Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 1, 2013

Research Article

DESIGN AND CHARACTERIZATION OF TWICE DAILY MINI-TABLETS FORMULATION OF PREGABALIN

NOORANA TEHSEEN[1], VINAY RAO[2], MOHD ABDUL HADI[3]*

[1]Department of Pharmaceutics, Trinity College of Pharmaceutical sciences, Pedapalli 505172, Karimnagar, Andhra Pradesh, India, [2]Institute of Pharmaceutical Sciences, 205, Mamatha Estate, Allwyn Cross Roads, Miyapur, Hyderabad. A.P, [3]*Department of Pharmaceutics, Bhaskar Pharmacy College, (J.B.I.E.T), Yenkapally (V), Moinabad (M), R.R District, Hyderabad-500075, India. Email: hadi.lcp@gmail.com

Received: 01 Dec 2012, Revised and Accepted: 06 Jan 2013

ABSTRACT

Objective: Pregabalin is used for treating pain caused by neurologic diseases such as neuralgias as well as seizures. The starting recommended dose for postherpetic neuralgia is dosing at 75 mg two times a day or 50 mg three times a day (150 mg/day). The half-life of pregabalin is 5-6.5 hrs. So, in order to improve the half-life and bioavailability we have designed twice daily mini-tablets formulation of pregabalin.

Method: The system comprises of 15 matrix mini-tablets weighing 25 mg encapsulated in HPMC capsule (size1). For achieving the sustain release profile, various viscosity grades of Hydroxy propyl methyl cellulose polymer (HPMC K4M, K15M, K100M) were used. The mini-tablets were prepared by direct-compression method. The prepared mini-tablets were subjected for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies. Stability study carried out as per ICH guidelines for three months.

Results: The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. All the post-compressional parameter evaluated were within acceptable limits. The *in-vitro* performance of our best mini-tablets formulation showed the desired behavior, nearly 99.57 % of drug was sustained for a period of 12 hrs. FTIR results revealed that there was no interaction between dug and other excipients. The stability study revealed that the formulations were found to be stable.

Conclusion: From this, study it can be concluded that, matrix mini-tablets of pregabalin along with HPMC can be used to improve its half-life and improve its bio-availability.

Keywords: Pregabalin, Matrix mini-tablets, HPMC Capsule, Direct-compression method.

INTRODUCTION

Over recent years, controlled release combination products have become increasingly popular within the pharmaceutical industry. A number of products have reached global markets and several high-profile brands have generated considerable revenues. Significant advances have been attained in developing and commercializing oral controlled release products[1]. Delayed drug delivery system (DDS), zero-order DDS, and site-specific DDS are focuses of oral controlled-release solid dosage forms for researchers[2].

The term Modified release drug product is used to describe products that alter the timing and/ or the rate of release of the drug substance. Whereas the Extended release dosage forms allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate release form. Extended release dosage forms are formulated in such manner as to make the contained drug available over an extended period of time following administration. Expressions such as controlled release, prolonged action, repeat action and sustain-release have also been used to describe such dosage forms. A typical controlled release system is designed to provide constant or constant drug levels in plasma via reduce fluctuations via slow release over an extended period of time [3].

Controlled release capsules often containing plurality of coated pellets or mini-tablets is yet another category of solid oral formulation that offers analogous therapeutic benefits. A relatively more recent approach that has come into existence is the one that combines the features of both controlled release tablets and modified release capsules in one dosage form [4]. A multifunctional and multiple unit system for oral use can be developed by filling versatile tablets in a hard capsule. This can be developed by preparing Rapid-release Mini-Tablets (RMTs), Sustainedrelease Mini-Tablets (SMTs), Pulsatile Mini-Tablets (PMTs), and Delayed-onset Sustainedrelease Mini-Tablets (DSMTs), each with various lag times of release. Based on the combinations of mini-tablets, multiplied pulsatile drug delivery system (DDS), site-specific DDS, slow/quick DDS, quick/slow DDS, and zero-order DDS could be obtained **[5,6]**. The concept of this technology is characterized by the fact that the dose is administered as a number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits **[7]**.

Multi-particulate (MP) modified release drug delivery systems have several performance advantages vs. single unit dosage forms. After ingestion, MP units are released from the capsule in the stomach, predictably transit to the small intestine and spread along the gastrointestinal tract resulting in a consistent drug release with reduced risk of local irritation. MP formulations generally have a more reliable *in-vivo* dissolution performance when compared to a single unit dosage form, resulting in more uniform bioavailability and clinical effect [8].

Pregabalin S-(3)-amino methyl hexanoic acid, is a structural analogues of γ-amino butyric acid (GABA) (see Fig. 1 for chemical structure). They constitute an important group of compounds that are used in the treatment of epilepsy and neuropathic pain. It is a white and crystalline solid. It is soluble in water and both acidic and basic aqueous solutions. Pregabalin has been studied for use in variety of disorders, including monotherapy in refractory partial seizures, diabetic neuropathy, surgical dental pain and other pain syndromes, post therapeutic neuralgia and social anxiety disorders. Pregabalins innovator is Pfizer-global and appears world wide under the brand name lyrica. The half-life of pregabalin is 5-6.5 hrs [9]. The present work describes such delivery system, which will improve the biological half-life and provides all the advantages of Multiple unit drug delivery system, thus improving patient compliance.

The major objectives of this study was to develop and to evaluate encapsulated mini-tablets systems, in order to achieve desired target product profile (DPP) for a period of 12 hours so that the starting recommended dose for postherpetic neuralgia dosing at 75 mg two times a day (150 mg/day) [10,11] can be given.

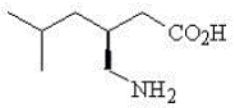

Fig. 1: Chemical structure of pregabalin

MATERIALS AND METHODS

Pregabalin was obtained as a sample from IPS Institute, Hyderabad, HPMC K4M, HPMC K15M, HPMC K100M and PVP K 30 were obtained from FMC Biopolymer, Avicel PH 102 and Aerosil was purchased from SD Fine Chemicals, Mumbai, Magnesium stearate was purchased from Himedia Chem Lab, Mumbai and HPMC Capsules were obtained as a gift sample from ACG Associated capsules Pvt, Ltd.Mumbai.

Experimental Methods

Drug-excipient compatibility studies [12]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the pre-formulation stage during the development of solid dosage form. Therefore, the pure drug and the formulations mixed with polymers were subjected to infra-red (IR) studies.

Fourier Transform Infrared (FTIR) spectral analysis

The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by taking 2 mg sample in 200 mg KBr (Perkin Elmer, spectrum-100, Japan). The scanning range was 400 to 4000 cm^{-1} and the resolution was $1cm^{-1}$. This spectral analysis was employed to check the compatibility of drugs with the excipients used.

Preformulation studies

Micromeritic properties [12]

Evaluation of granules

Angle of repose

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2 cm above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation:

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

Where, θ is the angle of repose

h is height of pile

r is radius of base of the pile

Bulk density and tapped density

Both loose bulk density and tapped bulk density were determined. A quantity of 2gm of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 10ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals. The tapping was continued until no further change in the volume was noted LBD and TBD were calculated using the following formulas:

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.

Carr's index (%) = [(TBD-LBD) * 100] / TBD

Where,

LBD: Weight of the powder/volume of the packing.

TBD: Weight of the powder/Tapped volume of the packing.

Hausner's ratio

Hausner's ratio can be determined by the following equation,

Hausner's ratio = TBD / LBD

Where, TBD -Tapped bulk densities & LBD- Loose bulk densities

Preparation of pregabalin mini-tablets (PMT) [12]

According to the formula given in Table 1 and 2. A total number of 19 formulations were prepared by direct compression method. Mini-tablets of pregabalin were prepared by using various viscosity grades of polymers (HPMC K4M, HPMC K 15M and HPMC K 100M) as matrix forming material. All ingredients (Drug pregabalin, polymer, PVP K-30, Avicel, Magnesium stearate and AAerosil) were passed through a #100 sieve, weighed, and blended. The lubricated formulations were compressed by a direct compression technique, using using 3 mm flat round convex punches in a rotary tablet press (Rimek mini press, model RSB-4, M/S: Karnavathi engineering, Ahmadabad).

Preparation of pregabalin mini-tablets-in-capsule system (PMTICS) [5]

A number of 15 mini-tablets each containing 5 mg of drug (total 75 mg) were filled into an empty HPMC capsule (size 1).

Evaluation of mini-tablets [13]

Hardness test

The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability

A friability test was conducted on the mini-tablets using a veego friabilator. Twenty mini-tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The mini-tablets were initially weighed (Winitial) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the mini-tablets were removed. Any loose dust was removed from the mini-tablets as before and the tablets were weighed again (Wfinal).The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of mini-tablets less than 1% is considered acceptable.

Weight variation

The weight variation test was conducted by weighing 20 randomly selected mini-tablets individually, calculating the average weight and comparing the individual mini-tablet weights to the average. The specification of weight variation is 10%.

Uniformity of thickness

The tablet thickness was measured using screw gauge.

Drug content uniformity [9]

30 mini-tablets weighted and crushed in a mortar then weighed powder contained equivalent to 75 mg of drug was diluted in 6.8 phosphate buffer. Absorbance measured at 276 nm using UV-Visible spectrophotometer.

In- vitro dissolution studies [9]

Dissolution rate of pregabalin from all mini-tablets filled capsule formulations were performed using Electro-lab dissolution apparatus (USPXXIII) with paddle. The dissolution Media used was initially 0.1N HCl up to 2hrs, then continuation with phosphate

buffer having pH 6.8 and was rotated at a speed of 50 rpm and a temperature of 37º C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filler of 0.5 µm at different time intervals, suitably diluted and assayed for pregabalin by measuring absorbance at 276 nm. The dissolution experiments were conducted in triplicate. For all tests 5ml samples of the test medium were collected at set intervals (1, 2, 4, 6, 8, 10 and 12hrs) and were replaced with equal volume of dissolution medium in distilled water.

Stability studies [5]

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F21), by keeping at 40°± 2°C, in air tight high density polyethylene bottles for three months, at RH 75±5%. Drug content data was evaluated for F1 and F19 mini-tablets as these were filled in optimized F21 formulation. In-vitro release profile was evaluated for complete encapsulated mini-tablets for optimized F21 formulation.

Table 1: Composition of mini-tablets formulations (From F1 to F10)

S. No.	Ingredients	0	5%			15%		30%			
		mg/mini-tablet (15 Mini-tablets into an HPMC capsule)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Pregabalin	5	5	5	5	5	5	5	5	5	5
2.	HPMC K4M	0	1.25			3.75			7.5		
3.	HPMC K15M			1.25			3.75			7.5	
4.	HPMC K100M				1.25			3.75			7.5
5.	PVP K 30	1	1	1	1	1	1	1	1	1	1
6.	Avicel PH 102	18.5	17.25	17.25	14.75	14.75	14.75	14.75	11	11	11
7.	Magnesium Stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8.	Aerosil	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
	Total tab wight	25	25	25	25	25	25	25	25	25	25

Table 2: Composition of mini-tablets formulations (From F11 to F19)

S. No.	Ingredients	45%		60%				75%		
		mg/mini-tablet (15 Mini-tablets into an 1 HPMC capsule)								
		F11	F12	F13	F14	F15	F16	F17	F18	F19
1.	Pregabalin	5	5	5	5	5	5	5	5	5
2.	HPMC K4M	11.25			15			18.75		
3.	HPMC K15M		11.25			15			18.75	
4.	HPMC K100M			11.25			15			18.75
5.	PVP K 30	1	1	1	1	1	1	1	1	1
6.	Avicel PH 102	7.25	7.25	7.25	3.5	3.5	3.5	0	0	0
7.	Magnesium Stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8.	Aerosil	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
	Total tab weight	25	25	25	25	25	25	25	25	25

RESULTS AND DISCUSSION

Evaluation of granules

Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. Results of all the pre-compessional parameters of all the granule formulations are shown in **Table 3.** The results of angle of repose (<30) indicates good flow properties of the granules. This was further supported by lower compressibility index values. Generally compressibility values up to 15% results in good to excellent flow properties.

Table 3: Pre-compressional parameters of the prepared granules

Blend. No	Angle of repose (degree) ± SD, n=3	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	Carr's index (%) ± SD, n=3	Hausner's ratio ± SD, n=3
F1	26°.12"±0.22	0.45±0.013	0.51±0.027	11.76±0.75	1.13±0.058
F2	27°.65"±0.49	0.50±0.009	0.58±0.25	13.79±0.60	1.16±0.036
F3	28°.34"±0.76	0.46±0.010	0.53±0.022	13.20±0.38	1.15±0.044
F4	27°.21"±0.30	0.50±0.018	0.58±0.029	13.59±0.49	1.16±0.012
F5	29°.19"±0.88	0.48±0.015	0.55±0.034	12.72±0.45	1.14±0.039
F6	26°.64"±0.17	0.49±0.013	0.56±0.027	12.50±0.30	1.14±0.078
F7	28°.55"±0.20	0.46±0.019	0.52±0.056	11.53±0.66	1.13±0.080
F8	29°.59"±0.26	0.51±0.022	0.59±0.017	13.55±0.42	1.15±0.036
F9	25°.41"±0.38	0.47±0.018	0.53±0.026	11.32±0.10	1.12±0.028
F10	26°.44"±0.40	0.52±0.005	0.59±0.030	11.86±0.40	1.13±0.060
F11	27°.28"±0.18	0.50±0.010	0.58±0.038	13.79±0.18	1.16±0.076
F12	26°.64"±0.14	0.51±0.008	0.59±0.026	13.55±0.80	1.15±0.083
F13	29°.10"±0.12	0.48±0.028	0.55±0.040	12.72±0.92	1.14±0.056
F14	29°.74"±0.50	0.52±0.006	0.59±0.018	11.86±0.88	1.13±0.010
F15	28°.51"±0.64	0.46±0.009	0.54±0.038	14.81±0.70	1.17±0.066
F16	29°.68"±0.52	0.52±0.017	0.60±0.018	13.33±0.66	1.15±0.034
F17	28°.25"±0.57	0.50±0.025	0.57±0.045	12.28±0.30	1.14±0.012
F18	29°.58"±0.67	0.48±0.010	0.54±0.026	11.11±0.16	1.12±0.070
F19	26°.26"±0.38	0.45±0.012	0.51±0.038	11.76±0.20	1.13±0.094

Drug excipients interaction studies

FTIR Studies

Spectra of the pure drug, polymers and physical mixture of drug and polymers **(see Fig. 2)** were recorded in between 400-4000 wave number (cm^{-1}). The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug pregabalin and in the physical mixture which confirms the absence of chemical interaction between drug and polymers.

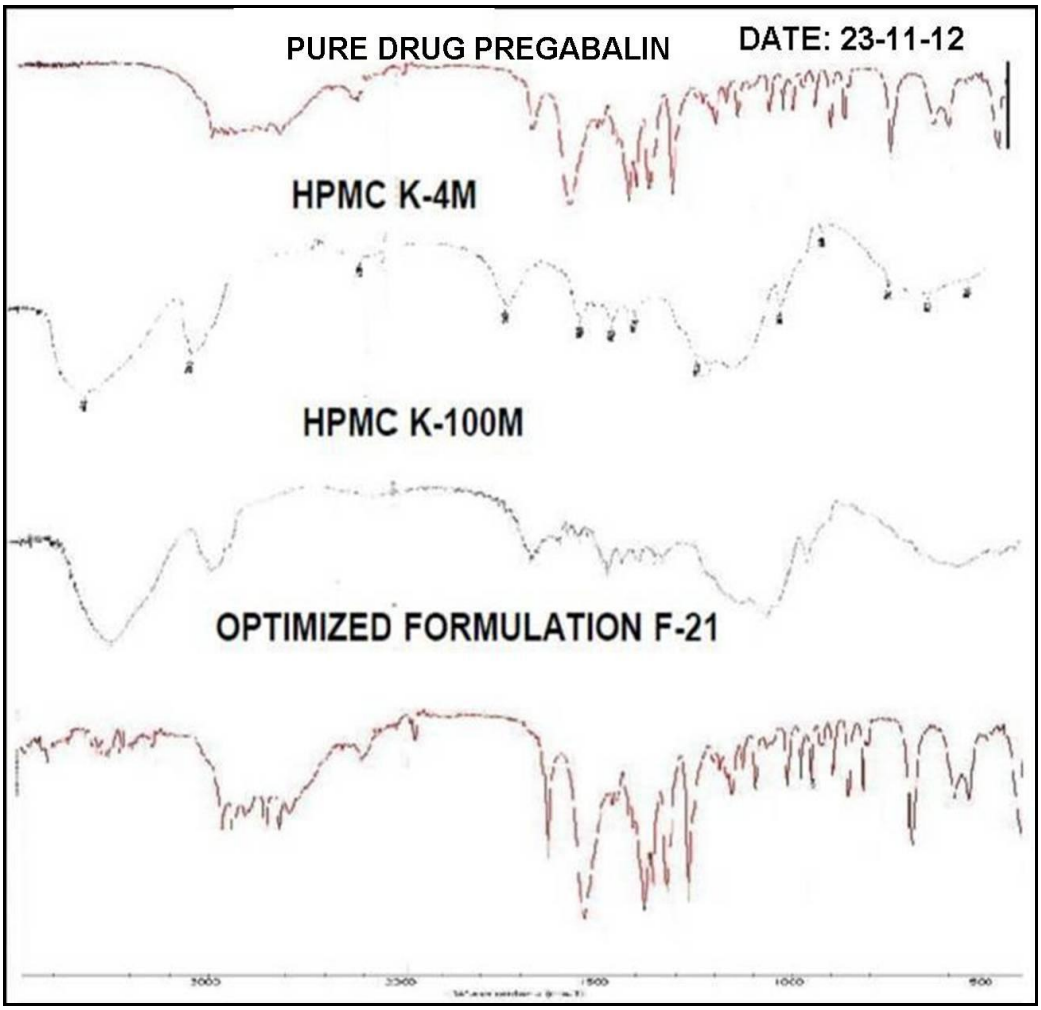

Fig. 2: IR spectra of a) Pure drug Pregabalin b) HPMC K4M C) HPMC K100M d) Optimized formulation F21.

Table 4: Post-compressional parameters of the prepared core mini-tablets

Formulation batches	Thickness (mm) (±SD), n=6	Hardness (kg/cm2) (±SD), n=6	Friability (%) (±SD), n=6	Weight variation (mg) (±SD), n=20	% Drug content (±SD), n=3
F1	2.38±0.017	3.7± 0.23	0.45 ± 0.01	24±0.56	98.5±0.44
F2	2.51±0.059	3.6 ± 0.40	0.28 ± 0.04	26±1.20	98.1±0.93
F3	2.47±0.038	3.8 ± 0.34	0.75 ± 0.03	25±0.94	95.08±0.18
F4	2.53±0.026	3.7 ± 0.32	0.10 ± 0.06	25±1.14	96.4±0.30
F5	2.62±0.021	3.8 ± 0.20	0.28 ± 0.07	24±0.80	91.1±0.52
F6	2.28±0.063	3.9 ± 0.26	0.68 ± 0.0	27±0.76	90.5±0.44
F7	2.37±0.027	3.6 ± 0.33	0.47 ± 0.0	27±1.42	99.4±0.14
F8	2.46±0.054	3.5 ± 0.27	0.59 ± 0.03	26±1.38	93.5±0.47
F9	2.49±0.076	3.7 ± 0.16	0.49 ± 0.08	25±0.95	96.4±0.19
F10	2.60±0.036	3.8 ± 0.28	0.13 ± 0.07	25±0.80	92.7±0.37
F11	2.37±0.067	3.6 ± 0.10	0.26 ± 0.02	24±1.13	97.8±0.36
F12	2.58±0.085	3.8 ± 0.38	0.79 ± 0.04	26±0.68	93.7±0.85
F13	2.42±0.032	3.6 ± 0.26	0.15 ± 0.01	25±0.96	99.2±0.27
F14	2.56±0.055	3.7 ± 0.39	0.83 ± 0.06	27±0.76	99.4±0.11
F15	2.34±0.012	3.7 ± 0.48	0.58 ± 0.03	27±0.62	99.7±0.64
F16	2.51±0.085	3.6 ± 0.52	0.39 ± 0.01	26±1.26	98.5±0.96
F17	2.55±0.074	3.8 ± 0.47	0.16 ± 0.09	25±0.96	96.7±0.54
F18	2.44±0.020	3.6 ± 0.43	0.47 ± 0.08	24±1.34	92.4±0.84
F19	2.39±0.092	3.9± 0.31	0.35± 0.06	25±0.74	99.6±0.92

Evaluation of mini-tablets

The data obtained from post-compression parameters for the core mini-tablets of all the formulations such as thickness, diameter, hardness, friability, average weight, and drug content is shown in **Table 4.** For all the formulations, hardness test indicated good mechanical strength was found to be range between 3.5 ± 0.27 to 3.9 ± 0.26 indicating that they possessed sufficient mechanical strength to withstand physical and mechanical stress conditions. Friability is less than 1% indicated that tablets had a good mechanical resistance. The mean thickness (n=6) was almost uniform in both the batches and values for all the batches of core mini-tablets was found to be range between 2.28±0.063 to 2.60±0.036. All the formulations passed the weight variation test i.e., average percentage weight variation was found to be within the pharmacopoeial limits of ±10%. The drug content was found to range between 90.5±0.44 % and 99.7±0.64 % of pregabalin for all the batches of core mini-tablets indicating good content uniformity in both the batches. That indicates drug was uniformly distributed through out the core mini-tablets.

Dissolution Profile Testing

In order to achieve a controlled release formulation which would give controlled release product for 12 hours, a target product profile (TPP) was first set. The TPP range is shown in **Fig 3.**

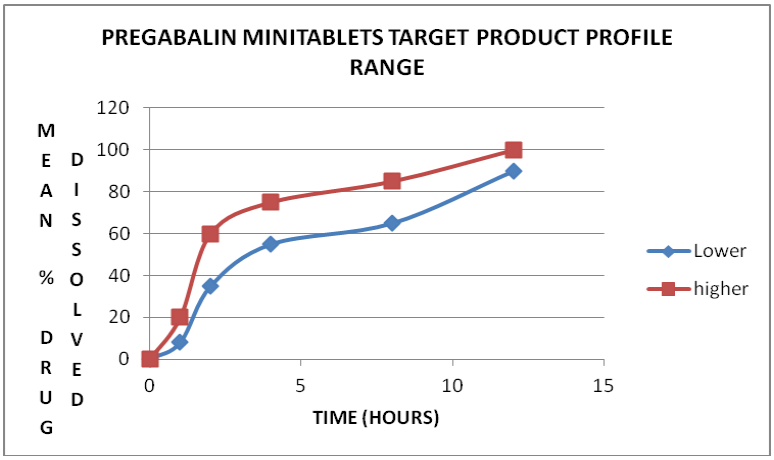

Fig. 3: Pregabalin mini-tablets target product profile range

(Note-The in-vitro dissolution profiles of all formulations were compared with respect to the TPP)

When the formulations F1-F10 containing 0%, 5%, 15%, 30% of various viscosity grades of polymers (HPMC K4M, K15M, K100M) were subjected to in-vitro dissolution testing it was found that the mini-tablets completely disintegrated in the dissolution bath within 1 hour and hence the drug release could not be controlled. **(see Fig. 4 for release profile).**

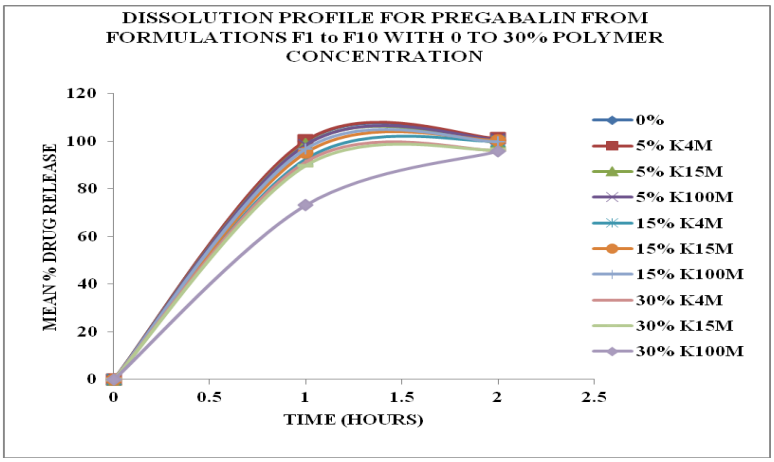

Fig. 4: Dissolution profile for Pregabalin from formulations F1 to F10

For formulations with 45% of polymer, the mini-tablets could withstand the vigors of the dissolution profile testing for around 2 hours in case of K4M and K15M and for around 4 hours in case of K100M. In case of tablets containing 60% of the release controlling polymer, all formulations are able to withstand the dissolution testing for up to 12 hours. However, only formulation with 60% of K100M is able to sustain the release within the TPP upto 4 hours. However, all values are on the higher border of the TPP and the 8th hour release is failing the target product profile. In case of formulations with 75 % level of HPMC (F17-F19), again all formulations withstand the dissolution profile testing for upto 12 hours. The drug release from F17 is similar to than of F16, in that all the values are within the TPP but on the higher side and the 8th hour value marginally out of the TPP range. In case of F18, (75% K15M), all values upto 8 hours are well within the TPP but the 12th hour time point is showing incomplete drug release. In case of F19, the drug release is significantly lower than the TPP from the 4th hour time point itself. (**see Fig. 5** for release profile).

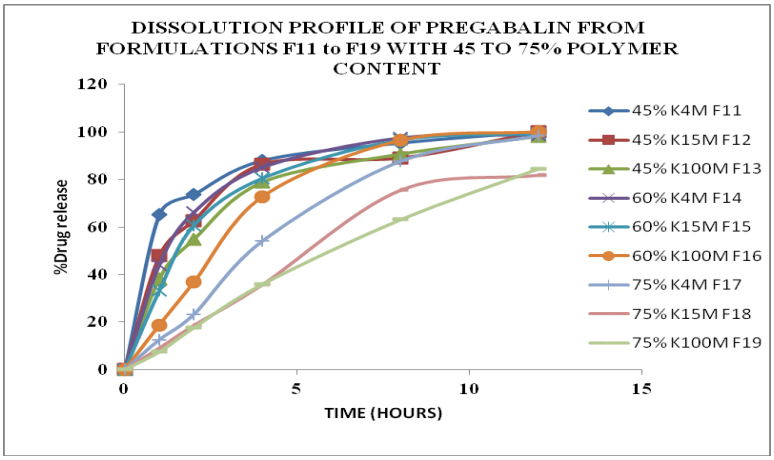

Fig. 5: Dissolution profile for Pregabalin from formulations F11 to F19

From the above study, it could be concluded that minimum 75% level of HPMC polymer is required to control drug release. However none of the formulations are comfortably passing as per the target product profile. Formulation F19 seems to be the most controlled formulation even though the release is slower than the TPP. Hence it was decided to formulate two formulae, F20 and F21. In formula F20, 1 immediate release mini-tablets (F1) and 14 tablets of F19 (with 75% K100M) was used for testing dissolution profiling. Another formula which had 2 tablets of F1 and 13 tablets of F19 were mixed and subjected to dissolution profile testing. Formulation F20 is still failing the 2, 4 and 8th hour time points release criteria. However formulation F21, is comfortably passing as per the TPP. The dissolution profile of F21 with respect to the TPP is shown in **Fig. 6.**

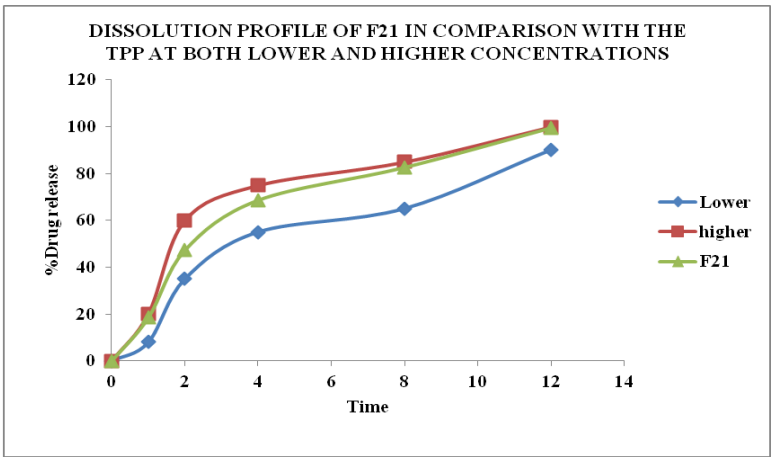

Fig. 6: Dissolution profile of F21 in comparison with the TPP at both lower and higher concentrations

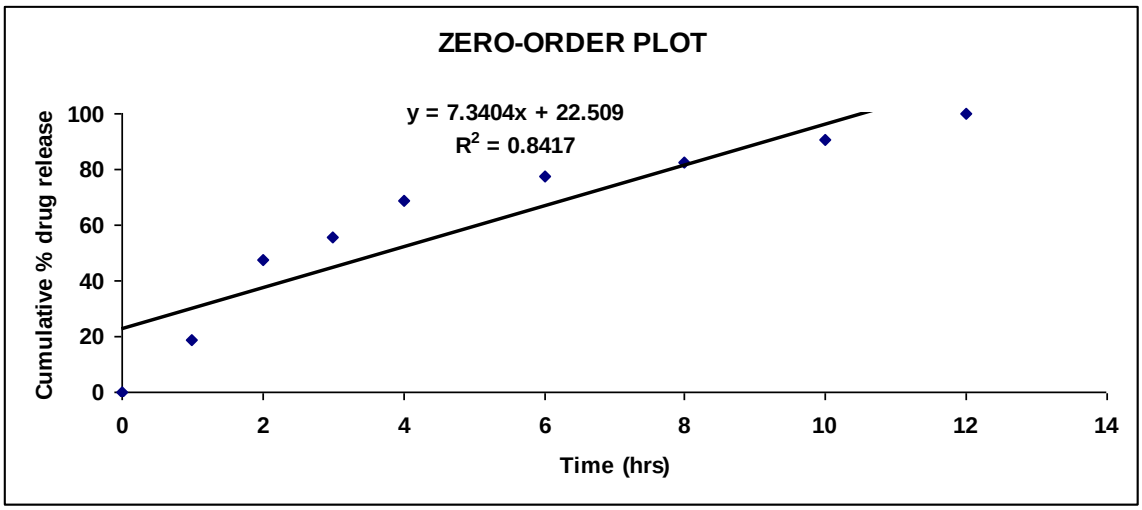

Fig. 7: Zero-order plot

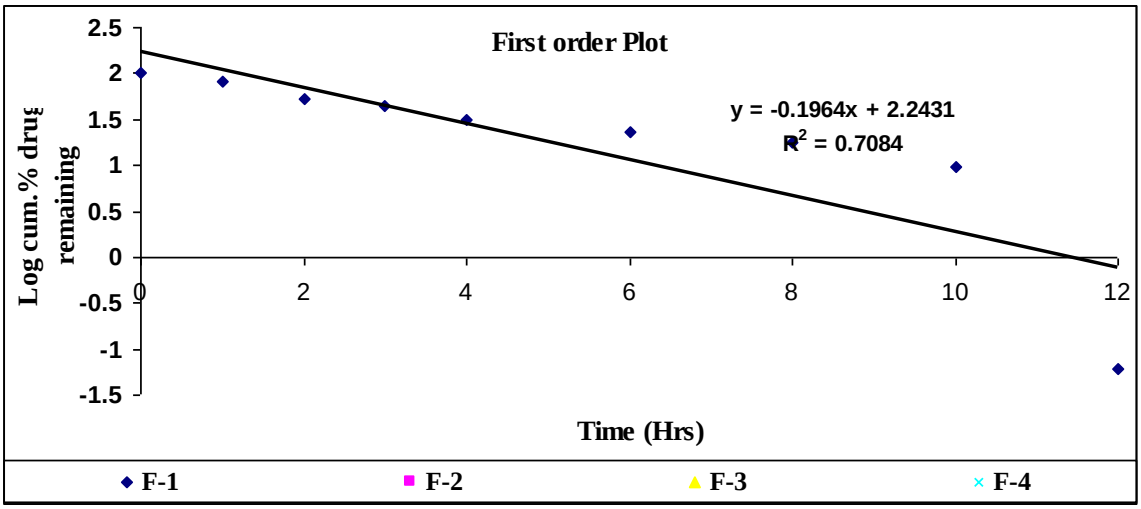

Fig. 8: First-order plot

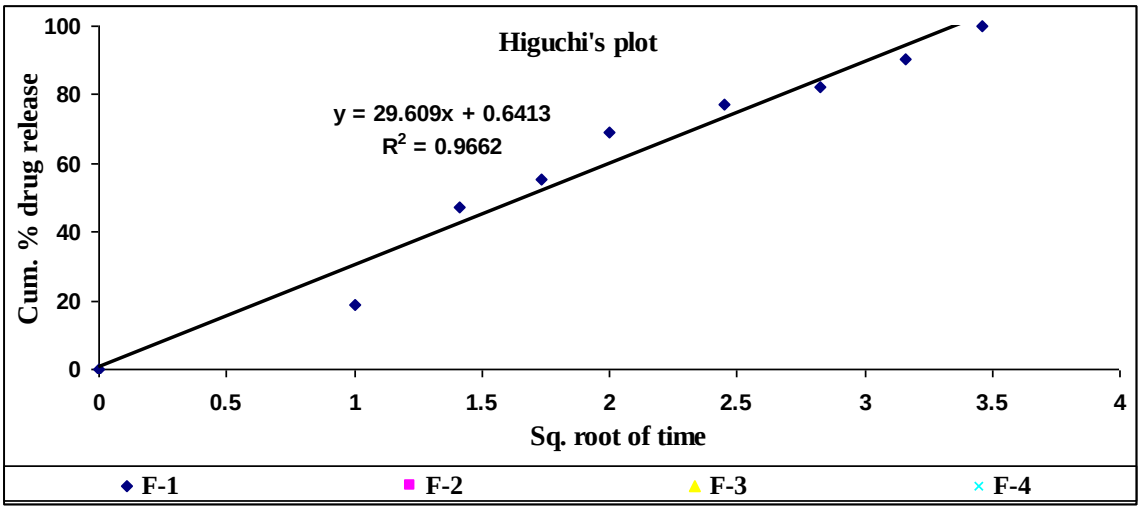

Fig. 9: Higuchis plot

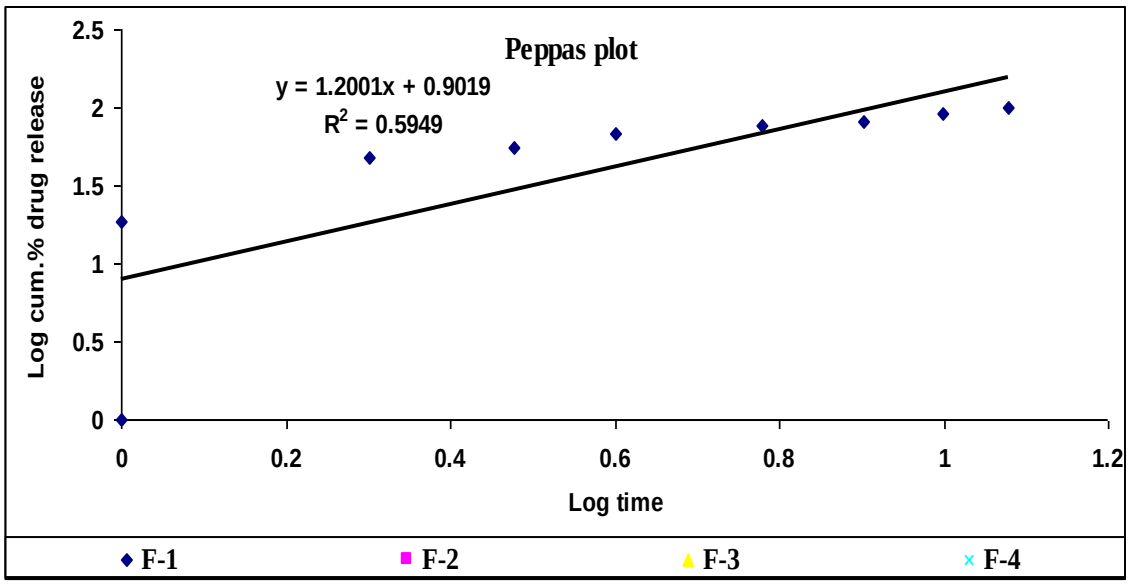

Fig. 10: Peppas plot

Drug release study

The kinetic data of all the formulations are graphically represented in **Figures 7-10**. In order to determine the mechanism of drug release form the formulations , the in-vitro dissolution data was fitted to Zero order, First order, Higuchi plot and Korsemeyer-peppa's plot was drawn for optimized formula and interpretation of release exponent value (n) was calculated. The results of R^2 for zero and first order were obtained as 0.8417 and 0.7084 respectively. Based on that we have confirmed that the optimized formulation followed Zero- order release.

To ascertain, the drug release mechanism the *in-vitro* release data were also subjected to Higuchi"s diffusion plots and Peppas plots and the correlation coefficient values was found to be 0.9662 and 0.5949 respectively. So it confirms that, the calculated R^2 values for Higuchi plot and Peppas plots were nearer to one (1) in all the cases suggesting that drug released by diffusion mechanism. The value of release exponent 'n' is an indicative of release mechanism. The value of 'n' obtained for the optimized formulation F21 was found to be 1.20 suggesting probable release by super case-II transport.

Stability studies

The promising formulations were subjected to short term stability study by storing the formulations at 40 ^{0}C / 75% RH for 3 months as per ICH guidelines. The formulations F-21 was selected. After 3 months the mini-tablets were again analyzed for drug content and *in-vitro* drug release profile. The data for stability studies revealed that no considerable differences in drug content and dissolution rates were observed. The results of drug content and dissolution rate after 3 months was given in **Tables 5,6.**

Table 5: Drug content data of stability formulation for F-1 and F-19 mini-tablets batches

M.T.C	1ST day (%)	30th day (%)	60th Day (%)	90th Day (%)
F-1	98.5±0.44	97.78 ±0.32	97.45±0.48	97.34±0.73
F-19	99.6±0.92	98.48±0.52	98.16±0.78	98.04±0.91

All values are expressed as mean ± SD, n=3, M.T.C= Mini-tablets codes.

Table 6: *In-vitro* release data of stability formulations F-21

Time (Hrs)	Formulation-F21			
	1ST day (%)	30th day (%)	60th Day (%)	90th Day (%)
1	0	0	0	0
2	18.45	18.05	17.94	17.58
4	47.32	47.07	46.66	46.64
6	68.67	68.32	68.05	68.00
8	82.68	82.17	82.03	81.86

All values are expressed as mean ± SD, n=3.

CONCLUSION

A Controlled release dosage form was sucessfully developed by filling 15 matrix mini-tablets into an empty HPMC capsule shell (size 1) which releases nearly the total dose for a period of 12 hours. Number of mini-tablets can be filled ranging from 15 to 21 depending upon the size of the capsule shell and the diameter or weight of mini-tablets. With the help of this technology the release profile can be totally controlled as per the targeted profile by the formulater. The proposed fast/slow delivery devices show a wide flexibility in the modulation of the delivery program. The two different release phases can be easily adjusted in a wide range of values of both delivery rate and ratio of the dose fractions, on the basis of the pharmacokinetics and therapeutic needs, to perform the desired *in-vivo* profile.

ACKNOWLEDGEMENTS

Authors thanks to IPS Institute, Hyderabad for providing a gift sample of Pregabalin and ACG Associated capsules Pvt Ltd, Mumbai, for providing the HPMC capsules. The authors are also thankful to Trinity College of Pharmaceutical Sciences (Karimnagar), Bhaskar Pharmacy college (R.R.District), and IPS Institute (Hyderabad) for providing the research lab facilities to carry out this research work.

REFERENCES

1. Xiaoming Chen, Hong Wen, Kinam Park.Challenges and New Technologies of Oral Controlled Release. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. 2011; 16: 257-277.
2. Pankaj Ostwal P, Pankaj Salunkhe S, Mayur Jain S, Sumit Jain P. Development and evaluation for tablet-in capsule of nefedipine and atenolol. International Journal of Pharmacy and Biological Sciences. 2011; Vol 1 (4): 468-473.
3. Shaik Haroon Rasheed, Mulla Arief, Sandhya Vani P, Silpa Rani Gajavalli, Venkateshwarulu G, Vineela PAJ, Anjaneyulu N, and Naga Kishore R. Formulation and evaluation of sustained release tablets of Bupropion hydrochloride, Research Journal of Pharmaceutical Biological and Chemical Sciences. 2010; 1(4): 1017-1025.
4. Mangesh Bhad E, Shajahan Abdul, Sunil Jaiswal B, Anil Chandewar V, Jayesh Jain M, Dinesh Sakarkar M. MUPS Tablets – A Brief Review. International Journal of PharmTech Research. 2010; 2 (1): 847-855.
5. N. G. Raghavendra Rao, Mohd Abdul Hadi, Harsh Panchal. A Novel approach to sustained Montelukast sodium release: Differentially coated mini-tablets in HPMC capsules. International Journal of Pharmaceutical and Biomedical Sciences. May 2011; 2(2): 90-97.
6. Bin Li, JiaBi Zhu, ChunLi Zheng, Wen Gong. A novel system for three-pulse drug release based on "tablets in capsule" device. 2007; 1-6.
7. Carla Lopes M., Jose Manual Souza, lobo, Jaao F., Pinto, Paulo, Costa. Compressed Mini-Tablets as a biphasic delivery system. International Journal of Pharmaceutics. 2006; 323: 93-100.
8. Mohd Abdul Hadi, Raghavendra Rao NG. Novel Techniques in Formulations: An Overview. World Journal of Pharmaceutical Research. May 2012; 1(3): 1-17.
9. Pawar RG, Gadhave MV, Jadhac SL, Gaikvad DD. Formulation and evaluation of pregabalin sustained release matrix tablet. International Journal of Pharmaceutical Research and Development. 2011; 4(2): 153-159.
10. Pregabalin, Lyrica. Available at http://www.medicinenet.com/pregabalin_lyrica/article.htm
11. Lyrica. Available at http://www.rxlist.com/lyrica-drug.htm
12. Mohd Abdul Hadi, Lokeswara Babu V, Narottam Pal, Srinivasa Rao A. Formulation and evaluation of Sustained release Matrix tablets of Montelukast Sodium. International Journal of Pharmacy. 2012; 2(3): 574-582.
13. Mohd Abdul Hadi, Lokeswara Babu V, Narottam Pal. Formulation and evaluation of sustained release matrix tablets of glimepiride. Journal of Applied Pharmaceutical Sciences. 2012: 02 (06); 101-107.