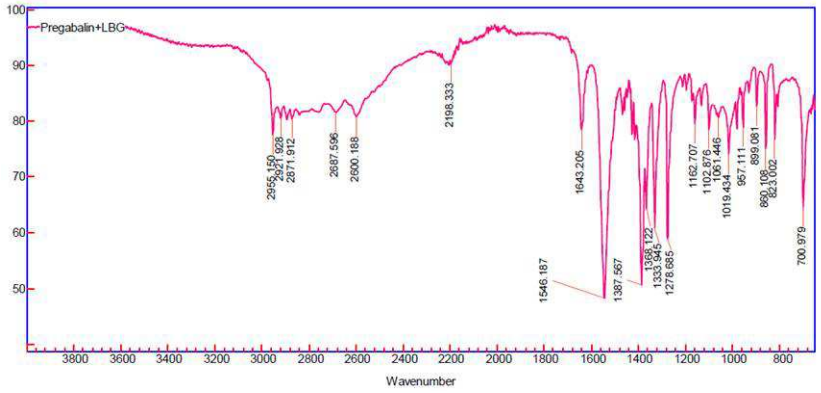


FIG 8: FTIR Spectroscopy of LBG + Pregabalin

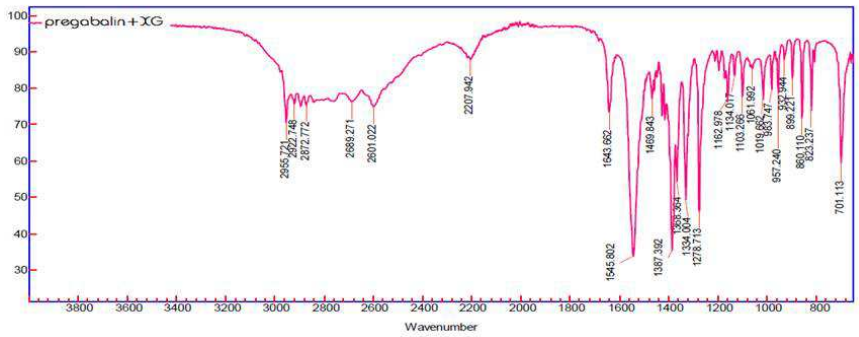


FIG 9: FTIR Spectroscopy of Xanthan gum + Pregabalin

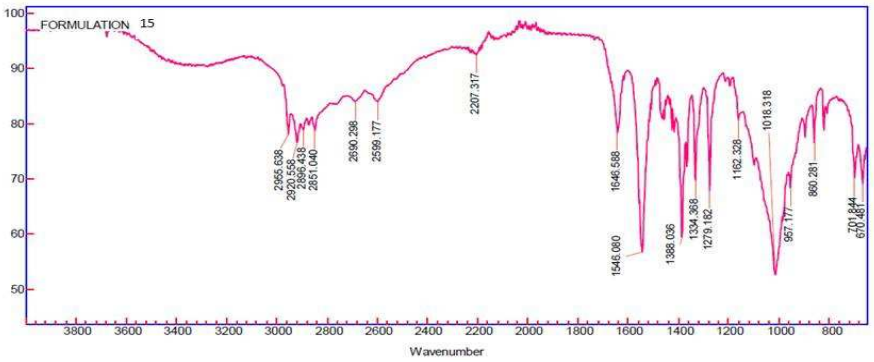


FIG 10: FTIR Spectroscopy of Optimized Formulation F-15

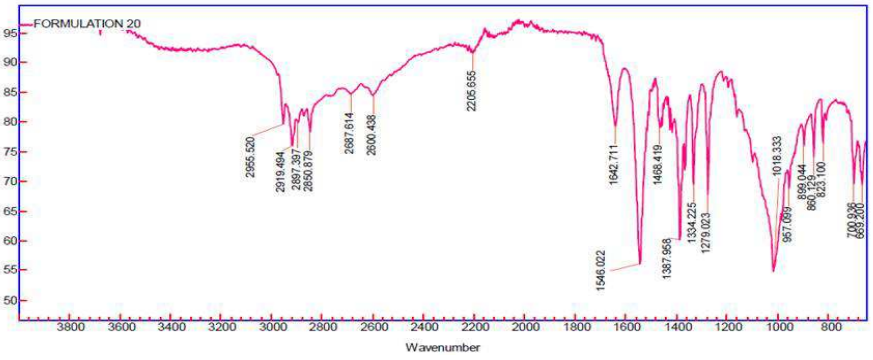


FIG 11: FTIR Spectroscopy of Formulation F-16

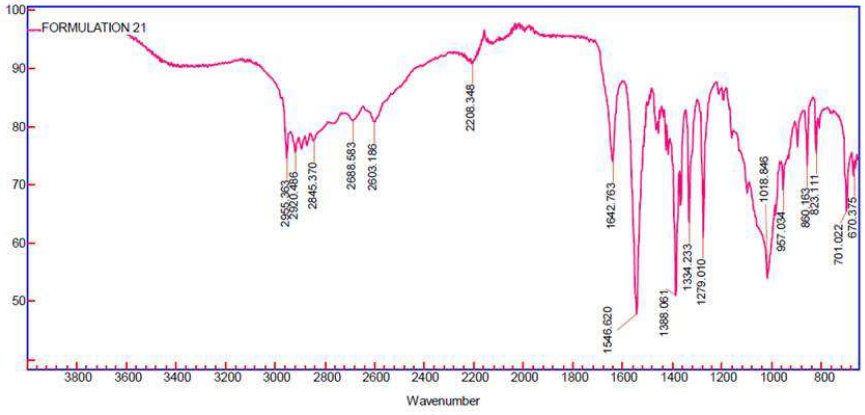


FIG 12: FTIR Spectroscopy of Formulation F-17

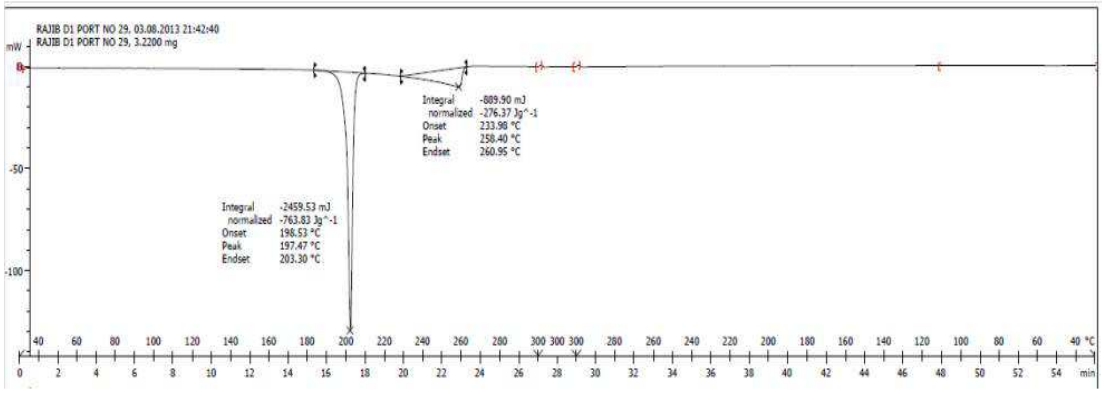


FIG 13: DSC Thermogram of pure Pregabalin

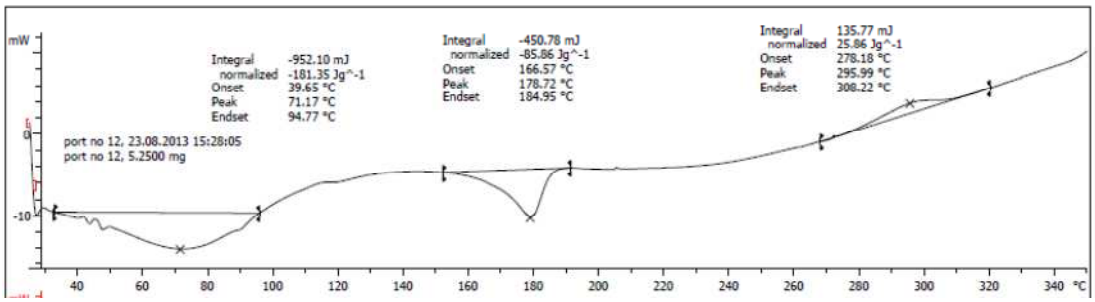
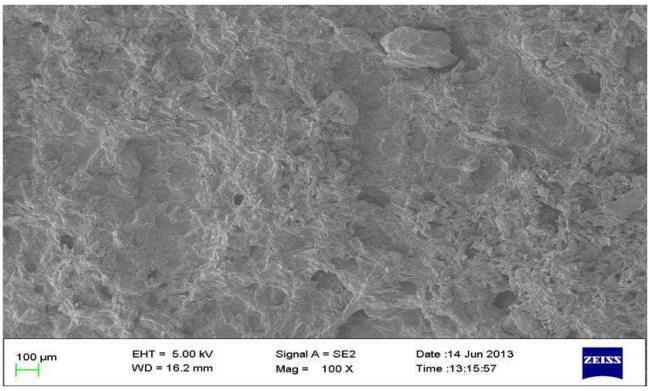
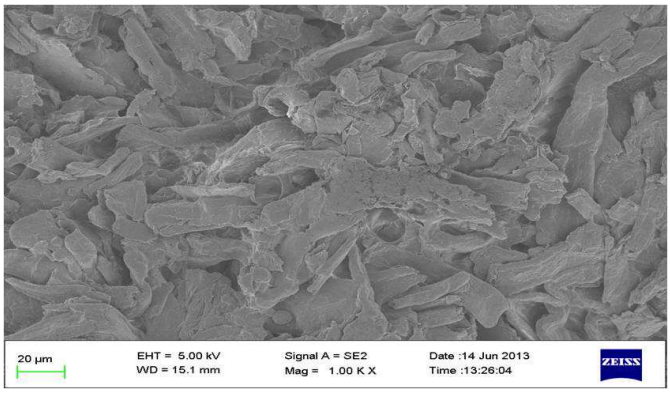


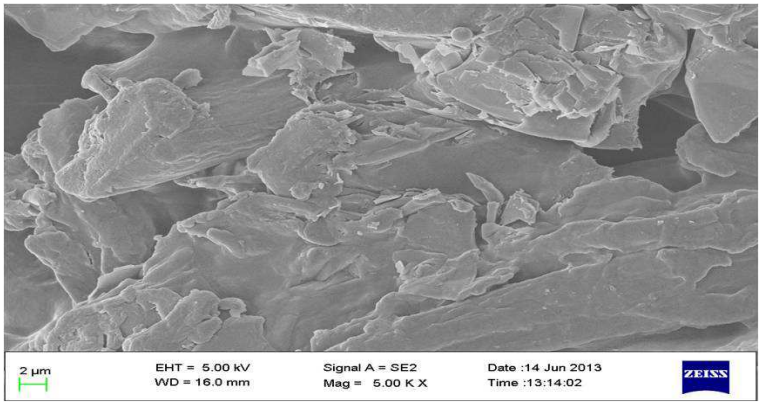
FIG 14: DSC Thermogram of optimized formula F-15



(A) 2 ND HOUR



(B) 6 TH HOUR



(C) 12 TH HOUR

FIG 15: SEM photomicrographs of Optimized matrix tablet (F-15) at the end of 2, 6 and 12TH hours of dissolution study.

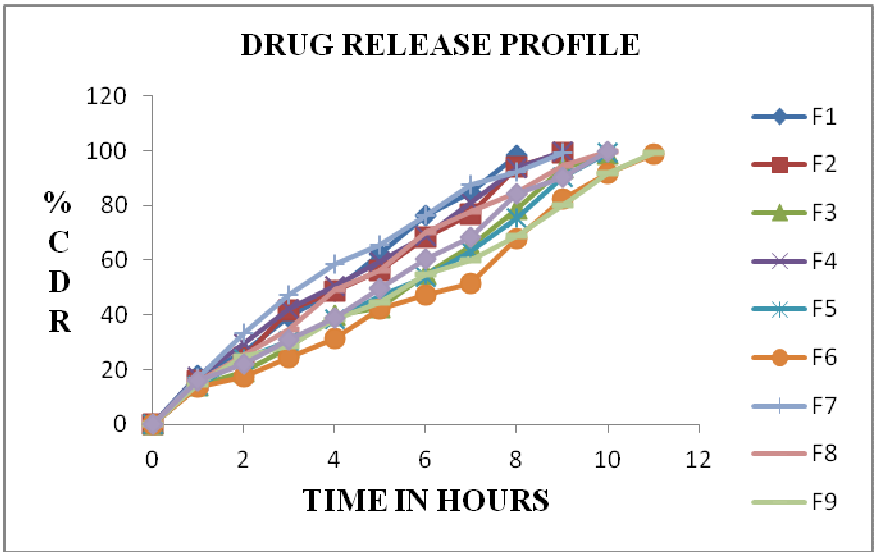


FIG 14: *In Vitro* Dissolution Profile of F-1 to F-10 Formulations

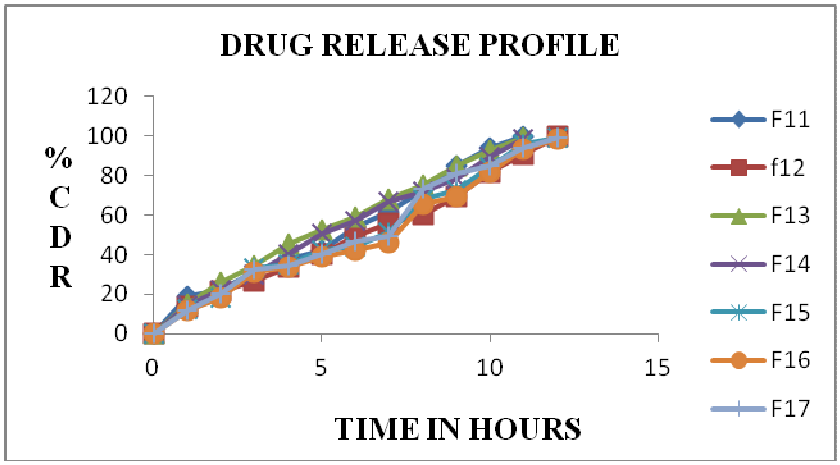


FIG 15: *In Vitro* Dissolution Profile of F-11 to F-17 Formulations

Discussion

The FT-IR Spectrum of pure Pregabalin and its physical mixture with polymers and different excipients are shown in Figure.1 to 12. Pure Pregabalin showed peaks at 2955.508 cm-1 (C–H stretch), 1644.495 cm^{-1} (N–H bend), 1545.665 cm^{-1}(N–O asymmetric stretch), 1470.186 cm^{-1} (C–H bend), 1368.144 cm^{-1} (C–H rock), 1333.857 cm^{-1} (N–O symmetric stretch), 1278.548 cm^{-1} (C–O stretch), 933.038 cm^{-1} (O–H bend) and 933.038 cm^{-1} (O–H bend).Infrared absorption spectrum of formulation F-15, F-20 and F-21 showed peaks at 2955.508 cm^{-1} (C–H stretch), 1644.495 cm^{-1} (N–H bend), 1545.665 cm^{-1}(N–O asymmetric stretch), 1470.186 cm^{-1} (C–H bend), 1368.144 cm^{-1} (C–H rock), 1333.857 cm^{-1} (N–O symmetric stretch), 1278.548 cm-1 (C–O stretch), 933.038 cm-1(O–H bend) and 933.038 cm-1 (O–H bend). As the sharp characteristic peaks of Pregabalin did not change in the formulations with polymer and different excipients, indicating no possible interaction. Hence these release retarding

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materials were selected for formulation of sustained release tablets.

In order to find out drug and excipients compatibility DSC analyses were also performed. Pure Pregabalin displayed sharp endothermic peak at 198°C. The DSC curve of formulation F-15 demonstrated endothermic peak at 179°C due to various concentration of physical mixture. But, in the formulation, there was a slight change in peak temperature (Figure. 14), which might be due to the mixing of the drug and excipients which could have reduced the purity level of each component. DSC results did not show any major interactions.

Granules of different formulations are evaluated for angle of repose, bulk density, tapped density, compressability index value and drug content .The values obtained for angle of repose were observed < 30 indicates good flow properties of granules. The above values of angle of repose were further supported by lower compressibility index values. All these results indicate that the granules passed acceptable flow properties, compressibility and drug content.

The tablets of different formulations were evaluated for thickness, uniformity of weight, drug content, hardness, friability and *in vitro* dissolution. All the formulations showed uniform thickness. In a weight variation test the pharmacopeial limit for the percent deviation for tablets of more than 250 mg is ± 5%. The percentage deviation of all tablet formulations found to be within the above limit and hence all the formulations passed test for uniformity weight as per official requirements. Good uniformity in drug content was found among different batches of tablets and the percentage of drug content is more than 99%.

From the formulations F-1 to F-3, the release rate was decreased in the following order: F-3 < F-2 < F-1. When the polymer concentration of carbopol and ethyl cellulose increased the drug release rate was reduced from the above formulations. The above effect from carbopol 934 is due to hydration, swelling, stronger gel network formation quality and from ethyl cellulose is probably due to less water permeability character. In the case of formulation F-4 to F-6 drug release was decreased when the polymer concentration of xanthan gum and locust bean gum increased. The reason is because of the synergism between LBG and xanthan gum is the most effective and results in a swelling and firm thermo reversible gel formation. [27]

Tablets F-7 to F-9 decrease in drug release was observed with higher concentration of polymers (HPMC K 100 and Tamarind seed polysaccharide). This might be due to quick hydration on the outer layer of tablet and gelatinous layer formation character of HPMCK100 and hydration, swelling and gelatinous layer formation nature of Tamarind Seed Polysaccharide. The results of dissolution studies of these tablets indicates decrease in drug release from the formulation F10 to F-13 by using eudragit RSPO and eudragit RLPO which gave better controlled release for 12 hours. Reason for the above could be because of low permeable nature of eudragit RSPO and greater permeability, more swelling nature and leads to increase the porosity of the matrix of eudragit RLPO.

Incorporation of locust bean gum along with HPMC K 100 in the formulation F-13 to F-15 showed better retarded the release rate of drug compared to all other formulations and drug release was decreased with increased polymer concentration. This might be due to quick

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hydration on the outer layer of tablet and gelatinous layer formation character of HPMC K100, the involvement of synergism between LBG and HPMC K100 gum is also the reason for the decrease in drug release. Formation of a gel layer was obtained from the interaction between the above two polymers.

Effect of fillers like Mcc, Starch1500 and DCP had comparable dissolution profile of Pregabalin. The drug release follows following order MCC>Starch1500>Dibasic calcium phosphate. All the three did not show any major variations from their dissolution profile. The less concentration of different fillers might be the reason for the above effect.

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-17 could be best expressed by zero order equation as the plots showed highest linearity (R^2 : 0.973 to 0.998), than first order release kinetics (R^2: 0.536 to 0.905). The n values obtained from Korsmeyer Peppas plots range from (0.753 to 0.891) indicate that mechanism of release of formulations F-1 to F-21 was Anomalous (non-Fickian) diffusion.

SEM study further established both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet (F-15). SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact pores had formed throughout the matrix and also found formation of gelling structure.

The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

Conclusion:

The use of HPMC K100 with Locust bean gum was highly effective to achieve the sustained drug release for 12 hours from Pregabalin matrix tablets. The kinetics of drug release was paramount explained by zero order equation. The anomalous (non- Fickian) diffusion was found to be the mechanism of release. Association of both diffusion and erosion mechanism of drug release from the matrix tablets were established by SEM studies. Selection of polymer concenctration and combination played major role in retarding efficiency of matrix tablets. It was also examined that the rate of drug release decreases with increase in the matrix tablets. It was concluded from the present exploration that sustained released profile is maintained for an extended periods of time with in safety margin.

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