Research Article

Int J. Pharm. Drug. Anal, Vol: 11, Issue: 4, 2023;18-23

International Journal of Pharmaceutics and Drug Analysis

Content Available at www.ijpda.com ISSN: 2348:8948

DESIGN, DEVELOPMENT AND IN-VITRO CHARACTERIZATIONOF OF CYCLOBENZAPRINE HCl SUSTAINED RELEASE PELLETS

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Received: 19 Sept 2023 Revised: 29 Sept 2023 Accepted: 15 Nov 2023

Abstract

The aim of the present study is to formulate and evaluate the cyclobenzaprine hydrochloride extended release pellets by Wurster coating method using starch, PVP K-90, ethyl cellulose, isopropyl alcohol, talc and other polymers to release the drug slowly through an extend period of time. The method of preparation of Cyclobenzaprine Hydrochloride SR pellets involves in two steps, namely drug coating and polymer coating. In the drug coating process drug is coated as a suspension form to dummy pellets and dried and sieved. Drug loaded pellets are coated with SR polymer to form SR pellets. These SR pellets are dried, sieved and send to quality control. FTIR studies of the formulation indicating no chemical interaction between cyclobenzaprine HCl and excipients. In order to get the optimized formulation, the various process parameters were adjusted. The various evaluations for formulations were carried out, that to based on the *in-vitro* drug release studies of F5 formulation shows better drug release profile than other formulations. The results conclude that trial F5 has met the objective of extended release, cost effective as once day of drug.

Keywords: Cyclobenzaprine hydrochloride, extended release pellets, sugar spheres, starch, PVP K-90, ethyl cellulose

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DOI: https://doi.org/10.47957/ijpda.v11i4.563

Produced and Published by

South Asian Academic Publications

Introduction

Pellets are small, free-flowing spherical or semispherical solid unit particulates made by agglomerating fine powders or granules of drug substances and excipients using appropriate processing technologies (layering of the drug solution, suspension, or powder on the inactive cores, extrusion, spheronization, and agglomeration in rotogranulators or rot processors, compression, spray drying, and spray congealing

They help in the development of modified release multiple dose forms with various release patterns such as immediate and sustained release patterns, drug taste masking, gastro retentive floating, and self-emulsifying. Pellets have several advantages, including the capacity to induce sustained drug release, limit adverse effects without compromising bioavailability, and promote patient acceptability [1-5].The chemical formula for cyclobenzaprine HCl is 3-(5H- dibenzo [a,d] cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride ($C_{20}H_{21}N$ HCl). It is a tricyclic antidepressant, similar to amitriptyline and imipramine, and it may aid with sleep and pain control in fibromyalgia patients. It is excellent for providing immediate relief from back pain, neck discomfort, and muscular spasms. It operates directly on skeletal muscle by inhibiting calcium release from the sarcoplasmic reticulum, which reduces muscular contraction. Musculoskeletal pain is treated using skeletal muscle relaxants that have antispastic effects. It has a melting point of 217 degrees Celsius and a pKa of 8.47 at 25 degrees Celsius. It is soluble in water and alcohol, weakly in isopropanol, and completely insoluble in hydrocarbon solvents [6-9].

The goal of this study is to create prolonged release pellets of cyclobenzaprine HCl in order to minimize dose frequency, improve patient compliance, and investigate the physicochemical characterisation of the medication in pellet formulation.

Materials and Methods

Materials

Cyclobenzaprine hydrochloride was provided by Aurabindo labs (Hyderabad, India). Sugar spheres (24#30 PVP K-90, talc was obtained as gift samples from SD fine Chemicals Ltd. Ethyl cellulose, Methylene dichloride, talc obtained from bross chemicals all reagents and chemicals were of analytical grade.

Methods

Determination λ_{max} of cyclobenzaprine HCl:

Determination of λ_{max} of cyclobenzaprine HCl by Ultraviolet absorption spectrophotometer (Hitachi- U2000, Japan) based on the measurement of absorbance at spectral range of 260-400 nm of U.V. region by using methanol as medium.

Calibration curve of cyclobenzaprine HCl Primary stock solution preparation

The standard solution was prepared by dissolving 100mg of Cyclobenzaprine HCl in 100ml of 0.1N HCl in volumetric flask.

Preparation of secondary stock solution:

From the primary stock solution 5ml of solution was pipetteout and then it was made up to 100ml using0.1 N HCl in 100 ml volumetric flask.

Preparation of suitable concentrations

From the secondary stock solution 1ml, 2ml, 3ml, 4ml, 5ml of solutionwerepipetteout,takenin10mlofvolumetric flasks and volume was made up to 10ml using 0.1 N HCl, in order to get the solution concentrations of 5, 10,15,20,25 µg/ml. The absorbance of those dilutions was measured in Hitachi-U2000 spectrophotometer at 290 nm against 0.1 N HCl as blank. The linear regression analysis was carried on absorbance data points.

Pre-formulation studies

The pre-formulation studies are performed such as melting point, solubility, drug excipient-compatibility studies. Melting point API was determined by capillary method by using Mel-Temp melting point apparatus. The solubility of drug can be determined as, weighed accurately about 1gm of pure drug and dissolved each in 1ml of the solvent system i.e.water, chloroform, IPA, dichloromethane, n-hexane, ethanol, methanol, acetone, isopropyl myristate in a well closed air tight containers. Then add the successive amount of the solvent in to the containers containing drug until the solution became saturated solution.

Drug-excipient compatibility studies:

Fourier Transform Infrared analysis (FT-IR) measurements of pure drug and drug-loaded pellet formulations were obtained using a Perkin- Elmer system 200 FT IR spectrophotometer. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm^2;the spectra were scanned over the wave numberrangeof4000to400cm^{-1}attheambienttemperature.

Physicalproperties[10]

Bulk density

Bulk density is defined as a mass of a powder divided by the bulk volume. Accurately weighed (weighing balance-Essae, DS-852 series) amount of powder was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by using the formula,

$$\textbf{Bulk density } (\rho_0) = M/V_o;$$

Where, **M** = mass of the powder**;**

V_o= volume of the powder.

Tapped Density

Tapped density is defined as amass of powder divided by tapped volume. Accurately weighed amount of powder was filled in 100 ml graduated cylinder. The cylinder was equipped to USP tapped density tester, it was subjected to 300, 500 taps/min from height of 14±2mm, note down the volume occupied by powder. The difference in volume after each taps is 300, 500 taps is more than 2%, then repeat the taps to 750, 1200 taps until the difference between succeeding measurements is less than 2%. It is expressed in g/ml and is calculated by using the formula,

$$\textbf{Tapped density } (\rho_t) = M/V_f$$

Where, **M** = weight of sample powder;

Vf= tapped volume.

Compressibility Index

Tapped density and bulk density were measured and the compressibility index was calculated by using the formula,

$$\%\text{Compressibility index} = [(\rho_t-\rho_o)/\rho_t] \text{ X } 100;$$

Where ρ_t= Tapped density;

ρ_o= Bulk density.

Hausner's ratio

Tapped density and bulk density were measured and the Hausner's ratio was calculated by using the formula,

$$\text{Hausner's ratio} = \rho t/\rho o;$$

Where,ρ_t=Tapped density**;**

ρ_o= Bulk density.

Angle of repose

Accurately weighed quantity of powder is poured in funnel and the height of funnel is adjusted to a height of 2.5cm and the radius of the circle is measured by taking the diameter values of average of four values and the half of the diameter is the radius. It can be calculated by using the formula,

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

Where,**h**=Height of the funnel**;**

r=Radius of circle

Formulation development [11-14]

Cyclobenzaprine Hydrochloride sustained release pellets are prepared by wurster coating method using different excipients and polymers to release the drug slowly through an extend period of time. The method of preparation of Cyclobenzaprine Hydrochloride SR pellets involves in two steps, namely drug coating and polymer coating. In the drug coating process drug is coated as a suspension form to dummy pellets and dried and sieved. Drug coated pellets are coated with SR polymer to form SR pellets. These SR pellets are dried, sieved and send to quality control.

Fig.No.1 Prepared SR Pellets of Cyclobenzaprine HCl

Evaluation of pellets

Description of pellets:

A small quantity of pellets for all formulations taken individually in butter paper, examined physically for observing shape, color.

Determination of Sieve analysis (%)

To determine the sieve analysis, arrange the sample collector, #20ASTM (American Society of Testing and Materials) sieve, #16ASTM sieve, Weigh andtransfer around 100g of the sample into #16 ASTM sieve and sieve shaker was operated at 60 amplitude for 5min. Collect and weigh the retainsfrom #16, #20 ASTM sieves respectively. The % retains and passing's can be calculated by using the formula.

$$\%\ Retains\ on\ 16\ Astm = \frac{W_{16} in\ g}{Weight\ of\ sampleing}\ X\ 100$$

$$\%\ Passing\ through\ 20\ Astm = \frac{W_{20} in\ g}{Weight\ of\ sampleing}\ X\ 100$$

Determination of Moisture Content (% w/w)

Take suitable quantity of Methanol in titration flask of Karl Fischer Titrator and titrate with Karl Fischer reagent to end point. Then add 200 mg of sodium tartarate dihydrate to the titration flask and titrate with Karl Fischer reagent to end point and note the titrant value.

$$Factor = \frac{Weight\ of\ scodium\ tartarate}{\text{Titrant value(V)}}\ X\ 100$$

Grind the pellets to fine powder in a dry mortar, weigh accurately about 0.5 g of the sample, transfer quickly to the titration flask, dissolve by stirring and titrate with Karl Fischer reagent to end point. The percentage of moisture content can be determined by using the formula.

$$Water\ \% \frac{VxF}{weight\ of\ sampleing} X100$$

Where, **F** = Factor of Karl Fischer reagent;

V = Volume in ml of Karl Fischer reagent consumed for sample titration.

Determination of percentage drug entrapment of efficiency

A known amount of drug was loaded in pellets during preparation. It was centrifuged and the supernant was diluted suitably with distilled water and the absorbance of resulting solution was measured at 290 nm on UV-VIS spectrophotometerto determine the amount of cyclobenzaprine present in the supernant .Drug entrapment was calculated by using the formula,

$$\%\ \text{Drug entrapment efficiency} = \frac{(W1 - W2)}{W1}\ x100$$

Where, **w**1=Total amount of drug added to the system;

w2= Drug present in the solution outside.

Estimation of drug content

Accurately weighed quantity of the pellets equivalent to about 30.0mg of cyclobenzaprine HCl in a 50ml volumetric flask add 40ml of 0.1 N HCl dissolve and dilute to the volume with 0.1NHCl and take 5ml of above solution in 50ml volumetric flask and dilute to the volume with 0.1NHCl and again take 5 ml of above solution in 50 ml volumetric flask and dilute to volume with 0.1NHCl and analyzed spectrophotometrically at 290 nm, drug content calculated using regression equation derived from the standard graph. All the experiments are done in triplicate (n=3).

Determination of drug release by UV -Visible spectrophotometer

The *In-vitro* dissolution studies were carried out in a USP Apparatus- II (Paddle- Electro lab, India) type dissolution assembly. Cyclobenzaprine HCl extended pellets equivalent to 30mg of drug introduced into 900ml of the dissolution medium (0.1N HCl) and stirred at 50 rpmat37±0.5ºC.At different time intervals solution is withdrawn and the same quantity fresh dissolution medium is replaced. Determine the amount of cyclobenzaprine HCl release in UV absorption at the wavelength of maximum absorbance at about 290nm on filtered portions of the solution under test, suitably diluted with Dissolution medium, if necessary in comparison with a standard solution having a known concentration of cyclobenzaprine HCl standard in the same medium. The percentage of drug release is calculated by using the regression equation as derived from the standard graph. All the experiments are done in triplicate (n=3).

Kinetics of drug release

The analysis of the mechanism of drug release from pharmaceutical dosage form is an important but complicated problem. The dissolution data obtained was fitted to zero order, first order, Higuchi, erosion and exponential equation to understand the order and mechanism of drug release from the pellets [11-15].

Zero order release kinetics

It defines a linear relationship between the fractionof drug released versus time.

$$Q = k_o t$$

Where, Q is the fractionofdrugreleased at time t and k_o is the zero order release rate constant.

A plot of the fraction ofdrug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most slow release tablets could be described adequately by apparent first-order kinetics.

The equation used to describe first order kinetics is $\ln(1-Q)=\Delta k_1 t$

where, Q is the fraction of drug released at time, (t) and k_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q=k_2 t^{½}$$

Where, k_2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation [15].

Erosion equation

This equation defines the drug release based on erosion alone.

$$Q=1-(1-k_3 t)^3$$

where, Q is the fraction of drug released at time t, k_3 is the release rate constant. Thus, a plot between $[1-(1-Q)^{1/3}]$against time will be linear if the release obeys erosion equation.

Results and Discussion

Determination of λ_{max} of Cyclobenzaprine HCl

The standard solution was prepared as per the method described in methodology section and scanned by UV-visible spectrophotometer. The UV absorption spectrum of cyclobenzaprine HCl shows highest peak at 290.0 nm against reagent used blank and the same was used for further analysis. The absorbance of the standard solution of cyclobenzaprine hydrochloride at 5-25 µg/ml were plotted as absorbance versus concentration which gave a straight line passing through the origin with regression coefficient 0.999. So it followed Beer's-Lambert's law at the concentration range of 5-25 µg/ml.

Pre-formulation studies

The following pre- formulation studies were performed on cyclobenzaprine HCl and excipients. The melting point of cyclobenzaprine HCl was found to be in the range 217°C-219°C by using melting temperature apparatus, which complied with USP standards, indicating purity of the drug sample. The solubility study of pure cyclobenzaprine HCl were summarized and it indicate that the pure drug cyclobenzaprine HCl was freely soluble in water, alcohols such as methanol, ethanol and isopropylalcohol as well as in chloroform, dichloromethane, acetone also acids like HCl when compared to the n- hexane, isopropyl myristate and and it indicates that the pure drug cyclobenzaprine HCl was freely soluble in water, alcohols such as methanol, ethanol and isopropyl alcohol as well as in chloroform, dichloromethane, acetone also acids like HCl when compared to the n-hexane, isopropyl myristate.

Drug-excipient compatibility

FT-IR spectra of cyclobenzaprine HCl and formulation containing all excipients were recorded. The cyclobenzaprine HCl present in the formulation was confirmed by FT-IR. Compatibility study of drug and excipient was conducted by employing I.R. spectral studies.The IR spectrum of cyclobenzaprine hydrochloride and its physical mixture is showingFig Nos. 2 and 3.

Physical properties

The bulk density values of all formulations varied from 0.71 g/cm^3 to 0.78 g/cm^3. The tapped density values ofall formulations ranges from0.84 g/cm^3 to 0.89 g/cm^3.The compressibility index for all formulations was determined by the equation given for compressibility index in methodology section. The compressibility index for all formulations lies within the range of 12.35 to 12.39; and hence they are showing good compressibility. The hausner's ratio values obtained by using the formula as described in the methodology section. The hausner's ratio values for all formulations varied from 1.00 to 1.04, which is nearer to optimum hausner's ratio of 1.11, which indicates excellent flow of powder. The angle of repose values obtained by using the formula as described in the methodology section. The angle of repose values for all formulations varied from33.69^o to 37.99^o, which indicates moderate flow.

Evaluation of pellets

Pellets observed visually, they are semispherical or spherical shape and white color. Sieve analysis for pellets was done as method described in the methodology section. The % Moisture content present in all the formulations (F1to F6) ranges from 1.92% to 2.63%, it was determined by Karl Fischer Titration method. The % of drug entrapment efficiency in all the formulations (F1 to F6) were ranging between 89.1% to 98.6%.

In-vitro drug release studies

After 12th hour the percentage drug release from the formulations were 93.6%, 89.1%, 91.6%, 02.9%, 98.6%, 83.4% for the formulations containing EC N14 2.5%,5% , 7.5% and EC N50 10%, 12.5% and 15% respectively. The dissolution profile was shown in figure and mean dissolution time (MDT) of pellets was given in Table. The burst release of Cyclobenzaprine HCl from formulations with EC N50 is comparatively lower than the one with EC N14, due to the fact that EC N50 is more viscous and release retarding capacity is more when compared to EC N14.Formulation F5 was identified to be the best as it matches well with the innovator (f2 = 71).

Drug release kinetics

The release curve of best formulation fits better for First order kinetics (r^2 = 0.982), Higuchi (r^2 = 0.968) and Hixoncrowl (r^2 = 0.944) model equations. The regression values are given in Table. It implies that the release kinetics follows a First order non-fickian super case-II

diffusion process. As it obeys Hixoncrowl model the drug release may also be due to erosion process. The drug release mechanism from pellets is following both diffusion and erosion phenomenon.

Conclusion

The present work aimed at developing SR pellets of Cyclobenzaprine HCl by Wurster process. FTIR studies showed no unacceptable extra peaks which confirm the absence of chemical interaction between the drug and polymer. Angle of repose, tapped density, bulk density values for the formulations was within the range which indicates that pellets prepared by Wurster process were satisfactory for further studies. The percentage drug content of Cyclobenzaprine was determined by extraction with methanol and analyzed by using UV-visible spectrophotometer at 290nm. After 12hours the percentage drug release from the all formulations 93.6%, 89.1%, 91.6%, 02.9%, 98.6%, 83.4%for the formulations containing EC N14 2.5%, 5% , 7.5% and EC N50 10%, 12.5% and15% respectively. The burst release of Cyclobenzaprine HCl from formulations with EC N50 is comparatively lower than the one with EC N14, due to the fact that EC N50 is more viscous and release retarding capacity is more when compared to EC N14. Formulation F5 was identified to be the best as it matches well with the innovator (f2 = 71). The release mechanism was explored and explained with Higuchi and Hixoncrowel equations, which indicates that pellets followed diffusion and erosion mechanisms for drug release. it can be concluded that the F5 (12.5%w/w EC N50) is robust one and the performance is less likely to be affected by the various factors studied. The formulations were kept at stability studies according to ICH guidelines for 3 months, which showed that all the formulations were stable.

Acknowledgement

The authors acknowledge the management of Sri Venkateswara College of Pharmacy, Chittoor for necessary support and giving valuable information during this research work.

Table No:1. Quantities of various polymers for the formulations of Extended Release Cyclobenzaprine HCl pellets.

S. No	Ingredients(gm)	F1	F2	F3	F4	F5	F6
	DRUG COATING						
1	Cyclobenzaprine HCl	50	50	50	50	50	50
2	PVP K-90	4.4	4.4	4.4	4.4	4.4	4.4
3	Sugar	22.	22.	22.	22.	22.5	22.
	Pellets	5	5	5	5		5
4	Lactose	30	30	30	30	30	30
5	IPA (ml)	56	56	56	56	56	56
	SR COATING						
6	EC N14	2.67 (2.5 %)	5.34 (5 %)	8.01 (7.5 %)	---	---	---
7	EC N50	---	---	---	10.69 (10 %)	13.36 (12.5%)	16.03 (15 %)
8	PEG 6000	0.7	0.7	0.7	0.86	0.86	0.86
9	IPA (ml)	14	14	14	44	44	44
10	Acetone (ml)	6	6	6	30	30	30
11	MDC (ml)	15	15	15	36	36	36

Table No.2 Preformulation Characteristics:

S. No	Formulations	Angle of Repose	Bulk Density (gm /ml)	Tapped Density (gm /ml)	Compressibility Index (%)	Moisture Content (%)
1	F1	28.7	0.72	0.86	16.27	2.41
2	F2	26.4	0.78	0.89	12.35	2.42
3	F3	27.3	0.74	0.86	13.95	1.92
4	F4	25.9	0.71	0.87	18.39	2.63
5	F5	28.1	0.72	0.84	14.28	2.34
6	F6	26.5	0.73	0.85	14.11	2.45

Table No.3 Dissolution Studies

S. No	Dissolution Time(hr)	Percentage Drug Release (%)						
		F1	F2	F3	F4	F5	F6	Innovator
1	1	28.4	23.4	21.9	18.8	18.4	11.4	18.6
2	2	40.8	39.4	36.5	33.2	30.6	27.4	31.4
3	4	59.3	57.3	54.1	49.3	45.2	40.1	45.6
4	8	73.9	68.6	66.4	58.3	60.4	50.2	62.1
5	12	93	72	73	75	73	65	74.2

		.6	.4	.8	.6	.9	.1	
6	24	-	89.1	91.6	92.9	98.6	83.4	99.1

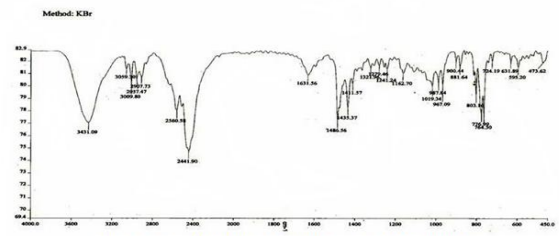

Fig.No.2 FT-IR Spectrum of Pure Drug

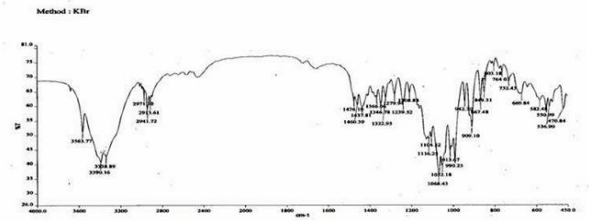

Fig.No.3 FT-IR Spectrum of Pure Drug and All Excipients

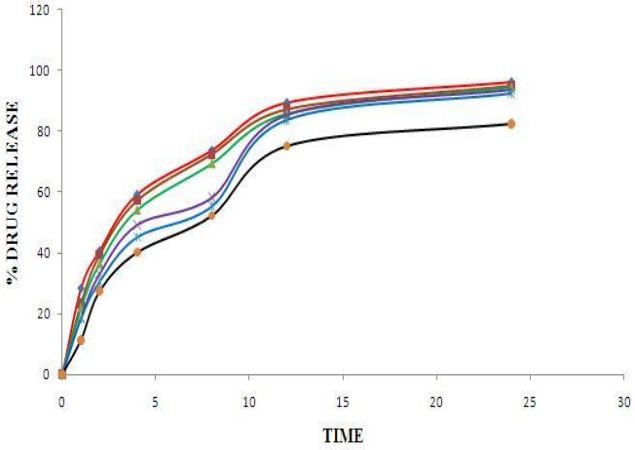

Fig.No.4. Dissolution Profile of the all Formulations

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