PREPARATION AND FORMULATION OF SUSTAINED RELEASE MATRIX TABLETS PREGABALIN

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Abstract : *The sustained release drug delivery is the drug delivery system that achieves the release of drug in the proper amount at regular time interval over an extended period of time and is time independent. The aim of present work was to formulate and evaluate sustained release tablets of Pregabalin using polymers in order to reduce the various side effects associated with Pregabalin as well as to overcome the manufacturing difficulties. The binders prolongs the dissolution rate of some slightly soluble drugs and can be chosen as good candidate for sustained release. Tablets were prepared by direct compression method using different drug-polymer concentration. FT-IR study revealed that there was no chemical interaction between the drug and polymers used. Pre-compression and post-compression parameters complied with Pharmacopoeial limit for the tablets. The in vitro release study was performed and the results indicated that the formulation F3 was found to be the optimized formulation which can extend the release up to a period of 8 hours. From the stability studies it was clear that the formulation was stable after 3 months at accelerated condition of $40^0C\pm2^0C/75\%$ RH±5% in a stability chamber.*

Keywords: *Pregabalin, FTIR studies, polymers, Direct compression technique, In vitro drug release studies.*

I.INTRODUCTION

Oral drug administration has been the predominant route for drug delivery. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration[1].Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose[2,3]. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. Matrix tablet is one of the most widely used approaches to sustain the drug action.[4]Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". Matrix drug delivery systems release the drug in continuous manner. These release the drug by both dissolutions controlled as well as diffusion controlled mechanisms[5,6]. Pregabalin is used to treat pain caused by fibromyalgia, or nerve pain in people with diabetes (diabetic neuropathy), herpes zoster (post-herpetic neuralgia), or spinal cord injury. Pregabalin is also used with other medications to treat partial onset seizures in adults[7].

II. MATERIALS AND METHODS

Pregabalin was collected as a gift sample from Hetero labs, Hyderabad and various excipients like, ethyl cellulose and HPMC K5M were purchased from AR chemicals, Hyderabad.

METHODOLOGY[8,9]

Compatibility studies of drug and polymers:

In the formulation of Pregabalin tablet formation, API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Pregabalin and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation Development

Table-: 1Formulation of Pregabalin tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4
1	PREGABALIN	50	50	50	50

2	HPMC K5 M	10	20	-	-
3	Crosspovidone	-	-	10	20
4	Microcrystalline Cellulose	125	115	125	115
5	Magnesium stearate	3	3	3	3
6	Mannitol	10	10	10	10
6	Talc	2	2	2	2
9	Total Wt	200	200	200	200

Preparation method

Direct compression

Sustained release tablets were prepared by direct compression method. All ingredients were weighed and passed through 40# sieve, blended except lubricant. These blend were lubricated with Magnesium stearate, which was previous, passed through 60# Sieve. The lubricated blend were for compressed 200 mg tablet using 10mm die and punches, with hardness between 5-6 kg/cm^2 In total, four formulations containing different combination of polymers were prepared.

EVALUATION STUDIES [10,11,12]

Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured.

Tapped density = weight of sample taken / tapped volume

Where,

V_o = initial volume

$V_{f=}$ final volume.

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

Hausner's ratio = Tapped density / Bulk density

Angle of repose:

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Evaluation of tablet[13,14,15]

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than

two of the individual tablet weight deviates from the average weight by more than the percentage.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Pregabalin. Dissolve the weighed quantity of powder into 100 ml of 6.8 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask, to it 10 ml of 6.8 phosphate buffer solution was added. Immediately analyze the drug by taking absorbance.

***In- Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for 8 hrs. Temperature maintained at 37±1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, to it add 10 ml 6.8 phosphate buffer solution. Immediately analyze the drug by taking absorbance.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared Matrix tablets of Pregabalin were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 30 days.

III.RESULTS & DISCUSSION

FTIR Studies

There was no interaction between drug and the polymers

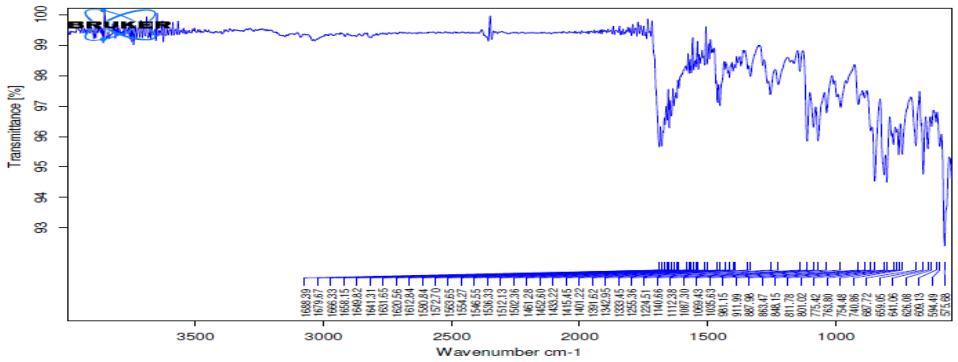

Fig- : 1 FTIR Studies of Pure Drug

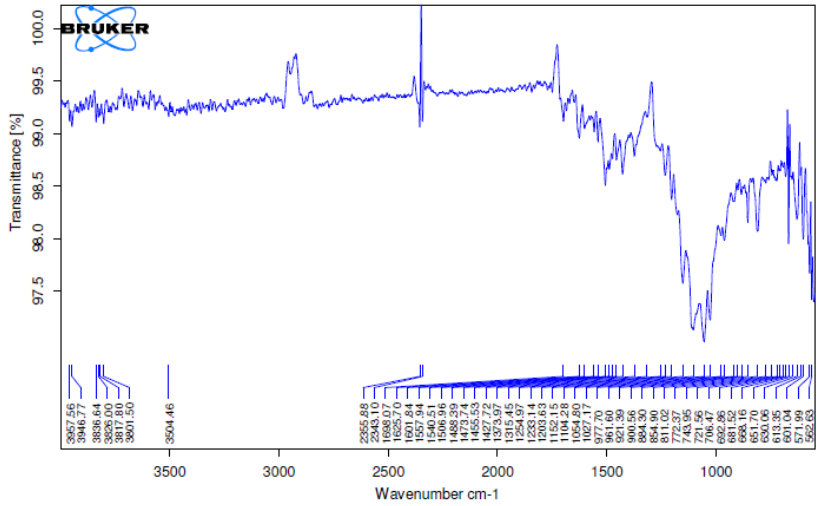

Fig -: 2 FTIR Studies of physical mixture of drug and excipients

Evaluation studies

Pre compression parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.319-0.332.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.421-0.443.

Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 26 ^{0} to 32 ^{0}

Compressibility index: Compressibility index was carried out, it found between 10% to 25.57% indicatir powder blend have the required flow property for compression.

Table-: 2 Results for pre compression parameters

F. no	**Bulk density**	**Tappeddensity**	**Compressibility index**	**Hauser ratio**	Angle of repose(^{0})
F1	0.320	0.424	24.52	1.32	29 ^{0}
F2	0.326	0.438	25.57	1.34	26 ^{0}
F3	0.328	0.440	25.45	1.34	28^0
F4	0.327	0.423	22.69	1.29	27^0

Post compression parameters

Weight variation:

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 3.25mm to 3.46mm.

Hardness:

The measured hardness of tablets of each batch ranged between 5.16 to 5.28 kg/cm^2 .This ensures good handling characteristics of all formulations.

Friability:

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

Content Uniformity:
The percentage of drug content for F1 to F4 was found to be between 88.55% and 97.89% ofPregabalin, it complies with official specifications.

Table-: 3 Physical parameters of tablets of each batch

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	200	3.21	5.16	0.45	95.36
F2	199	3.28	5.22	0.50	88.55
F3	198	3.27	5.28	0.48	92.50
F4	200	3.16	5.24	0.50	96.85

In-vitro Dissolution Study
All the four formulation of prepared matrix tablets of Pregabalin were subjected to in-vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table-: 4 Dissolution Profile of F1 to F4

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	21.36	18.20	24.12	20.10
2	30.29	25.30	31.18	31.45
3	48.58	35.32	46.89	49.90
4	50.18	44.65	53.95	56.70
5	63.96	59.28	69.95	65.16
6	70.18	68.55	78.15	72.22
7	75.25	80.10	88.52	82.26
8	90.23	92.11	96.17	94.50

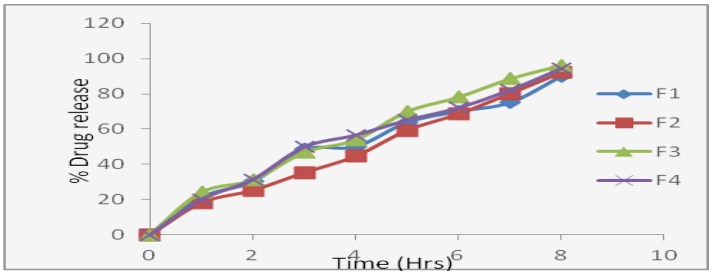

Fig-3: Dissolution profile of (F1-F4) Formulations

Stability studies
Sustained release matrix tablets of Pregabalin formulated in the present study were subjected to accelerated

stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40°c and 2-8°c for a period up to 90 days.

Table-: 5 Results of stability studies of optimized formulation F-3

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	25°C/60%RH % Release	96.17	96.15	94.78	94.10	Not less than 85 %
F-3	30°C/75% RH % Release	96.17	95.98	94.55	93.89	Not less than 85 %
F-3	40°C/75% RH % Release	96.17	95.80	94.50	93.52	Not less than 85 %

IV.SUMMARY AND CONCLUSION

The present study was aimed to formulate sustained release tablet of Pregabalin by direct compression method. IR spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer. The samples were prepared by pressed pellet technique. The IR spectra were determined using Bruker. Scanning range was between 500- 4000cm-[1]. FT-IR study revealed the absence of any chemical interaction between drug and polymer used. Preformulation studies of the sustained release powder blend were done. The results of the evaluation suggest that all the powder exhibit good flow properties, so all the formulations were directly compressed to tablets. Post formulation studies of Tablets. Tablets were evaluated for their physical parameters like hardness, thickness, friability, weight variation, and drug content uniformity complies with IP standards. The in-vitro drug release studies were performed using USP type 2 paddle type dissolution apparatus using 6.8 phosphate buffer for 8 hours. The formulation F3 showed the maximum release of drug (96.17 %) at 8th hour. From the release data it is clear that the best sustaining ability was revealed by the formulation F3. The tablets were loaded at accelerated condition at 40°C±2°C/75% RH±5% in a stability chamber. Samples were withdrawn at 30th , 60th and 90th day and evaluated for the physical appearance, drug content and dissolution characteristics. The result obtained from the study reveals that storage at 40 ºC had no effect on the hardness, disintegration time and dissolution time. The stability studies indicate that the sustained release tablet was suitable for drug delivery of Pregabalin without having any physical stability issues. The formulation F3 could give rise to tablets exhibiting sustained drug release.

Solid dosage forms also present significant administration challenges in other patient groups, such as children, mentally challenged, bed ridden and uncooperative patients[1]. Pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control[2]. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules. Therefore, to cater the needs of such patients, recent advancements in technology have resulted in development of viable dosage alternatives popularly known as orally disintegrating tablets (FDTS)[3].

These dosage forms are preferable alternative for oral medication in improving Sthe quality of life and patient acceptability. FDTS are also known as oro dispersible tablets, mouth dissolving tablets, rapimelts, melt-in-mouth tablets, fast disintegrating tablets and rapid dissolving tablets. FDTS are the solid unit dosage forms/entities containing medicinal substances which disintegrate[4] or dissolve rapidly in oral cavity usually within a few seconds even without the need of water or chewing. FDTS also combine the advantages of both liquid and conventional tablet formulations allowing the ease of swallowing in the form of liquid[6]. The advantages of these dosage forms are continuously and increasingly being identified in both pharmaceutical industries as well as in academia. The objective of present work is to highlight the development of FDTS, their significance, ideal characteristics, various techniques and aspects related to design and formulation, marketed preparations and future prospectives[7].Solid oral dosage forms are most convenient from patient as well as from manufacturing chemist's perspective[8]. Fast dissolving tablets are required to disintegrate within 3 mins in water at 15-25°C.The aim of this study is development and characterization of proponolol hcl fast dissolving tablets. Propranolol is a competitive antagonist of beta-1-adrenergic receptors in the heart. It competes with sympathomimetic neurotransmitters for binding to receptors, which inhibits sympathetic stimulation of the heart.The objective of present study is to design and develop a stable solid oral dosage form of proponolol hcl fast dissolving tablets to deliver with optimum concentration of drug at desired site at specific time comparable to the innovator product with better stability, high

production feasibility, and excellent patient compatibility[9].

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