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FORMULATION DEVELOPMENT AND EVALUATION OF OSMOTIC TABLETS OF PREGABALIN

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Abstract:

The purpose of this study was to formulate & evaluate osmotically controlled drug delivery system of Pregabalin. Pregabalin is use for epilepsy, neuropathic pain and anxiety which belongs to BCS class I with relative elimination half life of 6.3 to 11 hours. Main objective to formulate this system was to achieve zero order release for Pregabalin. The present study was also aimed to develop a system that would reduce the frequency of dosing and thus increase the patient compliance. Total 6 formulations were prepared. In that cellulose acetate was used as a semipermeable membrane. Sodium chloride potassium chloride and mannitol are use as a osmotic agents. FT-IR spectra of the physical mixture show that the drug is compatible with the polymers used. This system was developed in two stages: a) formulation of core tablet & b) coating of tablet and drilling of orifice. Tablets were evaluated for hardness, weight variation and content uniformity while coated tablets were evaluated for in-vitro release study. All the formulations showed good dissolution profiles. Among the all formulations F2 was optimized based on maximum drug release of 99.99% in 24 hrs.

Key words: *Osmotic tablet, Pregabalin, Sodium chloride, Mannitol.*

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INTRODUCTION:

Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipient, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility, etc [1,2]. Osmotic systems show drug release independent to gastric physiological factor as the release of drug from this type of system is guided by osmosis, which itself is independent of pH of environment. Osmotic drug delivery systems can be of various designs like implants, tablets etc [3]. In this group of Control drug delivery system (CDDS) the release of drug molecule from the drug delivery system is activated by some physical, chemical, or biochemical processes.

Osmotic system typically gives a zero order release profile after an initial lag. The release mechanisms are independent on drug concentration. Sustained and consistent blood levels within the therapeutic window. Reduce side effect. Deliveries may be delayed or pulsed if desired. Drug release is independent of gastric pH and hydrodynamic condition. They are well characterized and understood. Delivery rate is independent of agitation outside, including GI motility.

Its main site of action appears to be on the α_2 δ subunit of presynaptic, voltage dependent calcium channels that is widely distributed throughout the peripheral and central nervous system. Binding affinity for the α_2 δ subunit, and potency, is six times more than that of gabapentin [5,6]. Chemically, Pregabalin is (S)-4-amino-3-(2-methylpropyl) butyric acid. Pregabalin having molecular formula $C_8H_{17}NO_2$ & molecular weight: 159.2.

This drug Pregabalin is used for treatment of epilepsy, neuropathic pain and anxiety. Anticonvulsant medications are established treatments for neuropathic pain [7]. The main objective is to develop osmotic tablets of pregabalin by using various osmotic agents like Nacl, KCl, and Mannitol.

MATERIAL AND METHOD:

Material:

Pregabalin was obtained as a gift sample from Richter Themis Medicare Ltd, Vapi, Potassium chloride and Sodium chloride was supplied by Research lab fine chem. Industries, Mumbai. Mannitol and acetone was obtained from Pellav Chemicals & Solvents Pvt. Ltd, Boisar. Cellulose acetate, Microcrystelline celluiose and Mg stearate was obtained from Research lab fine chem. Industries, Mumbai. Dibutyl phthalet was obtained from Vishal Chem, Mumbai. All other reagents and solvents used were of analytical grade.

Preparation of tablet core:

- Microcrystalline cellulose, osmotic agents were weighed according to the given table and softed through 40 mesh sieve.
- To the above blend pregabalin was added and sifted through 18 mesh.
- The sifted material were mixed for 10 min.
- Magnesium Stearate and was weighed and sifted through 40 mesh.
- To the powdered blend, lubricated blend was added and mixed properly.
- The lubricated blend was compressed in the modified punch.

Table No.1: Composition of tablets:

Batch code							
EXCIPIENTS		F1	F2	F3	F4	F5	F6
Core tablet							
Drug (Pregabalin)		150	150	150	150	150	150
Sodium Chloride		125	150	-	-	-	-
Mannitol		-	-	125	150	-	-
Potassium Chloride		-	-	-	-	125	150
MCC		167	142	167	142	167	142
Magnessium Stearate		8	8	8	8	8	8
Total Weight (mg)		450	450	450	450	450	450
Coating							
Cellulose acetate	% w/w	4	4	4	4	4	4
Dibutyl phthalate	% w/v of CA	0.4	0.4	0.4	0.4	0.4	0.4
Acetone		q.s	q.s	q.s	q.s	q.s	q.s

Coating with semi-permeable polymer:
Core tablets were coated by using a coating machine with a pan. A solution of cellulose acetate in acetone at conc. of 4% w/v containing dibutyl phthalate at conc. of 10% of w/v of cellulose acetate, level of plasticizer was used as a coating solution .to the acetone, slowly cellulose acetate added with proper mixing. In between, plasticizer was added dropwise and through mixing was done to dissolve the cellulose acetate. Addition of plasticizer in the coating solution improves film properties like film flexibility. The final coating solution was filtered through 80 mesh sieve. The coating solution was sprayed over the tablet bed by a spray gun till a desired weight gain was obtained on the active core tablets. Later the osmotic pump tablets were dried at 50^{o}C to remove the residual organic solvent.

Evaluation of Pregabalin tablets [9-11]:
Hardness:
Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Pfizer hardness tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures.

Friability:
Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 minutes dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated.

% loss = Initial wt. of tablets - Final wt. of tablets / Initial wt. of tablets x 100

Weight variation test:
For Tablet weighing 200 mg or more, not more than two tablets differ from the average weight by 10 % deviation. The percent deviation in weight variation from average value for all formulation of design batches were within limit. The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in a unit. 20 tablets were taken and average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined.

Thickness and Diameter:
Thickness and diameter of tablets was important for uniformity of tablet size. The thickness and diameter of tablets were determined with the help of vernier caliper. The average diameter and thickness of the tablet was calculated. The test passed if none of the individual diameter and thickness value deviated by ± 5% of the average.

Drug Content:
From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to 200 mg was transferred to 250 ml volumetric flask. 50 ml of pH 6.8 phosphate buffer was added and then the solution was subjected to Sonication for a period of about 30 min. The solution was made up to 250 ml with 6.8 phosphate buffer.The solution was filtered and suitable dilutions were prepared with pH 6.8 phosphate buffer and then drug content was estimated by recording the absorbance at 210 nm by using UV-visible spectrophotometer.

In vitro Dissolution Studies
Medium : 0.1 N HCl (pH 1.2), Phosphate buffer (pH 6.8)
Apparatus : USP-type 1 (Basket)
RPM : 50
Temperature: 37^{o} ±0.5^{o} C
Volume : 900 ml

Procedure:
The release of Pregabalin from the prepared tablets was performed using a dissolution tester apparatus 1 (Basket). Studies were carried out at 37 ± 0.5 °C in 900 mL of 0.1 N HCl for a period of 2 h followed by release in phosphate buffer pH 6.8 (0.2 M) for Specific time interval at rotation speed of 50 rpm. Five-milliliter samples were taken. The withdrawn samples were filtered through millipore filter (0.45 µm) and UV-analyzed for percent Pregabalin at 210 nm for 0.1 N HCl and phosphate buffer (pH 6.8), respectively.

Kinetics of drug release [12]
'In vitro' dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence. Several theories or a kinetic model describes drug dissolution from sustained and modified release dosage forms.

The quantitative interpretation of the values obtained in dissolution assay is facilitated by the usage of generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms.

In most cases the theoretical concept does not exist and some empirical equations have proved to be most accurate or appropriate. The kind of drug its polymorphic form, crystallinity, particle size, solubility and amount in that pharmaceutical dosage form can influence the release kinetics. A water soluble drug incorporated in a matrix is mainly released by diffusion while for low water soluble drug the self-erosion of the matrix will be the principle release mechanism.

Accelarated Stability Studies [13]:

On the basis of In vitro evaluation of all the formulation batches for the various parameters, formulations were packed in thick aluminum foil and stored in ICH certified stability chambers for the accelerated stability studies. The tablets were stored in the stability chamber at the controlled conditions of temperature and relative humidity. The stability of the tablets was studied for the duration of 30 days, 60 days, 90 days at temperature $40^0C \pm 2^0C$ and 75% ± 5% relative humidity and room temprature. The tablets was then evaluated for various parameters viz. weight variation**,** thickness,diameter, hardness, friability, drug content and release studies.

RESULT AND DISCUSSION:

The compatibility of the drug and polymer was studied by FTIR. The IR spectra of drug and polymer mixture shows the major characteristic absorption bands of the polymer NaCl, KCl and Mannitol with negligible difference of absorption band values. So, FTIR spectra show there is no change in the nature and position of absorption bands which proves that there is no chemical reaction between Pregabalin and NaCl, KCl and Mannitol.

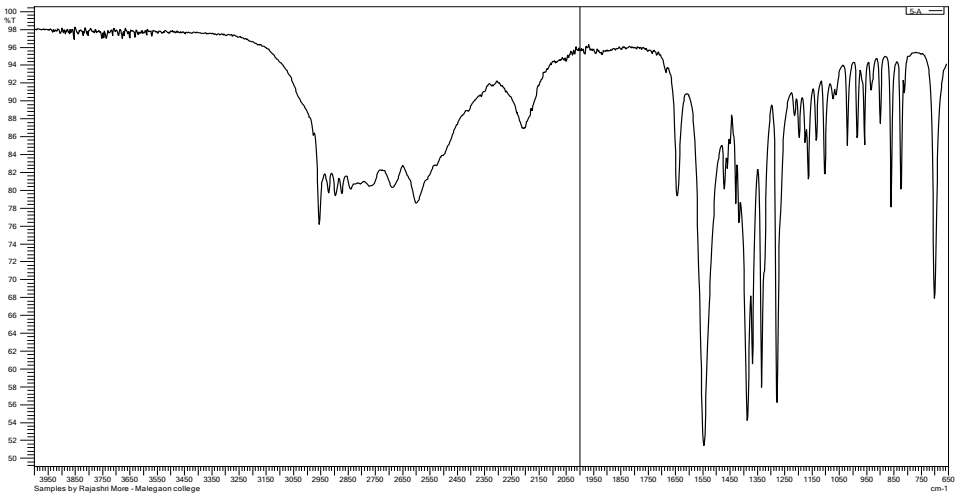

Fig 1: IR Spectrum of Pregabalin:

Characteristic peak of pregabalin

Functional group	Characteristic peak	Observed peak
C-H Stretching	3000-2850	2953
N-H bending	1640-1550	1550
-CH- bending	1465	1465
C-O	1300-1000	1276
C-N (amine)	1350-1000	1330

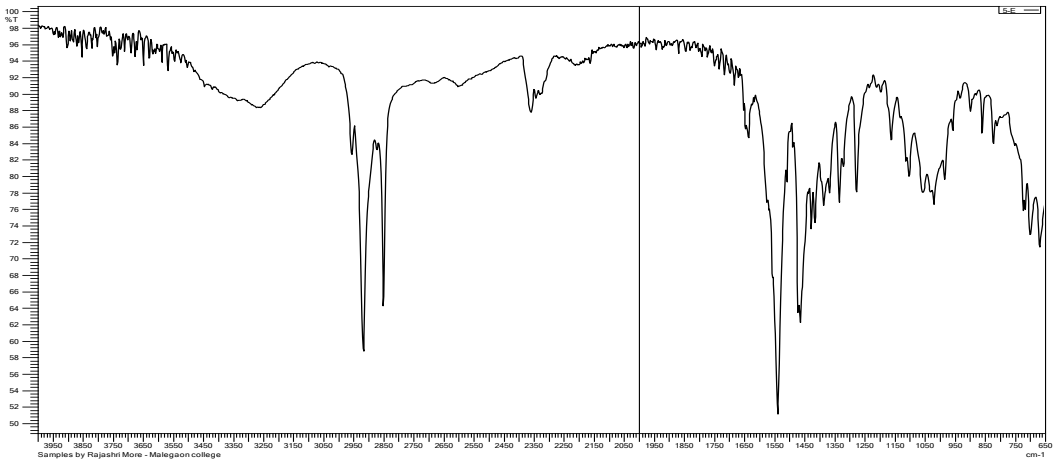

Fig 2: IR Spectrum of Pregabalin + Other excipient:

Table No 2: Characteristic peak of pregabalin + Excipient

Functional Group	Characteristic peak	Observed peak
C-H Stretching	3000-2850	2916
C=O Acid	1725-1700	1716
N-H Bending	1640-1550	1550
C-N Amine	1350-1000	1276

IPQC results of formulation batch F1, F2, F3, F4, F5, F6.

Table No. 3: IPQC results of formulation batch F1, F2, F3, F4, F5, F6.

Batch No	F1	F2	F3	F4	F5	F6
Bulk Density (gm/ml)	0.42± 0.2	0.40± 0.4	0.44± 0.2	0.42± 0.3	0.43± 0.2	0.42± 0.4
Tapped Density (gm/ml)	0.50± 0.2	0.47± 0.3	0.52± 0.3	0.49± 0.4	0.51± 0.2	0.49± 0.3
Carr's Index (%)	16	14.89	15.38	14.28	15.67	14.28
Housner Ratio	1.19	1.175	1.18	1.16	1.18	1.16
Angle of Repose	23.19 ± 0.56	23.80 ± 0.89	24.56 ± 0.46	26.56 ± 0.65	22.38 ± 0.36	23.62 ± 0.45

Post compression and coating parameters:

Table No. 4: Post compression and coating parameters:

Batch code	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Thickness in (mm)
F1	5.2± 0.35	450 ± 0.36	0.22	4 ± 0.38
F2	5.4± 0.47	451 ± 0.30	0.33	4 ± 0.40
F3	5.0± 0.26	452 ± 0.42	0.37	4 ± 0.24
F4	5.5± 0.49	449 ± 0.39	0.41	4 ± 0.12
F5	5.4± 0.21	448 ± 0.49	0.28	4 ± 0.23
F6	5.6± 0.49	450 ± 0.13	0.30	4 ± 0.48

Table No. 5: Post compression and coating parameters:

Diameter in (mm)	Drug content (%)	Initial wt. (mg)	Final wt. (mg)	% wt. gain
11 ± 0.28	99.65	450	487	8.22
11 ± 0.18	99.05	451	489	8.42
11 ± 0.34	99.4	452	491	8.62
11 ± 0.15	99.2	449	490	9.13
11 ± 0.24	99.6	448	488	8.92
11 ± 0.41	99.0	450	491	9.11

It is evident from the above table that all the trial formulations comply with the standard specification mentioned in the Indian Pharmacopoeia for average weight and weight variation and friability. Also the thickness and hardness parameters of the prepared tablets complied with the in house specifications.

Dissolution test:

Table No. 6: % drug release of formulation batch F1, F2, F3, F4, F5, F6.

Time in Hrs.	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	13.2	9	11.28	9.84	12.10	10.60
2	19.99	16.24	16.98	15.53	15.90	18.05
3	25.77	23.42	28.35	25.58	21.99	23.43
4	31.16	27.74	32.57	32.55	25.83	28.84
5	36.13	35.34	38.01	41.01	32.69	36.55
6	43.17	44.89	42.66	50.59	40.07	43.12
7	50.49	50.78	48.53	61.10	43.38	50.03
8	59.09	60.41	60.08	72.57	56.60	58.15
12	72.85	71.30	73.96	79.68	66.99	70.11
16	79.61	81.77	80.73	85.03	77.56	79.06
20	86.04	89.30	88.61	90.06	85.42	87.05
24	97.42	99.99	96.36	98.15	95.60	97.96

The dissolution study for all formulations F1, F2, F3, F4, F5, F6 could passed the dissolution test. The % drug release data for formulation F1, F3, F5 was found to be 97.42, 96.36, and 95.60, respectively. The % drug release data for formulation F2, F4, F6 was found to be 99.99, 98.15, and 97.96 respectively. In this case, the dissolution profile of F2 99.62% drug release for 24 hrs. So those, formulation F2 demonstrate excellent % drug release.

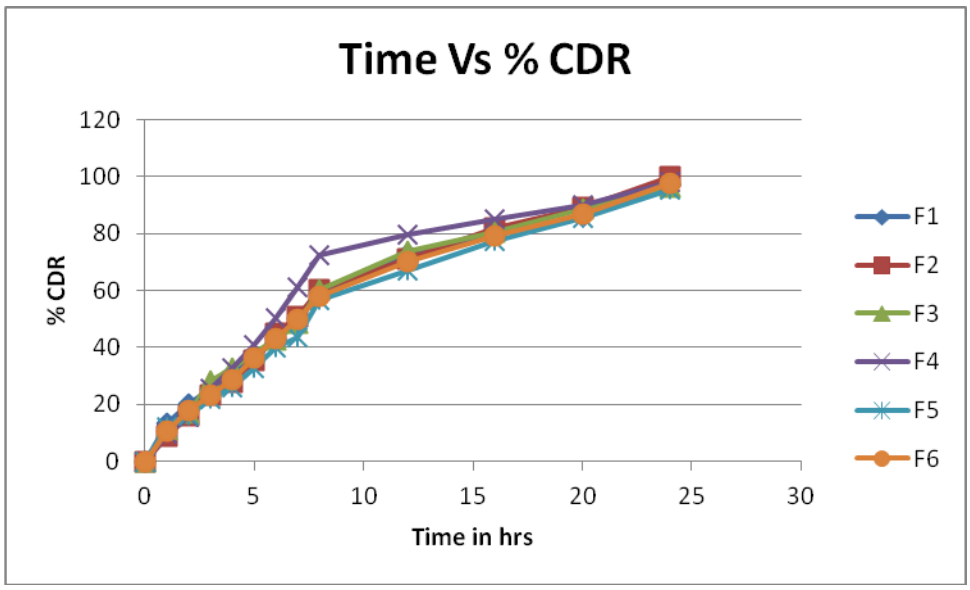

Fig 3: Time Vs % CDR

Table No. 7: Value of rate constants (k) and correlation coefficient (R) for osmotic tablets of Pregabalin

Batch code	Zero order	First order	Higuchi Model	Korsemeyer peppas	
				(R^2)	(n)
F1	0.977	0.964	0.953	0.987	0.653
F2	0.998	0.676	0.974	0.979	0.768
F3	0.965	0.896	0.952	0.981	0.695
F4	0.952	0.923	0.947	0.941	0.756
F5	0.931	0.955	0.957	0.982	0.703
F6	0.972	0.926	0.988	0.985	0.713

Zero order kinetics:

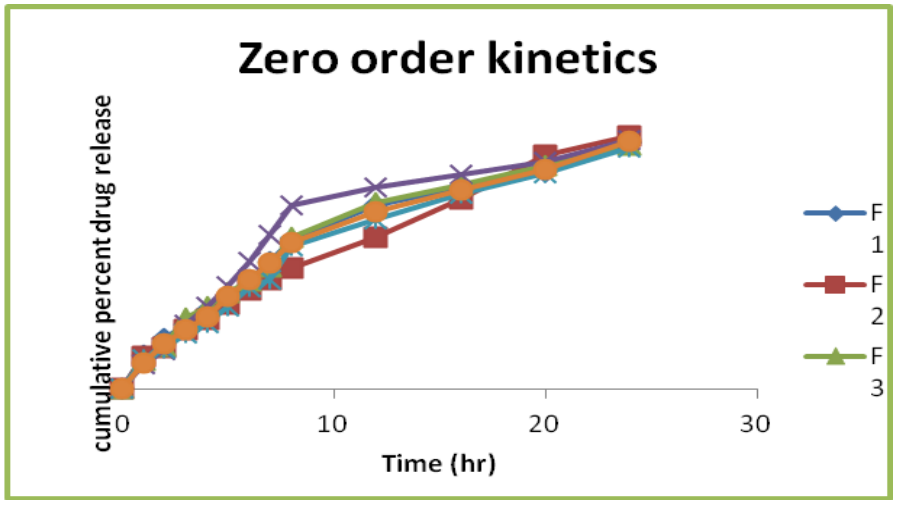

Fig 4: Zero order kinetics

First order kinetic

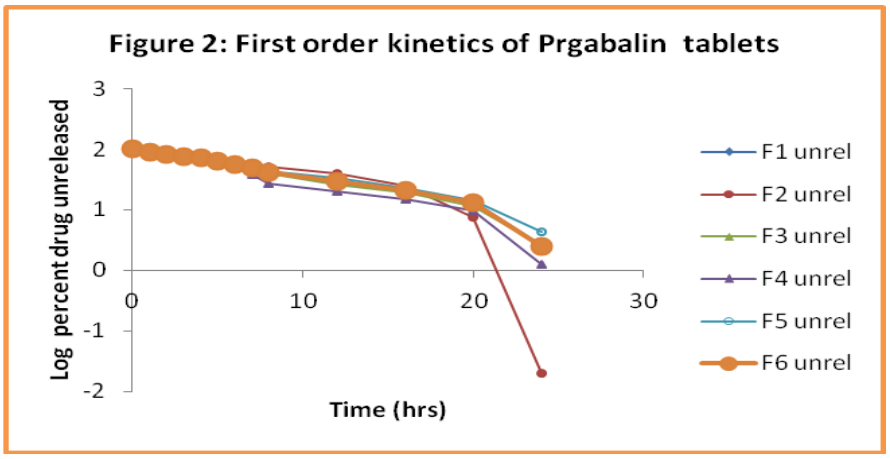

Fig 5: First order kinetics

Higuchi plot:

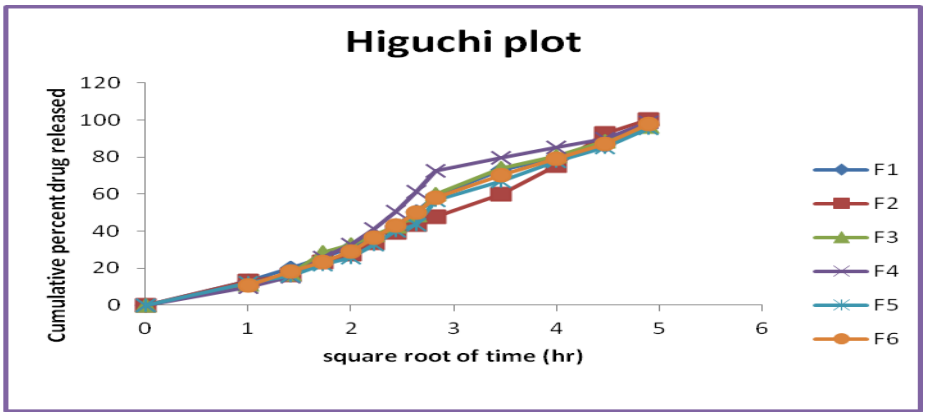

Fig 6: Higuchi plot

Korsmeyers and peppas mode

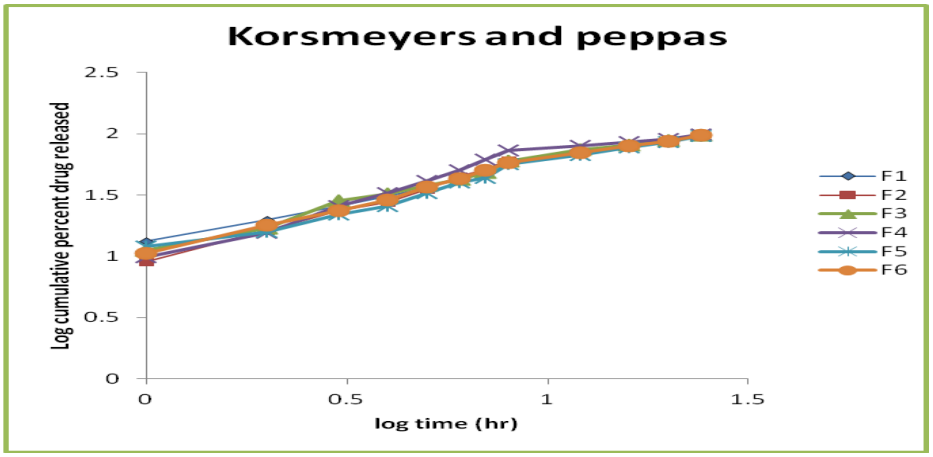

Fig: 7 Korsmeyers & peppas plot

The plots of % cumulative drug release v/s time, log % drug remaining v/s time, % drug release v/s square root of time, log % drug remaining v/s log time were drawn and represented graphically in Fig.No.17-19 respectively.

The regression coefficient of determinations (r^2) were listed in Table No.5 The coefficient of determination that the release data was best fitted with zero order kinetics, Higuchi equation explains the diffusion controlled release mechanism. All formulations indicating non-fickian of drug through tablets.

Stability studies:

The stability studies were carried out on optimized formulation of Osmotic tablet (F2). Samples were stored at 40 ± 2ºC and 75 ± 5 % RH for three months (Climatic zone IV condition for accelerated testing) to access their stability. After interval of 3 month, samples were withdrawn and analyzed for hardness, Dissolution study.

Table No. 8: Stability results of formulation batch F2 at 40 ± 2^0C and 75 ± 5 % RH

Parameters	1 month	2 month	3 month
Hardness (Kg/cm^2)	5.3	5.4	5.5
Thickness (mm)	2 ± 0.35	2 ± 0.35	2 ±0.35
Average weight (mg)	451	451	450
Dissolution test %	99.65	99.05	99.4

CONCLUSION:

The present work was aimed at formulating a solid dosage form system (tablets) for Pregabalin using the principles of osmosis which will bring down its dosing frequency to once a day and at the same time produce a zero-order release system. Release rate of pregabalin from osmotic tablets was dependent on the concentration of osmogen used. It was also concluded that increased concentration of osmogen in the formulation gives increased the release of the drug. Among the different formulations prepared in this study, formulation F2 was shown better results for percentage drug release It showed an almost perfect zero order release and almost 100% release after 24 hours.

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