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FORMULATION AND EVALUATION OF PREGABALIN SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT

*The aim of current study was to design and characterization of sustained release matrix tablets of **Pregabalin** in order to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The matrix tablets were prepared by using Hydroxylpropylmethylcellulose (HPMC K-100), Polyvinylpyrrolidone (PVP K-30) and microcrystalline cellulose (MCC 102) in varying proportions. The matrix tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content.*

Key words: *Sustained release, matrix tablets, **Pregabalin, drug content.***

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INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Advance in technology have resulted in novel modified release dosage form. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or sustainer release of drug delivery system.[1]

Sustained release products are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug.The goals of sustained drug delivery are to conserve and maintain effective drug concentration, eliminate night time dosage, improve compliance and decrease side effects thus, optimizing drug therapy.[2]

According to said preparation methods, as drug surface can be covered with hydrophobic substances at particulate or molecular level, release-delaying can be effectively induced by use of just small amount of hydrophobic additive, and the process is simple. However, majority of the hydrophobic additives used in melt granulation and melt extrusion has property of wax, thus the

surface of particles prepared by cooling after melting becomes to exhibit adhesion toward another surface. Therefore, problems occur in actual production, i.e. reduced flow of particles at hopper, severe adhesion to punch or die at the time of tablet compression and increased resistance at the time of removing tablet from tablet machine. Such adhesion problem can be covered to some extent by addition of lubricants, yet the masking power is limited, thus the amount of hydrophobic additives is to be limited.

The present study was conceived to resolve the problems of the conventional techniques, and its object lies in minimizing the amount of hydrophobic additives for imparting sustained-releasing property, and eliminating adhesion phenomenon of granules occurring during the tablet preparation, to keep the tablet size smaller, thereby allowing the production of tablet to be easy.

More specifically, the present study relates to sustained-release preparations characterized by being prepared from double granules which are obtained by primary granulation of drug according to melt granulation using hydrophobic release-delaying additives, and then by secondary granulation of the obtained granules according to wet granulation using hydrophilic wet-granulation material.

A drug is mixed with hydrophobic release-delaying additives and then the mixture is subjected to melt granulation thereby to prepare primary granules, and the granules obtained in step 1 are mixed with hydrophobic wet-granulating material and then the mixture is subjected to wet granulation thereby to prepare secondary granules.

The sustained-release preparations according to the present study enables maintenance of effective blood concentration of drug for many hours via sustained release of the drug over 8 hours or more, and further its production is easy owing to convenience of process.

Pregabalin (S)-3-amino methyl hexanoic acid, is a structural analogues of γ-amino butyric acid (GABA). They constitute an important group of compounds that are used in the treatment of epilepsy and neuropathic pain. It is a white crystalline solid. It is soluble in water and in both basic and acidic aqueous solutions. Pregabalin has been studied for use in a variety of disorders, including monotherapy in refractory partial seizures, diabetic neuropathy, surgical dental pain and other pain syndromes, postherpetic neuralgia, and social anxiety disorders. Pregabalin's innovator is Pfizer-Global and appears world-wide under the brand name Lyrica. The half-life of Pregabalin is also short (5-6.5 hrs) which makes it suitable candidate for sustained release formulation, moreover it reducing side effects, decreasing frequency and improve patient compliance[3-7]

. Keeping these factors in view it is aimed to formulate and evaluate sustainedrelease matrix tablets, to provide a controlled and predictable release of Pregabalin, which is an oral antiepileptic drug used in themanagement of epilepsy. For the sustain release layer it was intended to use four different polymers to formulate a polymer matrix systems namely hydroxylpropyl methyl cellulose (HPMC K-100), Polyvinylpyrrolidone (PVP K-30) and Microcrystalline cellulose (MCC 102).**Pregabalin** is a soluble drug thus it is difficult to render it in a sustained release oral formulation with hydrophilic release retardants because a high ratio of hydrophilic polymer is required that increase the tablet size.

MATERIALS AND METHODS

Pregabalin was obtained as gift sample from Dana pharmaceuticals Pvt.Ltd, Ambarnath, India.Hydroxy Propyl Methyl Cellulose (K-100), Glyceryl Behenate, Poly vinyl pyrrolidone (K-30), Microcrystalline cellulose (Avicel PH 102), Colloidal silica (Aerosil),Magnesium stearate, Isopropyl alcohol were purchased from SD Fine chemicals, Mumbai, India. All other reagents and solvent used were of analytical grade.

INSTRUMENTS USED:

Tablet punching machine, UV-spectrophotometer (shimadzu Lab.), Bulk density Apparatus (Electrolab), Dissolution Tester USP (TDT – 06T (Electrolab), Friability Tester (friabilator USP) (EF-2)

(Electrolab), Hardness Tester (Monsanto), Veriniercalliper's scale were the instruments used for this study.

METHOD:

Standard calibration curve of Pregabalin:

Accurately weighed 50 mg **Pregabalin** was dissolved in little amount of distilled water in a 1000 ml calibrated volumetric flask to get the stock solution. From this stock solution aliquots of 2, 4, 6, 8, 10 & 12 ml were withdrawn and further diluted to 100 ml with distilled water to obtain a suitable concentrations range. The absorbance of the solutions was measured at 276 nm by using UV spectrophotometer. A graph of Concentration vs. Absorbance was plotted.

Procedure of preparing Pregabalin 100 mg SR tablets: [8-11]

a) **Preparation of primary granules of Pregabalin**: Weighed amount of **Pregabalin** and glyceryl behenate was shifted with sieve # 30 and mixed thoroughly with the help of a planetary mixture. This mixture was then heated to 70^0C in a water bath until the mass softens. The mass was kept aside to become a solid mass and then was pulverized and passed through sieve # 20.

b) **Preparation of secondary granules of Pregabalin using granules of Step-I by wet granulation method**:- Required amount of Methocel K100M (Hydroxypropyl methylcellulose) and Avicel PH 102 (microcrystalline cellulose) was shifted with sieve # 30 and mixed with primary granules with the help of a planetary mixture. Wet mass was prepared by 5% polyvinyl pyrrolidone solution in isopropyl alcohol (IPA) and passed through sieve #16 and dried in 45-50^0C for one hour. The dried granules were again screened with sieve # 12 and final granules were formed.

c) **Lubrication of granules:** - The granules prepared were lubricated with magnesium stearate and Aerosil (colloidal silicon dioxide) and thoroughly mixed.

d) **Compression:** - The lubricated granules were compressed in rotary tablet machine (Minipress-II MT) using 8 mm flat punch, keeping the average tablet weight 230 mg. in process weight variation and hardness variation was tested.

Table no.1: Composition of **Pregabalin**100 mg sustained release matrix tablet:-

Ingredients	Quantity (mg)							
	DS-1	**DS-2**	**DS-3**	**DS-4**	**DS-5**	**DS-6**	**DS-7**	**DS-8**
Pregabalin	100	100	100	100	100	100	100	100
HPMC K100	110	105	100	95	90	85	80	75
Glyceryl behenate	00	5	10	15	20	25	30	35
Microcrystalline cellulose	4	4	4	4	4	4	4	4
Polyvinyl pyrrolidone K30	8	8	8	8	8	8	8	8
Colloidal silica (Aerosil)	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2

Evaluation of tablet blends

Angle of repose: The angle of repose of tablet blends was determined by the funnel method. Theblends were allowed to flow through the funnel freely onto the surface. The diameter of thepowder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where 'h' and 'r' are the height and radius of the powder cone, respectively.

Bulk density: Apparent bulk density was determined by pouring a weighed quantity of tabletblends into graduated cylinder and measuring the volume and weight.

Bulk Density = Mass of powder / Bulk Volume of the powder

Tapped bulk density: It was determined by placing a graduated cylinder, containing a knownmass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hardsurface from the height of 10 cm at 2 second intervals. The tapping was continued until nofurther change in volume was noted.

Tapped density = Weight of powder / Tapped volume of the powder

Carr's index: Carr's compressibility index CI (Carr, 1965) is defined as follows:

CI = ρt - ρa / ρt = Va – Vt / Vt

Where ρt and ρa – tapped and poured bulk density; And Vt and Va – tapped and poured bulkvolume respectively.

Hausner's ratio: A similar index has been defined by Hausner [12-15].

Hausner's ratio = Tapped density / Poured Density

Evaluation of Pregabalin 100 mg sustained release matrix tablet:

a) Weight Variation Test:[16]

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per United State Pharmacopoeial Specification, tablets with an average weight ranging between 130 to 324 mg, the percentage deviation should not more than ± 7.5 %.

b) **Hardness Test:**[16]

The hardness of tablets was carried out by using Monsanto type hardness tester. The hardness of the tablets kg/cm² was measured.

c) Thickness Test: [16]

Control of physical dimension of the tablets such as sizes and thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using digital micrometer calipers. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter.

d) Drug content:[16]

For this at least 30 tablets were randomly selected. Out of 30 tablets 10 tabletswere crushed into fine powder assayed individually after proper dilution at 210 nm using a UV spectrophotometer.

e) **Friability Test:**[17]

Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The apparatus was operated for 4 minutes and reweighed the tablets. Friability was calculate by the following formula—

$$F = 100\left[\frac{W_0 - W}{W}\right]$$

Where, F = Friability

Wo = Initial weight

W = Final weight

f) Dissolution Study:[18]

In-vitro dissolution study, presently, an important tool to estimate in-vivo drug availability. In-vitro drug release study was performed using USP-XXIII Dissolution test apparatus employing basket stirrer. The drug release from **Pregabalin** S.R. tablet was carried out in simulated gastric fluid i.e. in pH 1.2 for 0 to 2 hours and in simulated intestinal fluid i.e. in pH 6.8 for up to 10 hours.

Medium	: 900 ml pH 1.2 Hydrochloric acid buffer for 0 to 2hours.
	: 900 ml of pH 6.8 phosphate buffer for 2 to 8 hours.
Apparatus	: USP II (Basket).
Speed	: 50 rpm.
Time	: 0 to 8thhours.
Sampling	: 5 ml at 1 hour interval.
Temperature	: 37^{0}C ± 0.5^0 C

Six tablets from each formulations of prepared and marketed **Pregabalin**100mg SR tablets was tested at a time. Singe tablets was

placed in each basket and whole set up was placed in 900 ml pH 1.2 dissolution medium. A rotation speed of 50 rpm and temperature of 37±2^{0}C was employed. After first two hours the medium was replaced with pH 6.8 phosphate buffer and test was continued for further 8 hours. 5 ml of sample aliquots were withdrawn after every hour and same volume was replaced with fresh dissolution medium. Collected samples were suitably diluted and analyzed spectrophotometrically at 276 nm using distilled water as blank. Cumulated percentage of drug release was calculated.

g) Assay of Pregabalin100 mg SR tablet:[19]

Standard Preparation

Weigh accurately 50 mg of **Pregabalin** in 100 ml of volumetric flask and dissolve in sufficient 0.1M sodium hydroxide produce 100ml, Pipette 1ml of the resulting solution in 50ml volumetric flask and make up the volume with buffer solution of pH 7.4

Sample Preparation

Crushed 10 tablets, weighed accurately a weight equivalent to 50 mg of **Pregabalin** in 100 ml volumetric flask, and dissolve in sufficient 0.1 M sodium hydroxide solution to produce 100ml and stir for 1 hour. Centrifuge and Pipette 1 ml of the resulting solution in 50 ml of volumetric flask and add sufficient buffer of pH 7.4 to produce 50 ml.The absorbance of standard and sample solutions measured at 276 nm using pH 6.8 buffer as blank.

RESULTS AND DISCUSSION:

The blends of different formulations were evaluated for angle of repose, bulk density, tapped bulk density, compressibility index and hausner's ratio. The results of bulk density, tapped bulk density, compressibility index and hausner's ratio are mentioned in table no. 2.

Table no. 2: Physical characteristics of prepared blend of Pregabalin

Parameters	DS-1	DS-2	DS-3	DS-4	DS-5	DS-6	DS-7	DS-8
Angle of repose	33^0.12'	32^0.93'	30^0.41'	31^0.21'	33^0.27'	33^0.23'	33^0.08'	31^0.43'
Bulk density	0.476	0.474	0.477	0.476	0.473	0.476	0.474	0.475
Tapped bulk density	0.526	0.523	0.518	0.526	0.528	0.525	0.521	0.526
Compressibility Index	41.66	42.12	42.32	41.66	42.11	41.36	41.72	41.56
Hausner's Ratio	1.632	1.534	1.737	1.714	1.743	1.698	1.721	1.648

Uniformity of weight

The weight of Pregabalin sustained release matrix tablet of all batches(DS1 to DS8) was found to be 225 mg (Table 3). The uniformity of the weights of the tablet Complies as per USP specification.

Drug Content

For the various formulations (DS1 to DS8), % drug content was found to vary between 96 to 98.8 (Table 3). The estimation of drug content was found to be almost same.

Uniformity of thickness

The thickness of Pregabalin sustained release matrix tabletof all batches (DS1 to DS8) was found to be in range of 3.80 mm to 3.98 mm as shown in (Table 3). The measured thickness of all the eight formulations ensured uniformity in thickness.

Friability

For the various formulations (DS1 to DS8), % Friability was found to vary between 0.26 to 0.31 (Table 3). The result indicate that the percentage loss were not more than 1%.

Hardness

For the various formulations (DS1 to DS8), Hardness was found to vary between 4 to 6 (kg/cm^2) (Table 3). The result indicates that the

tablet having considerable mechanical stability to withstand packaging and shipment hazards.

Table no. 3: Evaluation of Pregabalin sustained release matrix tablet

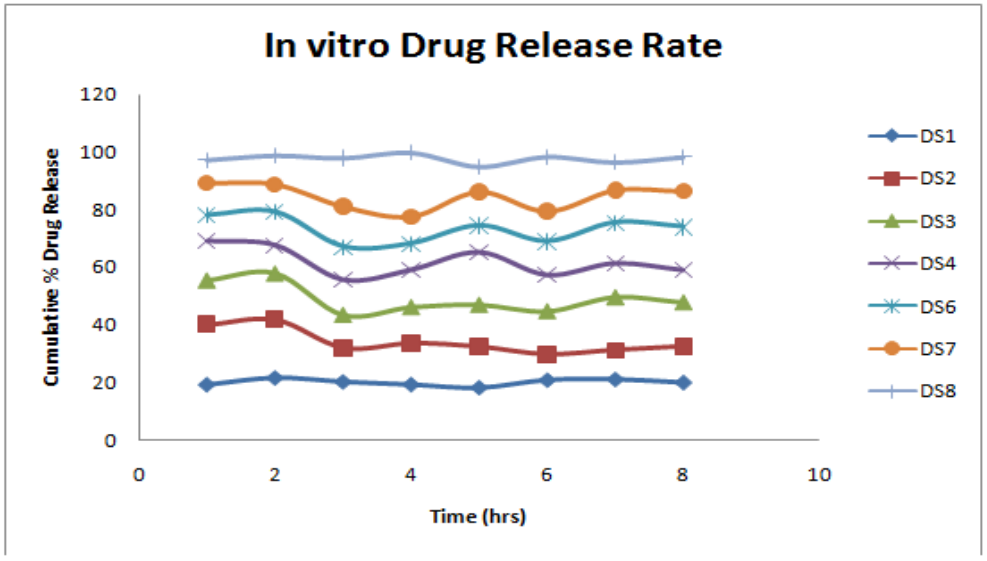
parameter	DS-1	DS-2	DS-3	DS-4	DS-5	DS-6	DS-7	DS-8
Uniformity of weight (mg)	225	225	225	225	225	225	225	225
Drug Content (%)	96.00	97.65	96.14	98.80	97.40	98.20	97.24	96.70
Thickness (mm)	3.84-3.94	3.82-3.94	3.82-3.94	3.84-3.96	3.80-3.94	3.82-3.94	3.84-3.98	3.80-3.92
Friability (%)	0.26-0.30	0.26-0.30	0.26-0.29	0.26-0.31	0.26-0.29	0.27-0.31	0.27-0.30	0.26-0.30
Hardness (kg/cm^2)	4 – 5	4 – 5	5 – 6	4 – 5	4 – 5	4 – 5	4 – 5	5 – 6
Assay (%)	100.11	99.97	100.08	99.87	99.24	100.17	98.78	99.56

Table no. 4: In vitro drug release data of Pregabalin sustained release tablets:

Cumulative Percent Drug Release

Batch Number	Time Interval (hours)						
	In pH 1.2		in pH 7.4				
	1	2	3	4	6	7	8
DS-1	19.11	40.11	55.25	69.11	78.16	89.21	97.21
DS-2	21.53	41.98	57.64	67.67	79.31	88.78	98.78
DS-3	20.12	31.95	43.31	55.86	67.22	81.1	97.88
DS-4	19.15	33.58	46.03	59.25	68.32	77.63	99.76
DS-5	18.04	32.43	46.82	65.25	74.58	86.17	94.87
DS-6	20.76	29.67	44.58	57.48	69.11	79.43	98.34
DS-7	21.01	31.23	49.45	61.45	75.64	86.73	96.38
DS-8	19.88	32.51	47.65	59.15	74.19	86.39	98.21

Figure 1: In-vitro drug release rate of all formulation



The result indicates formulation IV has better drug release over an extended period of 8 hours.

CONCLUSION

In this present study the attempt was made to formulate sustained release 'Twice daily formulation' of Pregabalin, which can provide effective drug release for 8 hours. Sustained Release matrix tablets Pregabalin, were prepared by double granulation initially melt granulation and finally wet granulation. Addition of hydrophobic substance to the formulation shows remarkable decrease in drug release, which may due to reduction of hydro-diffusion in the matrix and decrease in the diffusivity of the drug molecules through hydrophobic medium. Increase in the ratio of hydrophobic release retardant decrease the release of the drug from the matrix. In-vitro drug release study confirms that sustained release claimed for 100 mg Pregabalin matrix tablet is well suited. Comparison with marked product of Pregabalin100 mg sustained release tablet also confirms the sustained release claim.

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