FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF PREGABALIN

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ABSTRACT

The present investigation concerns the development of Gastro retentive floating tablets of Captopril. floating tablets of Captopril was formulated by using Ethyl cellulose, Isapgol husk and Fenugreek extract as a polymeric matrix forming materials in various concentrations to study their ability to retard the release. All the formulations showed good flow properties such as angle of repose, bulk density and tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 99.35 % in 12 hours. Hence it is considered as optimized formulation F5 which contains Isapgol husk. It followed Zero order release mechanism.

Key words: *Captopril, Isapgol, Fenugreek, Ethyl cellulose, Gastro retentive floating tablets.*

INTRODUCTION

In recent years, a major goal for the drug delivery research is turned towards the development of efficacious drug delivery systems with already existing active ingredients in case of new drug discovery. Many of pharmaceutical therapeutic agents are mostly effective when made available at constant rates or near to absorption sites. Much effort has been going on to develop sophisticated drug delivery systems such as osmotic devices for oral application. Oral drug delivery system is more favored on popular controlled drug delivery system in pharmaceutical research and development (R & D) business due to increase in awareness of medical and pharmaceutical community about the importance of safe and effective use of drug. This system aims to maintain plasma drug concentration within the therapeutic window for long period of time.

Traditionally, it is becoming increasingly more evident with the specific time that patients have to take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hr period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. In the human body systems such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally followed by the internal body clocks and are controlled by the sleep wake cycle. This system focused on controlled or sustained release of drug of

which has such advantages of nearly constant level of drug at site of administration, minimizing peak - valley fluctuation of drug concentration in body and avoidance of adverse effect because Reduction in dose, dosage frequency and patient efficacy and compliance by this delivery system also expected.

A release pattern of drug is not suitable in certain disease condition. At that time, release profile of a delivery system characterized by lag time. In other words, the drug should not release during its initial period of administration, followed by a rapid and complete release (pulse release) of drug that is called pulsatile drug delivery system. This system aims to deliver a drug via the oral route at a rate different than constant i.e., zero order release. The lag time is the time interval between the dosage forms is placed into the aqueous environment and drug get to release from its dosage form after rupturing or eroding outer layer. The lag time between 0.5 hr to 4 hr is desire for upper region of gastrointestinal tract and more than 4 hr for lower portion of small intestine.

"Chronopharmaceutics" consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. Mainly mechanical rhythms in our body are:
Circadian - this word comes from Latin word "circa" means about and "dies" means day and oscillation completed in 24 hr

Ultradian - oscillation of shorter duration (more than one cycle per 24 hr) Infradian - oscillations that are longer than 24 hr (less than one cycle per day)
Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hr and regulate many body functions like- metabolism, sleep pattern, hormone production etc. PDDS are widely important in such wide spread disease which is mentioned below

- Chronopharmacotherapy of diseases which shows circadian rhythms in theirpathophysiology Confidential
- Extended day time or night time activity
- Avoiding the first pass metabolism e.g., protein and peptides
- Biological tolerance **(**e.g., transdermal nitroglycerin)
- For targeting specific site in intestine e.g., colon
- For time programmed administration of hormone and drugs
- Gastric irritation or drug instability in gastric fluid
- For drugs having the short half life
- Lower daily cost to patient due to fewer dosage units are required in therapy
- Reduction in dose size and dosage frequency and also side effects

Materials: Pregabalin **Sura labs**, Sodium Starch Glycolate, Mannitol, PVP K 30, Sodium Stearyl Fumerate, Aerosil, Dammar gum, Guar gum, Xanthan Gum

from **S.D. Fine chemical limited** (Hyderabad).

Methods:

Analytical method development:

a) Preparation of calibration curve in 0.1N HCL:

10mg of Pregabalin pure drug was dissolved in 10 ml of methanol (stock solution 1). 1ml of solution was taken and makes up with10 ml of 0.1N HCL (100µg/ml) stock-2. From this 1ml was taken and make up with 10 ml of 0.1N HCL (10µg/ml) stock-3. The above stock-II solution was subsequently diluted with 0.1N HCL to obtain series of dilutions containing and 2,4,6,8 and 10µg/ml of solution. The absorbance of the above dilutions was measured at 276 nm for 0.1 N HCL by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The Same procedure repeated in pH 6.8 phosphate buffer.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

Formulation development of Tablets:

Formulation of core tablets by direct compression: The inner core tablets were prepared by using direct compression method as shown in the Table. Powder mixtures of Pregabalin, microcrystalline cellulose, Sodium Starch Glycolate, Aerosil ingredients were dry blended for 20 min. followed by addition of Sodium Stearyl Fumerate. The mixtures were then further blended for 10 min., 300 mg of resultant powder blend was manually compressed using , Lab press Limited, India with a 9 mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer: The various formulation compositions Containing Ethyl cellulose and HPMC K100M, Sodium Stearyl Fumerate, Aerosil And Microcrystalline Cellulose. Different compositions were weighed dry blended at about 10 min. and used as press coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets: The core tablets were press-coated with 150 mg of mixed blend as given in 150 mg of barrier layer material was weighed and transferred into a 10 mm die then the core tablet was placed manually at the center. The remaining of the barrier layer materiel was added into the die and compressed by using Lab press Limited, India

Formulation development of core tablets

Ingredients	C1	C2	C3

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core Tablet	300	300	300	300	300	300	300	300	300
Dammar gum	50	75	100	-	-	-	-	-	-
Guar Gum	-	-	-	50	75	100	-	-	-
Xanthan Gum	-	-	-	-	-	-	50	75	100
Sodium Stearyl Fumerate	3	3	3	3	3	3	3	3	3
Mannitol	95	70	45	95	70	45	95	70	45
Aeosil	2	2	2	2	2	2	2	2	2
Total weight	450	450	450	450	450	450	450	450	450

Pregabalin	150	150	150
Sodium Starch Glycolate	25	50	75
Mannitol	101	76	51
PVP K 30	15	15	15
Sodium Stearyl Fumerate	6	6	6
Aerosil	3	3	3
Total weight	300	300	300

Formulations for press coated tablets

Evaluation Parameters

Pre compression parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was calculated using the following formula: $\tan \theta = h / r$

$\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3.

The bulk density was calculated using the formula: Bulk Density = M / VO

Where, M = weight of sample

Vo = apparent volume of powder

Tapped density:

The tapped density was calculated, in gm per L, using the formula:

Tapped density = M / V Where, Tap= Tapped Density
M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100
Where, b = Bulk Density Tap = Tapped Density

Post compression parameters of core and press coated tablets

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, hardness, friability, drug content and *in vitro* drug release studies.

Hardness

The prepared tablets were subjected to hardness test. It was carried out by using monsanto, Mumbai, India and expressed in Kg/cm^2.

Thickness

The prepared tablets were subjected to thickness test. It was carried out by using the ve r n i e r caliper Mitutoyo, Japan and expressed in millimeter.

Friability test

The friability was determined using friability test apparatus Labindia, Mumbai, India and expressed in percentage (%). 10 tablets from each batch were weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W_{final}) and the percentage friability was calculated for each batch by using the following formula.

Friability = [(W1-W2) / W] × 100 Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Weight variation test

Twenty tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5%.

Drug content

The Pregabalin tablets were tested for their drug content. Ten tablets were finely po wder ed . They require quantities of the powder equivalent to 25 mg of Pregabalin were accurately weighed and transferred to a 100-mL of volumetric flask. The flask was filled with buffer and mixed thoroughly. The solution was made up to Volume and filtered. Dilute 1 mL of the resulting solution to 100 mL with distilled water and measure the absorbance of the resulting solution at the maximum at 276 nm using

UV spectrophotometer (Labindia, Mumbai, India). The linearity equation obtained from calibration curve as described previously was use for estimation of Pregabalin in the tablets formulations.

Disintegration time of core tablets

Disintegration test was carried out using the tablet disintegration test apparatus specified in Indian pharmacopoeia. pH 6.8 phosphate buffer at 37 ± 0.5 ºC was used as the

Disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining on the screen was measured in seconds.

***In* vitro drug release study of pulsatile Pregabalin tablets**

***In vitro* drug release of Pregabalin core tablets**

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. pH 6.8 phosphate buffer was used as dissolution medium. Release pattern was studied visually by taking sample of 5 mL at the specific time intervals. Also the sample was analyzed at 276 nm for 6.8 phosphate buffer using a UV spectrophotometer.

***In vitro* drug release study of coated tablets**

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL was removed and pH 6.8 phosphate buffer was added process was continued from up to 8 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 276 nm using UV-spectrophotometer.

Preformulation Studies

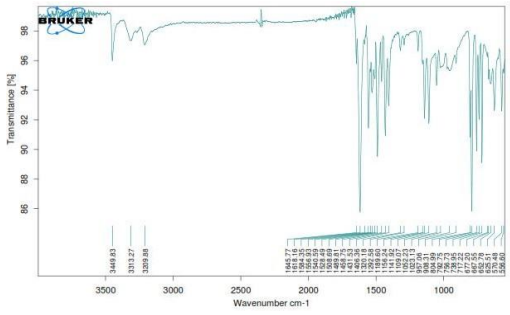
Standardization method for estimation of Pregabalin

Standard curves of Pregabalin were prepared in 0.1N HCL and phosphate buffer (pH 6.8).

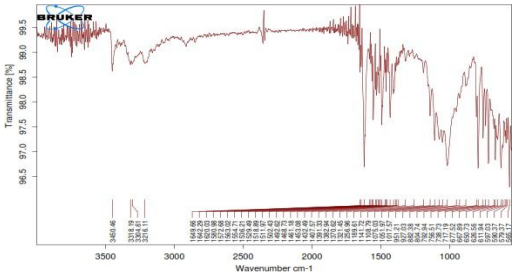
Standard graph of Pregabalin in 0.1N HCL

Pregabalin showed maximum absorbance in 0.1N HCL at 276 nm. The solution obeyed Beer-Lambert's law for concentration range of 0 µg / mL to 10 µg / mL with regression coefficient of 0.998. Standard curve of Pregabalin prepared in 0.1N HCL.

Standard graph of Pregabalin in phosphate buffer (pH 6.8): Pregabalin showed maximum absorbance in phosphate buffer (pH 6.8) at 276 nm. The solution obeyed Beer-Lambert's law for concentration range of 0 to 10 µg / mL with regr ession coefficient of 0. 999.



FTIR spectra of Pregabalin pure drug



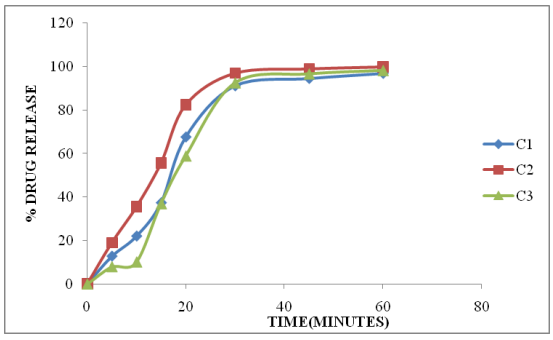
FTIR spectra of Optimized Formula

The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore it implies good compatibility of drug and excipients.

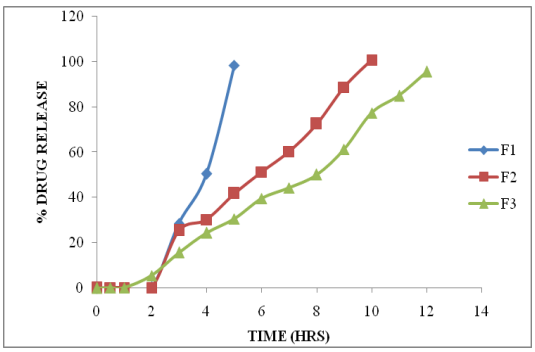
Pre compression parameters of Cap core tablets

Formulationcode	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* disintegration time (min)
C1	299.12	1.13	0.24	0.345	99.18	10
C2	300.28	1.25	0.18	0.287	98.27	15
C3	300.77	1.34	0.22	0.321	99.33	18

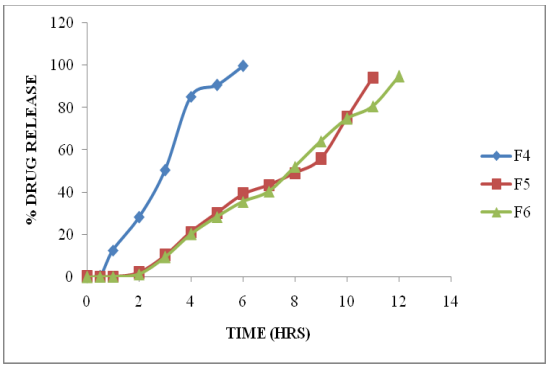
All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits



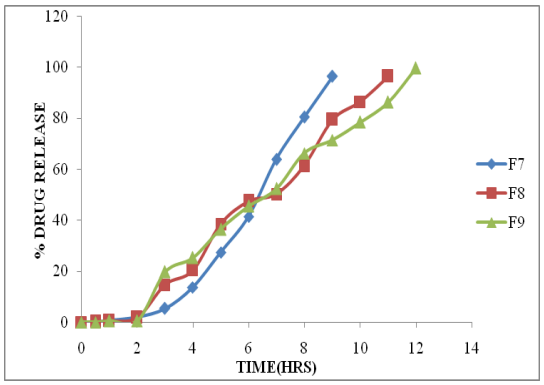
Cumulative % drug released of Pregabalin core tablets



Cumulative % drug release study of Pregabalin pulsatile tablets (F1, F2 & F3)



Cumulative % drug release study of Pregabalin pulsatile tablets (F4, F5 & F6)



Cumulative % drug release study of Pregabalin pulsatile tablets (F7, F8, F9)

CONCLUSION

Pregabalin Pulsatile dosage form was formulated by press coating technique.

The lag time and time-controlled release behavior of Pregabalin from press coated tablets could be modulated by varying the concentration of polymer in outer coating layer and thickness if compression coating. From formulation C1-C3 Pregabalin core tablets, C2 showed faster drug release than the other formulations. Faster drug release can be correlated with the high disintegration time. So, C2 formulation was selected as best formulation for further press coating and enteric coating formulations. Among All Formulations F9 was showed maximum % drug release 99.58% at 12 hours. Hence F9 Formulation was considered as optimized Formulation.

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