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FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF PREGABALIN

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Abstract

The aim of this study is to develop a once-daily controlled release matrix tablet of Pregabalin. It is decreasing the dose frequency and increases bioavailability of the drug. Controlled release formulation is the drug deliverysystem that is designed to achieve a prolonged therapeutic effect by continuously releasingmedication over an extended period of time after administration of single dose. Controlled release system release the drug in a predetermined period. The matrix tablets were prepared by using hydroxy propyl methyl cellulose (k4m), HPC k100m, and carbomer, Xanthum Gum, in varying proportions. The blended tablets were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content.

Key words: pregabalin matrix tablets, controlled release

Introduction

Controlled delivery systems provide an alternative approach to regulate the bioavailability of therapeutic agents. Controlled drug delivery system is designed in such a way that when an active medicament is encapsulated in the polymer structure then the release of drug will be in a predetermined way. Controlled drug delivery systems are to ensure safety by maintaining plasma drug concentration in therapeutic window for extended period of time, and enhancement of efficacy of treatment with improved patient compliance. So the use of such dosage forms is increasing in treatment of acute and chronic diseases. Thus, controlled drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects. Controlled release provides the most desirable dosing regimens with effective pharmacokinetic profile and pharmacodynamic response in chronic pain management. This approach prevents the

patient from experiencing pain intermittently through maintenance of consistent drug input and it may allaviates the variability involved in the administration of multiple doses per day. Hence, controlled release dosage form of pregabalin drug improves patient compliance and prevents the dramatic onset of a convulsions seen with immediate release dosage forms.[1,2,3]

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 painand other pain syndromes, postherpetic neuralgia, and social anxiety disorders. Pregabalin'sinnovator is Pfizer-Global and appears world-wide under the brand name Lyrica. The half-life ofPregabalin is also short (5-6.5 hrs) which makes it suitable candidate for controlled releaseformulation, moreover it reducing side effects, decreasing frequency and improve patientcompliance[5-8]. Keeping these factors in view it is aimed to formulate and evaluate controlled release matrix tablets, to provide a controlled and predictable release of Pregabalin, which is anoral antiepileptic drug used in the management of epilepsy.

Material and Method

Pregabalin is a gift sample obtained from the bio–Leo analyticallabs Ltd, Hyderabad. , HPMC-K4, HPC, xantham gum, carbomer, PEG,were obtained S. D. Fine Chemicals Ltd.Magnesium strearate and anhydrous calcium di hydrogen phosphate,aerosol, sodium lauryl sulfate, micro crystalline cellulose was obtained from king koti, Hyderabad.

InstrumentsUsed

Tablet punching machine (CADMAC),HPLC (WATERS C 2695), bulk density apparatus, dissolution tester (ELECTROLAB), friability tester (ELECTROLAB), hardness tester (Monsanto), verinier calliper's scale were the instruments used for this study.

Method

Preparation of matrix tablets

Matrix tablets were prepared by direct compression method. The composition of various formulations was shown in **Table 1.**Pregabalin,HPMC k4m,HPC,xanthumgum, carbomer, polyethylene glycol, and anhydrous calcium hydrogen

phosphate, talc, aerosiland Magnesium strearate. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes to ensure uniform mixing in geometrical ratio,and passed through #60 mesh and collect separately in polyethylene bag. Tablets were compressed at 550 mg weight on a 16-station rotary tablet punching machine (Cadmach Machinery pvt. Ltd) with 8.5mm circular shaped deep concave punches plain on both sides, the six different formulae, having different concentrations were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

Table-1: Composition of pregabalin550mg CR tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
PREGABALIN	150	150	150	150	150	150	150	150
Carbomer	85	-	-	-	150	75	-	-
HPMC K4	-	100	75	150	-	-	-	
HPCK100m	-	-	150	75	-	-	-	
Xanthum gum	-	-	-	-	75	150	75	150
Guar gum							150	75
Dicalcium phosphate	30	-	-	-	-	-		
Microcrystalline cellulose	150	150	70	70	85	85	85	85
Polyethylene glycol	20	25	15	15	20	20	20	20
Aerosil	35	35	20	20	-	-	-	-
Talc	25	25	25	25	25	25	25	25
Magnesium strearate	25	35	15	15	15	15	15	15
Sodium lauryl sulfate	30	30	30	30	30	30	30	30

Bulk density (Db)

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduate measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by

Db = M / V0

Where, M is the mass of powder, V0 is the bulk volume of the powder.

Tapped density (D_t)

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed ingm/ml and is given by,

$$\mathbf{D_t = M / Vt}$$

Where, M is the mass of powder.

$V_t$is the tapped volume of the powder.

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was thencalculated using following equation,

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

Where θ =Angle of repose**,** h=Height of pile**,** r=Radius of the base of the pile.

Carr's Consolidation Index (I)

Carr's index is an indication of the compressibility of a powder. It is

Expressed in percentage and is given by

$$\mathbf{I = D_t – Db / Dt \times 100}$$

Where D_t=Tapped density, Db=Bulk density.

Thickness and diameter

Control of physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured usingVernierCalipers. It is measured in mm.

Hardness

The Monsanto hardness tester was used to determine the tablethardness .The tablet was held affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm^2.

Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The% friability was then calculated by: -

F=100(initial weight- final weigh/final weight)

Weight variation as per IP

Randomly selected twenty 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 percentage limit. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

PD= (W_{avg}) – ($W_{initial}$) / (W_{avg}) x 100

Where PD= Percentage deviation, W_{avg} =Average weight of tablet,

$W_{initial}$ =Individual weight of tablet.

Drug content (Assay)

Drug content was determined by HPLC method by using Inertsil ODS-3; 250mmx4.6mm; 5µ or equivalent as column and mixer of 50:50 buffer and acetonitril was used as mobile phase, wave length 210nm, flow rate 1ml/min, and column temperature 30^0 C.

Procedure

Separately inject equal volumes (about 20 µl) of diluents as blank, five injections of standard solution and Test solution into the chromatograph, record the chromatograms, measure the drug peak Response. Drug content values were shown in

In- vitro **Release studies**

In vitro dissolution studies for all the Matrix tablets were carried out using USP type II Dissolution apparatus in 900 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at 37±0.5ºC at 50rpm. 5 ml aliquots were withdrawn at every 2 hour and replacedby 5 ml of fresh dissolution media (37ºC). The collected samples were analyzed after suitable dilution (if required) at 210nm usingHPLC(uv detector).

Results and Discussion

The matrix tablets of various batches formulate and evaluate Pregabalin matrix tablets for controlled release dosage form. The blends of different formulations were evaluated for the angle of repose, bulk density, tapped density, compressibility index, hausner's ratio are mentioned in Table no 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.The values of bulk density, tapped bulk density, compressibility index and hausner's ratio are mentioned in table 2. The bulk density of the tablet blend was in the range of 0.379± 0.03 to 0.453±0.39g/ml; the tapped density was in the range of 0.398± 0.25 to 0.509± 0.36 g/ml, which indicates that the powder was not bulky. The blend indicated good flow properties for all the formulation with the angle of repose values 24° 69' to 31° 37' according to fixed funnel and free standing cone method. The results of compressibility index lies between range from 5.89±0.60to 7.27±0.35, while hausner'sratio lies between 1.279±0.15 and 1.869±0.20 indicating good to excellent flow properties. The tablets of different batches formulated were evaluated for test such as hardness, friability, thickness, uniformity of weight and drug content. The results obtained from all formulations were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values and hence all formulation passed the test for uniformity of weight. The tablets mean thickness values ranged from 3.45±0.4 mm to 3.89±0.2 mm. The hardness of all the tablets was within the range of 4 to 6 kg/cm^2. The loss in friability test was in a range of 0.09 to 0.56%. The percentage drug content for different tablet formulations were discrete from 80% .66 to 98.16%, were found to be within range (table 3).

***In-vitro*evaluation of modified release controlled release tablet:**

The performance of modified release formulation has been reported to be greatly affected by physicochemical properties of polymer. The amount of polymer may influence the release of drug from the formulation. In vitro release study performed in PH6.8 phosphate buffer with 900 ml, paddle, 50 rpm, reveals that the release of drug was retarded with the proportional increase of the polymer concentration. When the hydrophilic matrix tablets of Class I drug come into contact with the dissolution medium, they take up water and swell, and release drug from the matrix.

Thedissolution studies of all the formulations of controlled release tablets of Pregabalin were carried out in PH 6.8 phosphate buffers for 24 hours. Only three (F3, F4 and F6) tabletformulations showed acceptable properties as shown in table 4.The result of the dissolutionstudy indicating that F1, F2, F5, F7 and F8 formulations released the less amount of drug at the end of 24hrs, Formulation F3, F4 and F6 released 91.92%, 98.16% and 92.24% at the end of 24 hrs. Here we observed that on decreasing the proportion of HPMC K4m and on increasing the quantity of HPC and carbomer, it retards the drug release from matrix. 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. It is expected that the developed formulation should have the following theoretical drug release profile, i.e., 100% for 24 hrs. Formulations F1, F2, F5, and F7, F8 failed to meet the needed theoretical drug release profile. Formulation F3, F4 and F6 met the needed theoretical drug release profile and has theControlled action i.e., retarding the drug release so the release is for a long time and thus more Bioavailability. Formulation F4 release 100% drug at the end of 24 hrs, for these reasons, it wasConsidered the best formulation amongall the eight formulations of this series.

Conclusion

From the present experimental results it can be concluded that the formulation prepared in combination with HPC K100M and HPMCK4m (F4) showed better similarity to the target formulation and has been optimized. The powder blend of the mixture of Pregabalin, HPC K100M, HPMC k4m, Xanthan gum and other excipients has a good flow property andcompressibility index. The overall drug release of the optimized formulation is more than that of the target release profile formulation but it has comparatively similar release pattern compared to target release profile formulation. The release of Pregabalinfrom matrix tablet is in a controlled manner. Controlled drug release following zero order (R^2=0.994) and korsmeyer peppas theory represents (R^2=0.936) release kinetics of Pregabalinmatrix tablets prepared from the polymers HPC K100M, HPMC k4m and Xanthan gum can be successfully employed as a once daily oral controlled drug delivery dosage form.

Table no-2:Physical Characteristics of prepared blend of pregabalin.

Formulation	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose
F1	0.472±0.01	0.509±0.36	7.27±0.35	1.279±0.15	31.37
F2	0.374±0.03	0.398±0.25	6.03±0.25	1.364±0.26	26.83

F3	0.398±0.17	0.425±0.32	6.26±0.30	1.466±0.15	24.69
F4	0.404±0.14	0.432±0.26	6.48±0.90	1.869±0.20	30.14
F5	0.412±0.02	0.468±0.25	5.89±0.60	1.634±0.36	28.16
F6	0.453±0.39	0.498±0.26	6.89±0.78	1.525±0.25	29.43
F7	0.415±0.03	0.468±0.25	6.03±0.25	1.464±0.20	28.0
F8	o.404±0.14	0.428±0.25	7.17±0.35	1.466±0.15	25.13

Table-3: Evaluation of pregabalin CR tablets.

Formulation	Uniformity Of Weight	Thickness(mm)	Friability	Hardness	Drug Content
F1	550 mg	3.74±0.1	0.14	5.5	80.66
F2	550mg	3.84±0.2	0.09	5.8	88.92
F3	550mg	3.74±0.7	0.12	6	91.92
F4	550mg	3.45±0.4	0.36	4.8	98.16
F5	550mg	3.56±0.6	0.48	6.5	90.15
F6	550mg	3.68±0.1	0.56	6.2	92.24
F7	550mg	3.74±0.1	0.36	4.8	87.81
F8	550mg	3.68±0.1	0.48	4.8	89.8

Table-4: in-vitro drug release of pregabalin CR tablets %Cumulative drug release profile.

formulation	0	2	4	6	8	10	12	14	16	18	20	24
F1	0	5.08	12.81	17.13	24.52	28.95	33.68	39.46	46.30	52.14	64.56	80.66
F2	0	4.66	8.08	13.86	20.61	28.88	38.2	47.61	56.71	64.84	71.10	88.22
F3	0	6.09	12.07	23.83	33.68	39.40	49.76	59.16	66.06	71.75	80.43	91.92
F4	0	9.07	20.01	29.99	37.86	45.74	52.73	60.74	68.38	75.52	82.1	98.16
F5	0	6.53	14.21	23.95	33.68	40.70	47.61	59.16	62.38	70.02	78.48	90.50
F6	0	7.19	19.50	28.95	33.02	41.52	49.76	57.20	66.06	75.52	82.39	92.24
F7	0	6.85	13.44	19.51	28.45	36.45	43.91	50.81	59.07	64.84	71.75	87.81
F8	0	7.85	16.86	23.95	31.29	39.40	45.35	52.73	60.74	69.20	76.99	89.8

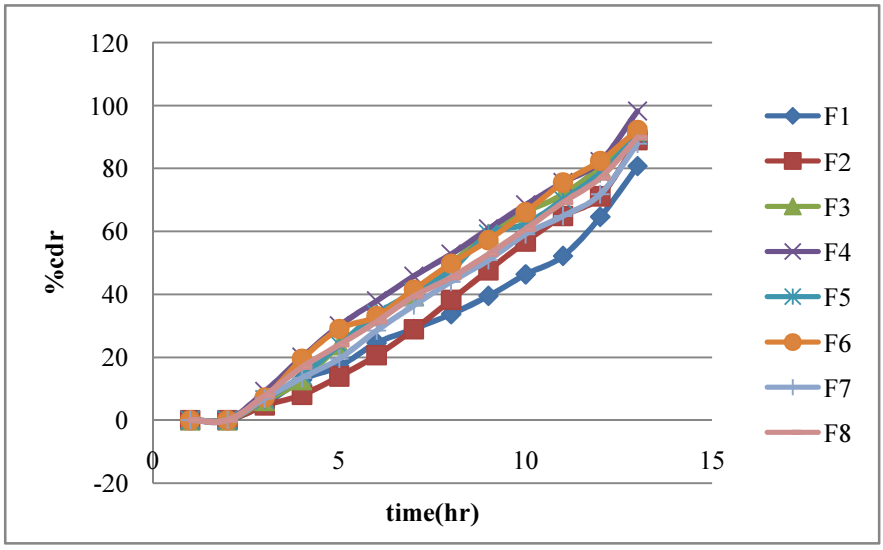

Fig-I

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