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An Investigation on *In vitro* Evaluation of Sustained Release Tablets of Cyclobenzaprine Hydrochloride

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ABSTRACT

This dynamic system is dependent on polymer wetting, hydration and dissolution for Controlled release of drug. At the same time other soluble recipients or drug substance will also wet, dissolve, and diffuse out of the matrix, whereas insoluble excipients or drug substance will be held in place until the surrounding polymer, excipients, drug complex erodes or dissolves away. By using two different hydrophilic polymers such as hydroxypropyl cellulose or hydroxy propyl methyl cellulose were tried for the formulation of SR of cyclobenzaprine tablet. The sustained release tablet was formulated by wet granulation technique. The cyclobenzaprine, extended release polymers, solubilizing agent, diluents are passed through Sieve no. 24, with the help of Blender these materials are kept for dry mixing at slow speed which leads to the formation for uniform matrix system. Non aqueous system is for the formation of granules such as Iso propyl alcohol along with the polyvinyl pyrrolidone K30 act as a binder, which leads to the formations of granules, the wet screening that wet mass, granules kept for drying in the dehumidifier environment for sufficient time. The matrix system had a low weight variation and high mechanical strength, the drug release profile was within the limit of USP acceptance criteria.

Keywords: Cyclobenzaprine; USP; Polyvinal pyrrolidone K30; Solubilizing agents.

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INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body in order to promptly achieve and there by to maintain the desired concentration· in recent years, various modified drug products have been developed to release the active drug from the product at a controlled rate. The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained release, sustained action, prolonged action, long action and retarded release[1].

Many of these terms of Controlled release dosage forms were introduced by drug companies to reflect a special design for a controlled release drug product or for use as a marketing term. Controlled-release drug products are designed for different routes of administration based on the physiological, pharmacologic and pharmacokinetics properties of the drug and upon the properties of the materials used in the dosage form. Several different terms are now defined to describe the available types of controlled-release drug products based on the drug release characteristics for the products[2]. Several definitions have been offered in the literature for denoting sustained release products. Lang used the term prolonged action products for formulations which provide a longer duration of therapeutics effect than the classical preparations. Abraham and Linn have stated that ideally an orally administered drug should be in such a form that a single dose would be continuously absorbed over an extended period of time, with optimal drug levels in the tissues to avoid unnecessary high peak concentrations of drug as well as wasteful depressions. Blythe described oral sustained preparations as those products which provide a sustained therapeutics effect by initially releasing the therapeutic dose of the drug followed by gradual and continuous release over prolonged period of time. Effort defined oral prolonged action forms as those products which permit control release of an active drug over a period of time but adds a provision that the relationships between absorption, elimination or metabolism of drug should have already been studied. The term modified-release dosage form is used to describe products that alter the timing and rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug release characteristics of time course and / or location are chosen to accomplish therapeutics or convenience objectives not offered by conventional dosage by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms are presently recognized. [3,4,5,6,7].

DRUG RELEASE KINETICS

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released vs. time, first order (Equation 2) as log cumulative percentage of drug remaining vs. time, and Higuchi's model (Equation3) as cumulative percentage of drug released vs. square root of time.

$$C = K_0 t \qquad (1)$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\mathrm{Log\ C = Log\ C_o - k\ t / 2.3032} \qquad (2)$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

$$\mathrm{Q = K\ t^{1/2}} \qquad (3)$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time. To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law:

$$\mathrm{CBT}\ Q_0 - \mathrm{CBR} Q_t = \mathrm{k_{HC} \times t} \qquad (4)$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet, and K_{HC} is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix vs. time.

MECHANISM OF DRUG RELEASE

To evaluate the mechanism of drug release from SR, data for the drug release were plotted in Korsmeyer et al's equation (Equation 5) as log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.

$$\mathrm{M\ t / M\ \infty = K\ t\ n} \qquad (5)$$

Where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

The zero-order rate (Equation 1) describes the systems where the drug release rate is independent of its concentration. The cumulative amount of drug release vs. time for zero-order kinetics. The first order which describes the release from systems where the release rate is

concentration dependent, which shows the log cumulative percent drug remaining vs. time. Higuchi's model (Equation 3) describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. Illustrates the Higuchi square root kinetics, showing the cumulative percent drug release vs. the square root of time. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined[8].

A **muscle relaxant** is a drug which affects skeletal muscle function and decreases the muscle tone. It may be used to alleviate symptoms such as muscle spasms, pain, and hyperreflexia. The term "muscle relaxant" is used to refer to two major therapeutic groups: neuromuscular blockers and spasmolytics. Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no CNS activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause paralysis. Spasmolytics, also known as "centrally-acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions. While both neuromuscular blockers and spasmolytics are often grouped together as muscle relaxants, the term is commonly used to refer to spasmolytics only[9].

MATERIAL AND METHODS

Material Used:

The following table gives a list of materials which are used for formulation of Cyclobenzaprine matrix tablet.

Table No. 1 showing the formulation ingredients for all formulation trials and analysis.

S.No	Formulation Ingredients	Uses
1	Cyclobenzaprine HCl	Active pharmaceutical ingredient
2	(High Viscosity Grade) Hydroxy Propyl Cellulose	SR Matrix former
3	Hydroxy Propyl Methyl Cellulose	SR Matrix former
4	Microcrystalline Cellulose	Diluent
5	Sodium Lauryl Sulphate	Solubilizer
6	Polyvinyl Pyrilidone K- 30	Binder
7	Talc	Glidant
8	Colloidal Silicone Dioxide(Aerosil)	Glidant
9	Magnesium stearate	Lubricant
10	HPLC grades water	Mobile Phase
11	Methanol (HPLC grade)	Mobile Phase

EQUIPMENTS USED:

Table No. 2 showing the equipments used for all formulation trials and analysis.

S.No.	Formulation Ingredients
1	Metler Toledo AB 204-S Electronic Balance
2	Electromagnetic Sieve Shaker EMS-8
3	Electrolab ETD-1020 Tap density Tester (USP)
4	Dr.Sheleunizer Pharmatron Model 5-Y Tablet Hardness Tester
5	Electrolab Roche Friabalator (USP) EF.1W,
6	Troical nortex dehumidifier
7	Trans-O- Sonic Sonicator
8	Hot air Oven
9	Planetary Mixer-Chef for granulation
10	Mitutoyo-Vernier Capillary
11	Sieves -Electro Pharma
12	Loss On drying tester HB-43, Halogen by Metler Toledo
13	Differential Scanning Calorimeter-822 by Metler Toledo
14	Perkin Elmer-Lambda 25 UV/Vis Spectrophotometer
15	Electrolab, TDT-80L Dissolution Tester USP
16	Cadmach 16 Compression Machine
17	Cone Blender- Electro Pharma

GENERAL METHODS FOR FORMULATION OF SUSTAINED RELEASE TABLETS

Wet Granulation:

1) Checking of Weights: Check the weights of all ingredients.
2) Sifting: Sift the Active Pharmaceutical agent, solubilizing agent, extended release retardants, and diluents through sieve No. 24.
3) Dry Mixing: Mix the required materials in Blender for dry mixing at slow speed for 10min.
4) Granulation: a) Preparation of Binder solution: Dissolve polyvinyl pyrrolidone k 30 in Iso Propyl Alcohol with constant stirring.
5) Kneading: Added slowly the binder solution of step 4a to dry mixer for all ingredients. Granulation to be did in planetary mixer. Optimized the granulation time. If granulation not to be completed then use extra Iso Propyl alcohol quantity sufficient. Note down the granulation time.

6) Wet Screenings; Pass wet mass through sieve No. 10.
7) Drying: Dry in the dehumidifier environment.
8) Rasping (Dry screenings): Pass the dried granules through sieve No.18.
9) Lubrication: Sift the talc, Aerosil200 and Magnesium strearate through sieve No.40. Firstly mix talc and aerosil200 along with granules and then put magnesium stearate.
10) Blending: Blend the rasped granules with the above materials. (talc, Aerosil 200) in the Blender of 15 min, at slow speed and then mix with mag.stearate for 4 min, collect in a suitable container and record the weights.
11) Compression: Precede the compression on tablet compression machine using 7 mm round shaped standard concave punch scored line on one side[10,11,12.]

FORMULATION TRIALS CHART

Comparative Formulation Ingredients for all 4 Formulations

Table No 3. Table showing the comparative formulation ingredients for all 4 formulation trial batches (All quantities are indicated in mg)

S.NO.	Ingredients	F1	F2	F3	F4
1	Extended release polymer concentration (%)	20	20	12	12
2	Cyclobenzaprine	30	30	30	30
4	HPMC	20.5	20.5	nil	nil
5	MCC	45.5	45.5	73.5	73.5
6	Sodium Lauryl Sulphate	5.25	5.25	5.25	5.25
7	PVP K- 30	10	10	10	10
8	Talc	10	10	10	10
9	Aerosil 200	4	4	4	4
10	Magnesium stearate	5	5	5	5
11	Iso propyl Alcohol(ml)	Q.S	Q.S	Q.S	Q.S
12	Average weight of Tablet	150	150	150	150

According to the scheme shown in the Table No.12, 4 possible treatment combinations were prepared and compressed into tablets, the formulation details are shown in table No. 12 So to cover all the variable 4 different batches of compressed tablets were prepared with Cyclobenzaprine as a drug.

Density and Compressibility index of Cyclobenzaprine granules: The most common method of accurately determining the volume of the solids in the true density (D_t) determination is by weighing the fluid occupying the void space around the powder particles at a specific temperature.

$$D_t = \frac{Weights\ of\ sample}{Volume\ of\ sample}$$

Tap density is calculated by the following formula

$$Tap\ density = \frac{Weights\ of\ sample}{Volume\ after\ tap}$$

Compressibility Index: Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations.

$$\%\ Compressibility = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} \times 100$$

In the following table indicates the value of compressibility index for indentifying the flow properties of granules.

Table No. 4. Showing Compressibility Index

% Compressibility	Flow Description
5 – 15	Excellent
12 – 15	Good
18 – 21	Fair
23-28	Poor
28-35	Poorest
35-38	Very Poor
> 40	Extremely Poor

Hausner Ratio: This ratio was introduced by Hausner in 1967 to characterize metal powder, but it is commonly used in pharmaceutical powder. **The higher the Hausner ratio, the poorer is the flow.** It is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from Hausner Ratio and Angle of Repose Measurement.

$$Hausner\ Ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

Table No. 5 Hausner Ratio values for different flow properties.

Hausner Ratio	Type of Flow
Less than 1.25	Good Flow
1.25 – 1.5	Moderate
More than 1.5	Poor Flow

Loss on Drying: In pharmacy, the term loss on drying, commonly referred to as LOD, is an expression of moisture content on a wet- weight basis, which is calculated as,

$$\% LOD = \frac{\text{Weight of water in sample}}{\text{Weight of the sample}}$$

Average weights of Tablets: Dedust the twenty tablets. Weigh accurately and note down the weights of twenty tablets. Calculate by the formula

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Diameter: Select randomly five tablets and measure the diameter of the tablets by means of previously calibrated vernier calipers.

Thickness: Select randomly five tablets and measure the thickness of the tablets by means of previously calibrated vernier calipers.

Hardness Test: Select five tablets randomly, place one tablet at a time in the hardness tester, which is already set to 0.Apply pressure by pressing the start button of hardness tester apparatus, till the tablet breaks. Note down the reading on the tester i.e. the hardness of the tablet in Newton's. Take the average of five such tablets and calculate the average hardness of the tablet

Friability Test: Dedust the twenty tablets. Weigh accurately, Note down the weight of the tablets(X).Add these tablets to the friability test apparatus rotate at 25rpm for 4mins.After completion of 4 min, remove the tablets, dedust it and note down the weight if the tablets weights (Y).

$$\% \text{ friability} = \frac{X-Y}{X} \times 100$$

Dissolution Test: As per USP

Dissolution parameters Dissolution Medium	: Water 900ml
Apparatus	: USP Type I (Basket)
Speed	: 100 rpm
Time point	: 3,6,12 and 24 hours
Temperature	: 37°C
Wavelength	: 290nm

Tolerances- Table No. 6. Dissolution acceptance parameters

Time (hours)	Amount dissolved
3	between 10% and 35%
6	between 35% and 65%
12	between 65% and 85%
24	85%

Standard preparation

Weigh accurately about 30mg of cyclobenzaprine working standard into 50ml volumetric flask. Add 30 ml of methanol, sonicate to dissolve and dilute to volume with methanol. Further dilute 1.0ml of this solution to 100ml with dissolution medium.

Procedure: Transfer one tablet into each vessel containing 900ml of water. Determine the amount of cyclobenzaprine released, by estimating the drug using the method given bellow: Estimation of Drug dissolved :(By UV/VIS spectrophotometer)

Test Aliquots: After completion of specified time intervals of Dissolution test, remove the aliquots and filter. Further dilute 2 ml of these aliquots to 50 ml with water. Measure the absorbance of the resulting solution at the maximum at about ***290nm*** using water as a blank.

Calculate the content by using the following formula

$$\% \text{ of Released Cyclobenzaprine} = \frac{A_T}{As} \cdot \frac{W_{std}}{50} \cdot \frac{1}{100} \cdot \frac{900}{L.C\ (in\ mg)} \cdot \frac{50}{2} \cdot \frac{P}{100} \times 100$$

Here, A_T : Absorbance of test, As: Absorbance of standard, W_{std} :weight of standard, L.C: label claim of tablet (30mg), P: Potency of Cyclobenzaprine (99.05%)[13.]

ASSAY BY HPLC: Chromatographic condition;

Column :Octadecyl Silane, 300mm X4.0mm, 10u (preferably Hypersil ODS)
Flow Rate : 2.0ml/min
Detector : UV-VIS
Wavelength : 290nm
Injection Volume : 10micro lit.
Column temp. : 30° C

Reagents Used:

- HPLC grades water (Milli Q or equivalent)
- Methanol (HPLC grade)
- Methylene chloride (AR grade)

Mobile Phase: Prepare a mixture of water, methanol and methylene chloride in the ratio of (600:450:450) Filter and degas. Make adjustments if necessary.

Internal Standard solution: Weigh accurately about 60mg of phenytoin into a 100ml volumetric flask. Add70 ml of methanol, sonicate to dissolve and make up the volume with methanol.

Standard Preparation: Weigh accurately about 100 mg of Cyclobenzapine working standard into a 50 ml volumetric flask. Add 40 ml of methanol sonicate to dissolve and make up the volume to 50 ml with methanol. Further dilute 5.0 ml of this solution to 50 ml with methanol. Pipette out 10.0 ml of this solution into a conical flask and add 10.0 ml of internal standard solution. Mix and filter.

Assay stock preparation: Weigh and powder 10 tablets. Weigh accurately a quantity of powder containing the equivalent of about 100mg of Cyclobenzapine into a 25ml volumetric flask. Add 10ml of methanol, sonicate for about 15 min, and allow cooling to room temperature. Make up the volume to 25ml with methanol. Mix and filter.

Assay Preparation: Dilute 5.0 ml of Assay stock preparation to 100ml with methanol and mix. Pipette out 10.0ml of this solution into a conical flask and add 10.0 ml of internal standard solution. Mix and filter.

Procedure: Wash the column initially with methanol at a flow rate of 1.0ml/min for 30 min. and then run mobile phase for 30 min. separately inject equal volumes (10micro lit) of the standard preparation and the assay preparation in the chromatograph, record the chromatogram and measure the peak responses for cyclobenzaprine. The system suitability parameters should be met. From the peak responses, calculate the content of cyclobenzaprine in the sample with the help of the following formula:

$$\% \text{ of Cyclobenzaprine in tablet} = \frac{Ru}{Rs} \times \frac{Wstd}{50} \times \frac{5}{50} \times \frac{25}{spl.wt} \times \frac{100}{5} \times \frac{P}{L.C} \times Avg.Wt\ (mg)$$

Ru/Rs: Peak response ratios of cyclobenzaprine to the internal standard obtained form the assay(sample)preparation and standard preparation, respectively, W_{stand}: Weight of Standard

preparation in mg, Spl.wt: Weight of Sample preparation in mg, L.C.: Label claim in mg (30), P.:Potency of cyclobenzaprine working standard, Avg.wt.: Average weight of tablet.

Drug Identification test

FT-IR spectrum of pure drug: The infra red spectrum of Cyclobenzaprine is taken and which is compared with the reference spectra of cyclobenzaprine. The functional group value of cyclobenzaprine is observed closer to the reference infra red spectra value of cyclobenzaprine. FT – IR is used to determine the degradation of the active compound in polymeric carrier system. The surface of the granules is investigated measuring alternated total reflectance. The IR beam passing through the ATR cell reflected many times through the sample to provide IT spectra mainly of surface materials. The FT – IR indicated that no chemical interaction between drug and polymers. It is also confirmed the stability of drug during compressed of the tablets.

Differential Scanning Colorimeter

For checking the melting point of pure cyclobenzaprine drug, DSC is taken and is observed near about the 219^0C.

Differential Scanning analysis measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. It is a micro technique and depends on the thermal equilibration with in the sample. Significant variables in these methods include sample homogeneity, sample size, particular size, and heating rate sample atmosphere.

Application - It is used to determine drug degradation, compatibility of excipients with drug analysis of coating and polymorphism, moisture content and characterization of drug loaded microcapsules.

Procedure - The instrument works on the temperature control of two similar specimen holders assembly. In its left half, there is a circuit for differential temperature control while in its right half there is a circuit for average temperature control.

In the average temperature control circuit. Signals representing the temperatures of the sample and reference are compared. If non reaction is taking place in the sample and reference heater is almost zero. However if a reaction is taking place a differential power is fed to the heaters. A signal proportional to this differential power is transmitted to the recorder pen. The integral of the peak so obtained gives the internal energy change of the sample.

RESULTS

Drug Identification test ***FT-IR spectrum of pure drug:***

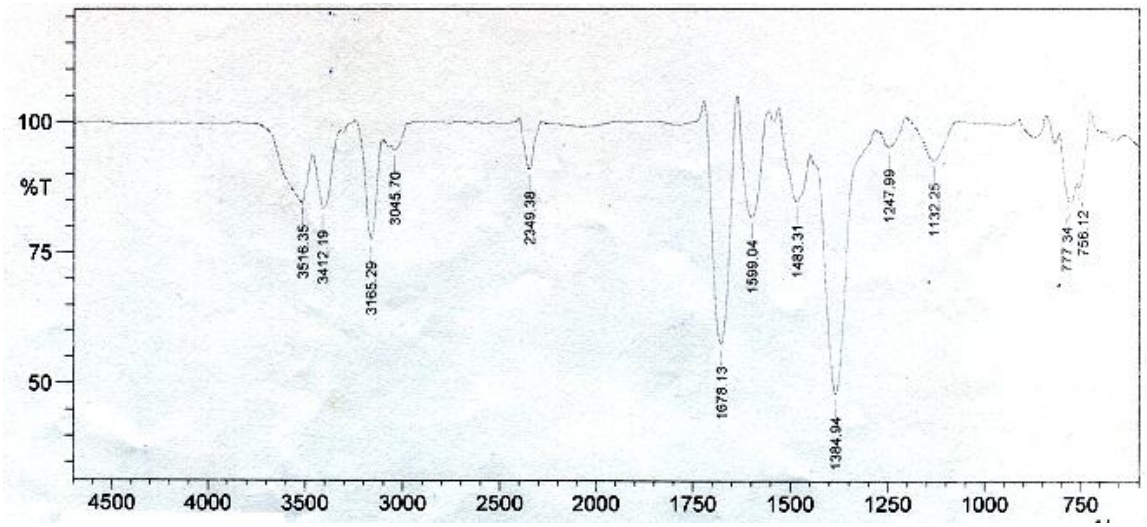


Figure No.1: Graph showing the FT-IR spectrum of pure cyclobenzaprine drug

Differential Scanning Colorimeter: For checking the melting point of pure cyclobenzaprine drug, DSC is taken and is observed near about the 219^0C.

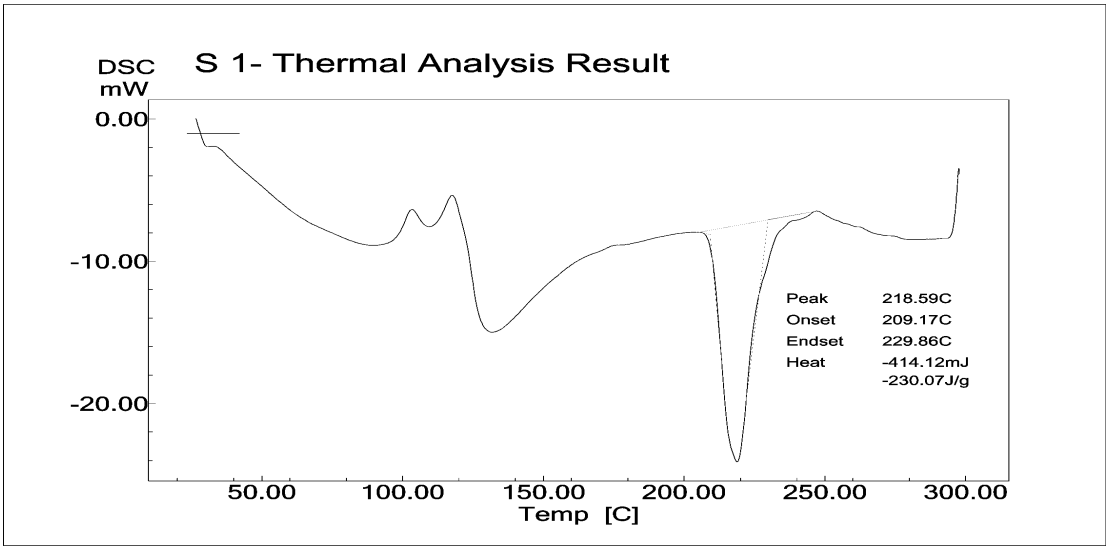


Figure No 2: Graph showing the DSC of pure cyclobenzaprine drug

Standard Graph of Cyclobenzaprine: 50 mg of standard drug i.e. Cyclobenzaprine was accurately weighed and transferred to a 50 ml of volumetric flask. To this small quantity of methanol is used and kept for sonication for dissolving the Cyclobenzaprine, then make up the volume up to 50ml with same solvents. This solution was considered as stock solution of 1000 mcg/ml. From the stock solution 10 ml

solution was pipette out to 100 ml of volumetric flask and make up the volume upto 100 ml with Millipore water and this solution considered as a 100 mcg/ml solution of Cyclobenzaprine. From this solution pipette out 10 ml solution volume make up upto 100ml. From this solution pipette out 2,4,6,8,10 ml in each 10 ml of volumetric flask and make up the volume upto 10 ml with Millipore water and these all solution was considered as a 2, 4, 6, 8, and 10 mcg/ml of Cyclobenzaprine solution. Measure the absorbance at 290 nm in UV/VIS Spectrophotometer. Graph is plotted as Concentration vs. Absorbance and determined the Correlation coefficient i.e. $R^{2.}$

Table No.7. Showing the Calibration curve value of Cyclobenzaprine.

S.No.	Concentration mcg/ml	Absorbance
1	2	0.225
2	4	0.441
3	6	0.671
4	8	0.878
5	10	1.09

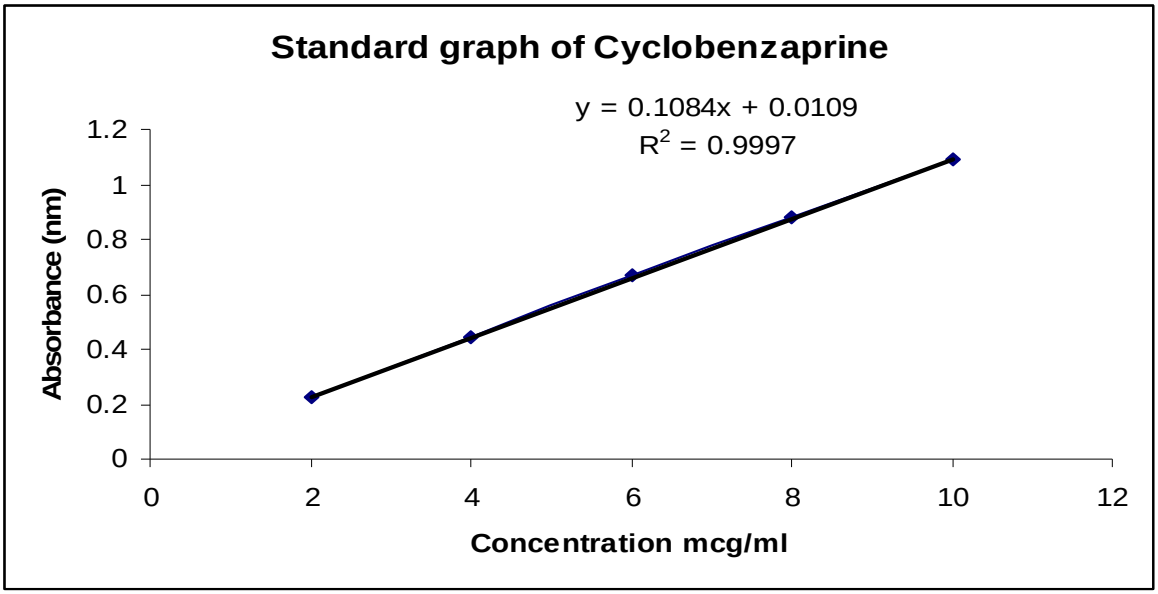


Figure No 3. Graph showing the Calibration curve of Cyclobenzaprine.

Physical characterization of Drug and granules

Table No.8. Showing the Physical Characterization of pure Drug and Granules of it for all 6 formulation trials.

S.No.	Formulation No.	Bulk Density gm/ml	Tap Density gm/ml	Compressibility Index %	Hausner Ratio	Loss on Drying %
1	F1	0.31	0.428	27.52	1.38	3.2
2	F2	0.315	0.435	27.58	1.38	3.88
3	F3	0.409	0.485	15.67	1.18	2.88
4	F4	0.39	0.44	11.36	1.12	2.98

Quality Control Parameters

Table No.9: post compression parameters for all 4 formulation trials of Extended Release tablet of Cyclobenzaprine.

S.No.	Formulation No.	Tablet Thickness (mm)	Hardness (N)	Friability %
1	F1	4.26	143	0.053
2	F2	4.22	140	0.081
3	F3	4.15	151	0.089
4	F4	4.15	150.2	0.102

IN-VITRO DISSOLUTION TESTS

FORMULATION TRIAL NO.1 (F1)

Table No. 10 : In-vitro release kinetics parameter for formulation trial no 1

Time (hrs)	%cumulative drug released	log % cumulative drug released	% cumulative drug remaining (x)	log % cumulative drug remaining	log T	√T	(x)⅓
3	12.4	1.093	87.6	1.942	0.47	1.73	4.441
6	26.1	1.416	73.9	1.868	0.77	2.44	4.196
12	51.4	1.71	48.6	1.686	1.079	3.46	3.649
24	78	1.89	22	1.342	1.38	4.89	2.802

Table No.11 and figure No. 4 : Zero order drug release kinetic along with the graph

ZERO ORDER DRUG RELEASE KINETIC	
Time(hrs)	**%Cum drug released**
3	12.4
6	26.1
12	51.4
24	78
Slope=3.067	*R^2=0.9687*

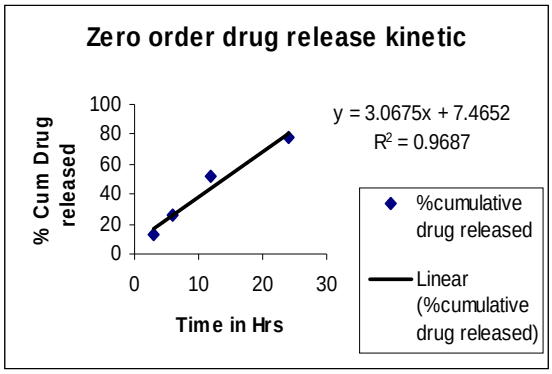


Table No. 12 and figure No. 5 :First order drug release kinetic along with the graph

FIRST ORDER DRUG RELEASE KINETIC	
Time(hrs)	**log % cum drug remaining**
3	1.9425
6	1.8686
12	1.6866
24	1.3424
Slope = -0.0288	*R^2=0.99960*

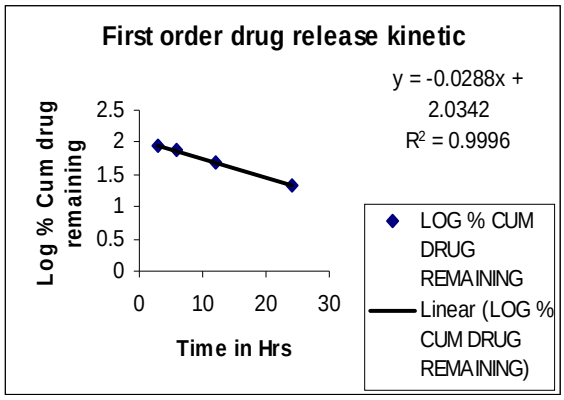


Table No.13 and figure No. 6 : Korsmeyer-Peppas drug release kinetics along with graph

KORSMEYER-PEPPAS DRUG RELEASE KINETIC	
log time	**log % Cum drug released**
0.4771	1.0934
0.778	1.4166
1.0791	1.71
1.3802	1.892
Slope = 0.8937	*R^2=0.9852*

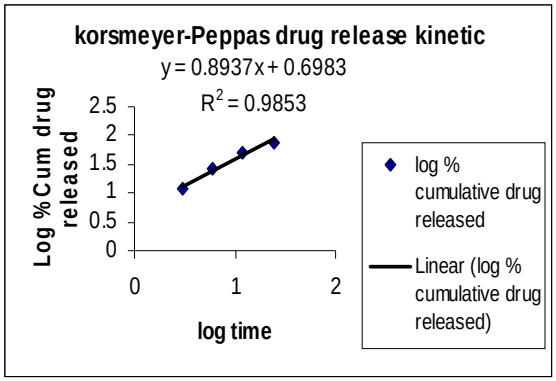
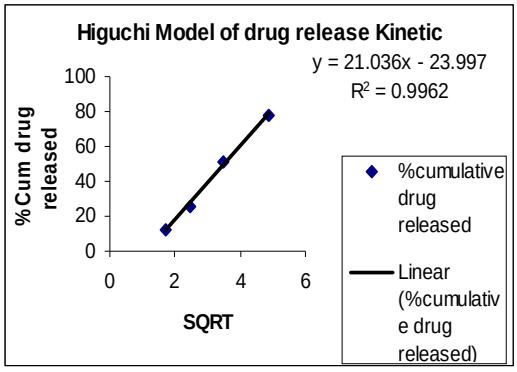


Table No.14 and figure No.7: Higuchi-Model drug release along with graph

HIGUCHI MODEL OF DRUG RELEASE KINETIC	
√T	%Cum drug released
1.732	12.4
2.4494	26.1
3.464	51.4
4.8989	78
Slope = 21.035	*R^2=0.9962*



FORMULATION TRIAL NO.2 (F2)

Table No. 15:In-vitro release kinetic parameter for formulation trial No.2

Time (hrs)	%cumulative drug released	log % cumulative drug released	% cumulative drug remaining(x)	log % cumulative drug remaining	log T	√T	(x)⅓
3	16.6	1.22	83.4	1.921	0.5	1.73	4.369
6	40.5	1.607	59.5	1.774	0.8	2.44	3.9
12	73.3	1.865	26.7	1.426	1.1	3.46	2.988
24	86.5	1.937	13.5	1.13	1.4	4.89	2.381

Table No.16 and figure No.8: Zero order drug release kinetic along with graph

ZERO ORDER DRUG RELEASE KINETIC	
Time(hrs)	%cumulative drug released
3	16.6
6	40.5
12	73.3
24	86.5
Slope =3.123	*R^2 =0.838*

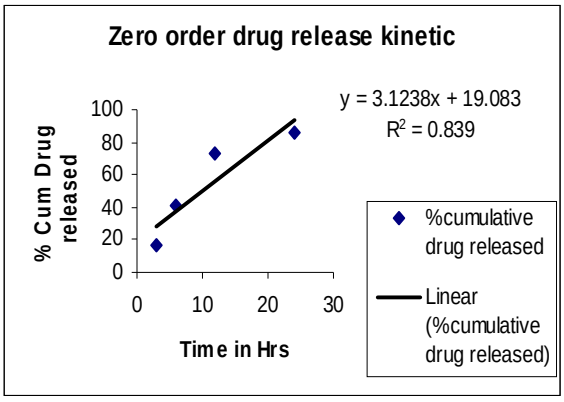


Table No.17 and figure No.9: First order drug release kinetic along with graph

FIRST ORDER DRUG RELEASE KINETIC	
Time(hrs)	**LOG % CUM DRUG REMAINING**
3	1.921166051
6	1.774516966
12	1.426511261
24	1.130333768
Slope =-0.0374	*R^2 =0.9567*

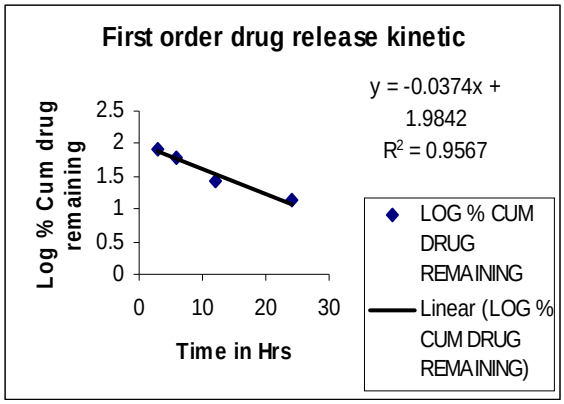


Table No.18 and figure No.10 : Korsmeyer-Peppas drug release kinetic along with graph

KORSMEYER-PEPPAS DRUG RELEASE KINETIC	
log time	**log % Cum drug released**
0.477121255	1.220108088
0.77815125	1.607455023
1.079181246	1.865103975
1.380211242	1.937016107
Slope =-0.800	*R^2 =0.920*

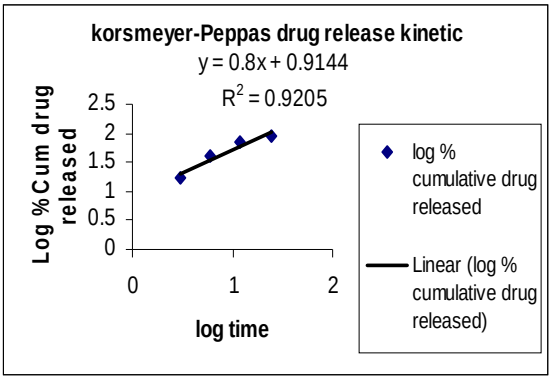


Table No.19 and figure No. 11:Hixson-Crowell cube root law along with graph

HIXSON-CROWEL CUBE ROOT LAW OF KINETIC	
Time(hrs)	**(x)⅓**
3	4.369066787
6	3.903962661
12	2.988847481
24	2.381101578
Slope =--0.092	*R^2 =0.9229*

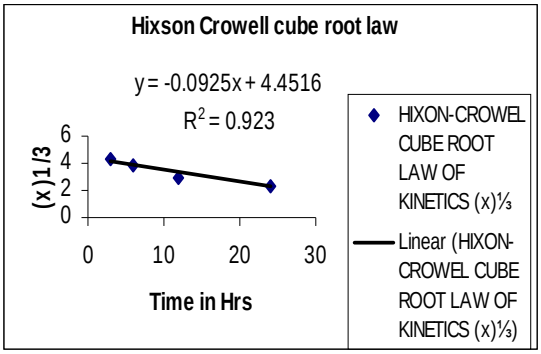
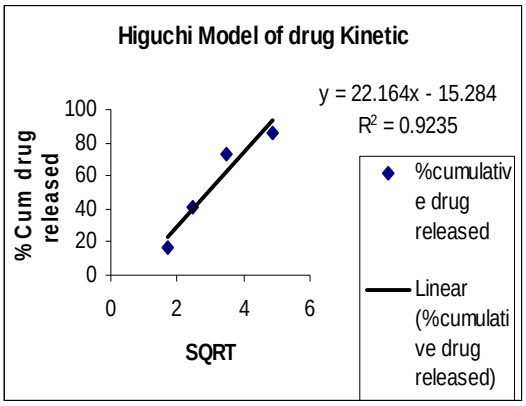


Table No.20 and figure No.12 : Higuchi-Model of drug release kinetics along with graph

HIGUCHI MODEL OF DRUG RELEASE KINETIC	
√T	%Cum drug released
1.732050808	16.6
2.449489743	40.5
3.464101615	73.3
4.898979486	86.5
Slope =-22.163	*R^2 =0.923*



FORMULATION TRIAL NO.3 (F3)

Table No. 21 : In-vitro release kinetic parameter for formulation trial No.3

Time (hrs)	%cumulative drug released	log % cumulative drug released	% cumulative drug remaining (x)	log % cumulative drug remaining	log T	√T	(x)⅓
3	27.6	1.4409	72.4	1.859	0.477	1.73	4.16
6	46.9	1.671	53.1	1.72	0.778	2.449	3.758
12	71.7	1.855	28.3	1.451	1.079	3.461	3.047
24	81.1	1.909	18.9	1.276	1.38	4.89	2.663

Table No.22 and figure No. 13: Zero order drug release kinetic along with its graph

ZERO ORDER DRUG RELEASE KINETIC	
Time(hrs)	%Cum drug released
3	27.6
6	46.9
12	71.7
24	81.1
Slope=2.372	*R^2=0.826*

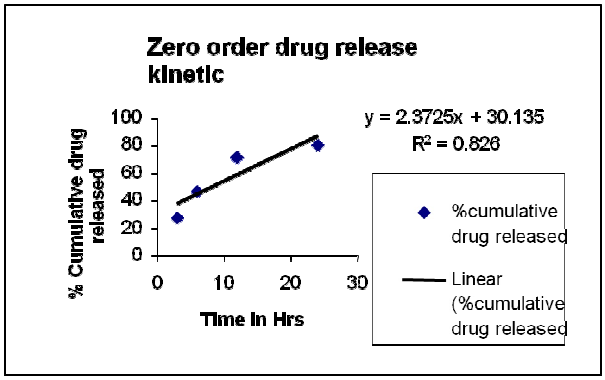


Table No.23 and figure No. 14 : First order drug release kinetic along with its graph

FIRST ORDER DRUG RELEASE KINETIC	
Time(hrs)	**log % Cum drug remaining**
3	1.859
6	1.725
12	1.4517
24	1.2764
Slope =-0.027	*R^2=0.9203*

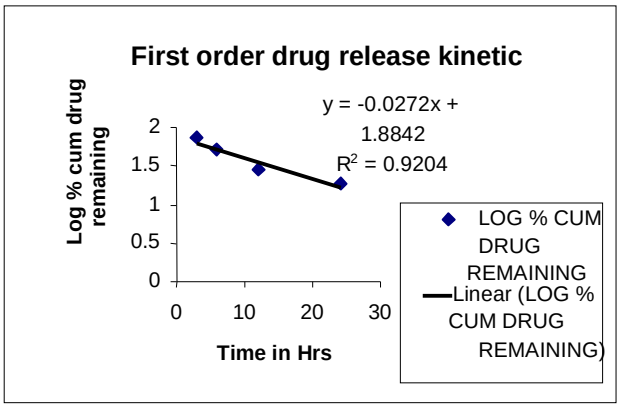


Table No.24 and figure No. 15: Korsmeyer-Peppas drug release kinetic along with its graph

KORSMEYER-PEPPAS DRUG RELEASE KINETIC	
log time	**log % Cum drug released**
0.477	1.4409
0.778	1.671
1.079	1.855
1.3802	1.909
Slope =-0.527	*R^2=0.939*

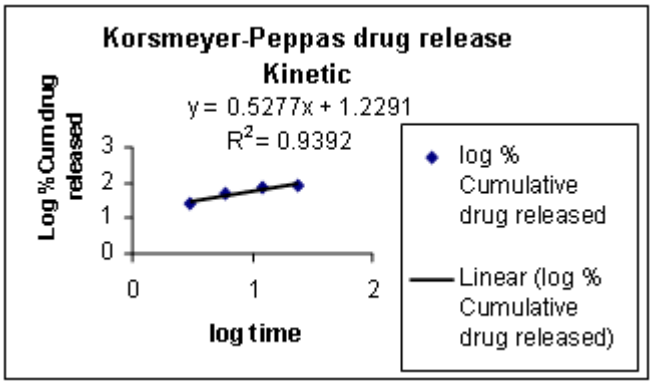


Table No.25and figure No.16: Higuchi Model of drug release kinetic along with its graph

HIGUCHI MODEL OF DRUG RELEASE KINETIC	
√T	**%Cum drug released**
1.732	27.6
2.449	46.9
3.464	71.7
4.898	81.1
Slope =-16.882	*R^2=0.914*

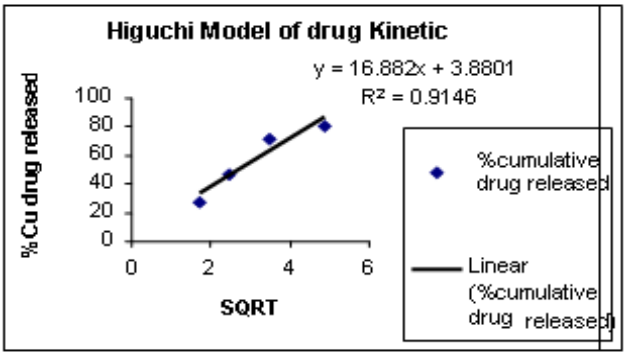
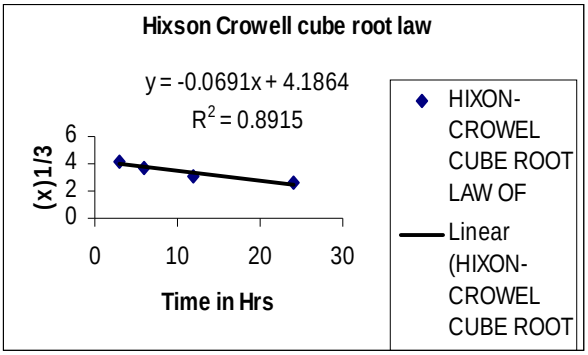


Table No.26 and figure No.17: Hixson–Crowell cube root law along with its graph

HIXSON-CROWELL CUBE ROOT LAW OF KINETIC	
Time(hrs)	**(x)⅓**
3	4.1678
6	3.7586
12	3.047
24	2.663
Slope =--0.069	*R^2=0.891*



FORMULATION TRIAL NO 4 (F4)

Table No. 27: In-vitro release kinetic parameters for formulation trial No.4

Time(hrs)	%cumulative drug released	log % cumulative drug released	%Cumulative drug remaining (x)	log % cumulative drug remaining	log T	√T	(x)⅓
3	28.6	1.456	71.4	1.853	0.4771	1.7321	4.14
6	58.1	1.7641	41.9	1.622	0.7782	2.4495	3.473
12	73.5	1.8662	26.5	1.423	1.0792	3.4641	2.98
24	83.3	1.92	16.7	1.222	1.3802	4.899	2.55

Table No.28 and figure No.18 : Zero order drug release kinetic along with its graph

ZERO ORDER DRUG RELEASE KINETIC	
Time(hrs)	**%Cum drug released**
3	28.6
6	58.1
12	73.5
24	83.3
Slope = 2.226	*R^2 = 0.7497*

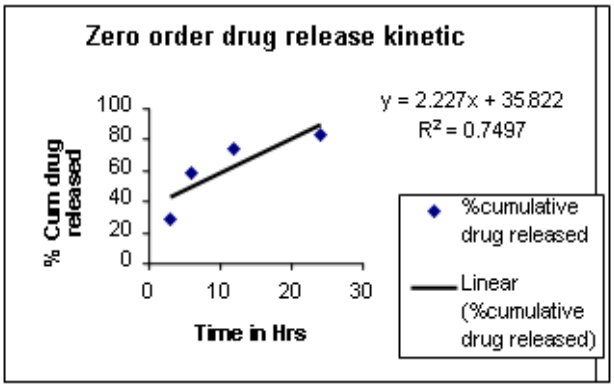


Table No.29 and figure No.19: first order drug release kinetic along with its graph.

FIRST ORDER DRUG RELEASE KINETIC	
Time(hrs)	**log % Cum drug remaining**
3	1.8536
6	1.622
12	1.4232
24	1.222
Slope = -0.0276	*R^2 = 0.9023*

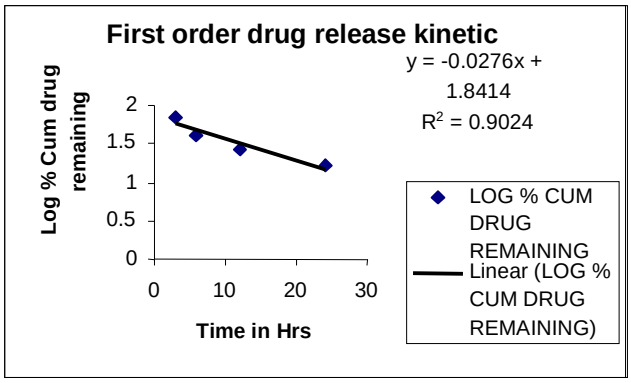


Table No.30 and figure No.20: Korsmeyer-Peppas drug release kinetic along with its graph

KORSMEYER-PEPPAS DRUG RELEASE KINETIC	
log time	**log % Cum drug released**
0.477	1.4563
0.778	1.7641
1.0791	1.866
1.3802	1.9206
Slope = 0.4966	*R^2 = 0.865*

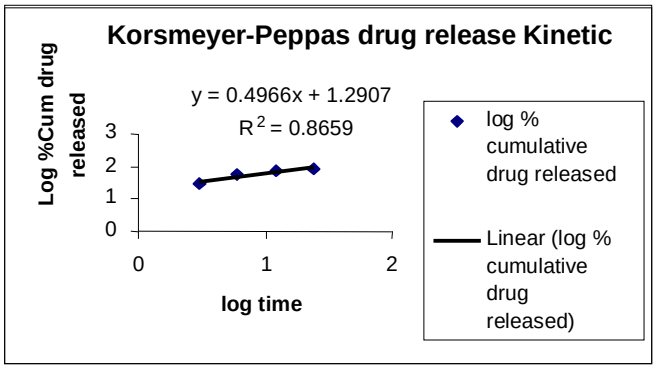


Table 1: Table No.51 and figure No.34: Higuchi Model of drug release kinetic along with its graph

HIGUCHI MODEL OF DRUG RELEASE KINETIC	
√T	**%Cum drug released**
1.732	33.2
2.449	49.4
3.464	77.4
4.898	98.1
Slope = 20.815	*R^2 = 0.9794*

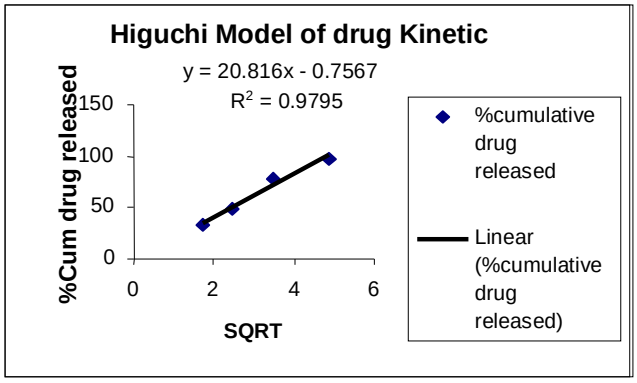
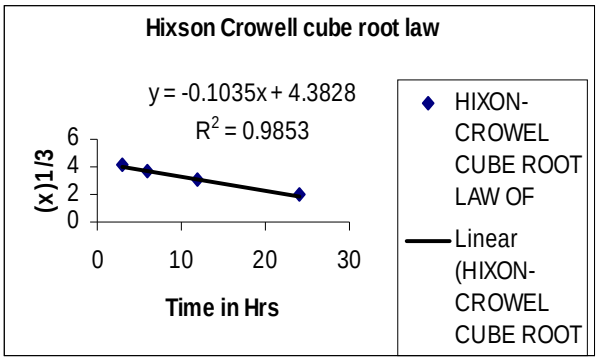


Table No.31 and figure No.21: Hixson-Crowell cube root law along with its graph

HIXSON-CROWELL CUBE ROOT LAW OF KINETIC	
Time(hrs)	**(x)⅓**
3	4.0575
6	3.698
12	2.827
24	1.2385
Slope = -0.135	*R^2 = 0.9991*



ASSAY

The % containing of Cyclobenzprine HCl sustained Release (SR) tablets was performed for optimized formulation trial No.06. In-vitro dissolution study of this trial which matches with the USP limit. The % containing of Cyclobenzprine HCl from SR tablet was find out with the help of High Performance Liquid Chromatography (HPLC) and detailed procedure was already mentioned in the section of Materials and Methods. To determine the % of Cyclobenzprine HCl present in SR tablet, five standard solutions were injected in the HPLC System and then two sample solutions was injected in the same HPLC System.All respective graph of that solution is as follows

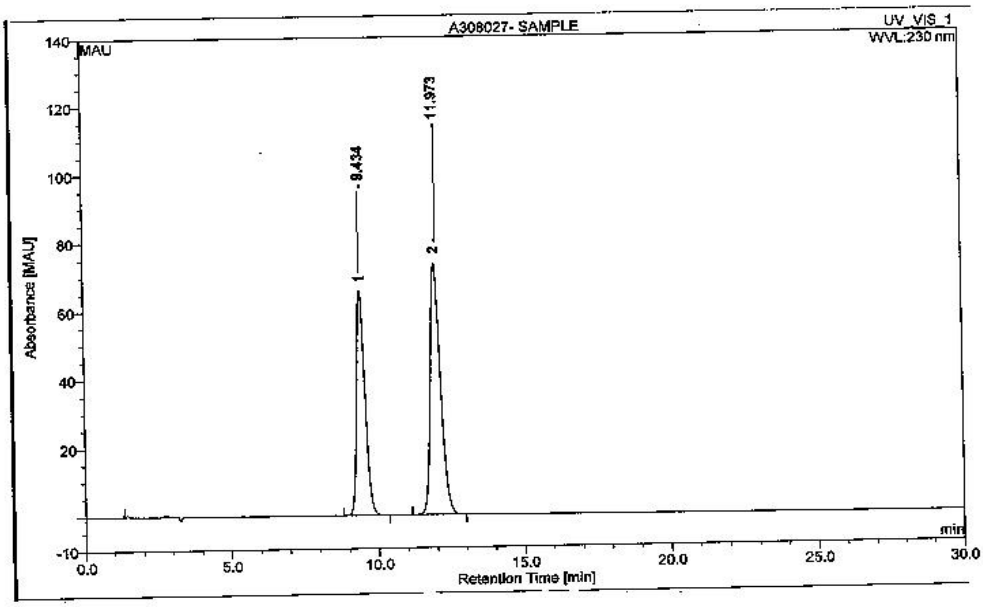


Figure No.22: HPLC graph showing for the sample 1

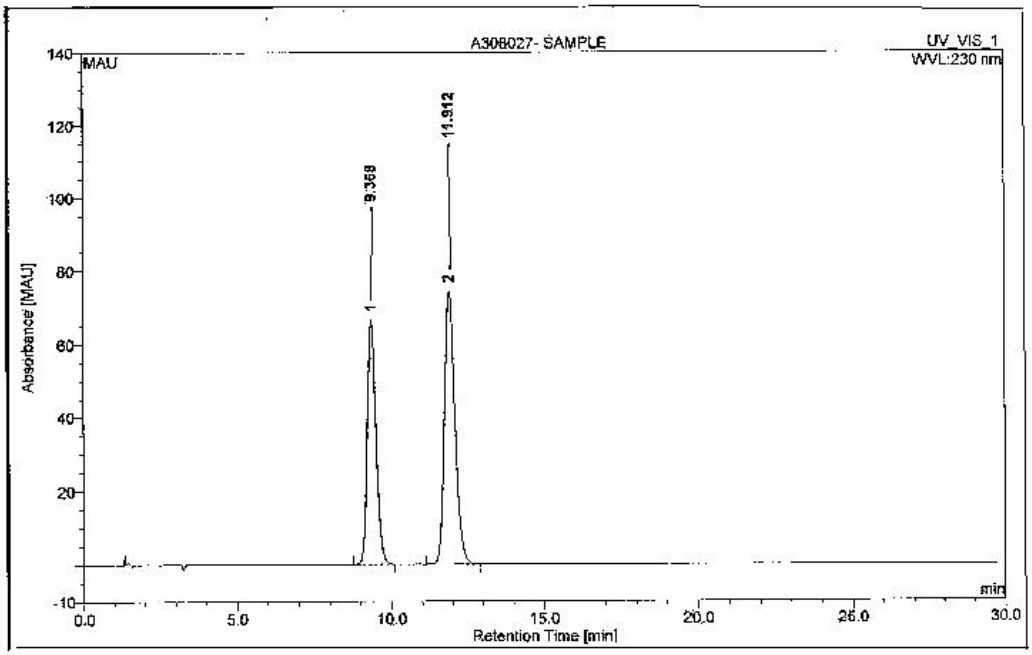


Figure No.23: HPLC graph showing for the Sample 2

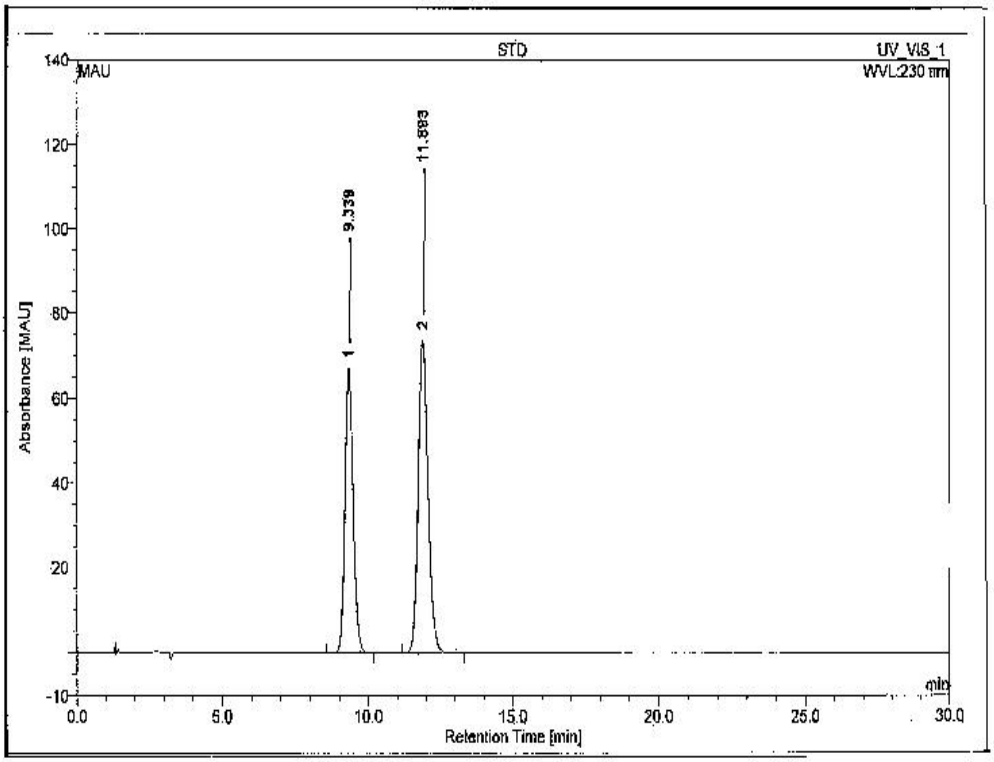


Figure No.24 HPLC graph showing for Stand 1

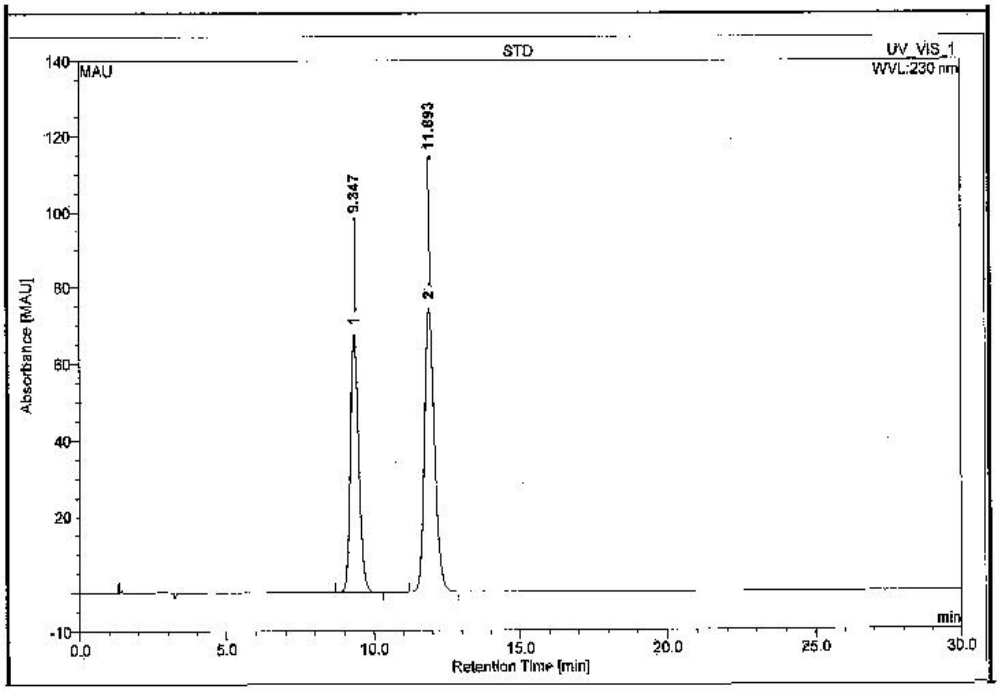


Figure No.25: HPLC graph showing for Stand 4

CONCLUSION

A consistent and robust sustained release Hydrophilic matrix tablet of Cyclobenzaprine HCl utilizing a Hydroxy Propyl Methyl Cellulose (HPMC) of a low Viscosity grade in the concentration of 27% was successfully developed. The matrix system had a low weight variation and high mechanical strength, the drug release profile was within the limit of USP acceptance criteria. Inclusion of Sodium Lauryl Sulphate (SLS) in the formulation enhances the solubility of the Cyclobenzaprine allowing more than 98.1 % of Cyclobenzaprine HCl to release at the end of 24 hr. Further optimized formulation i.e. F4 is ready for the bioavailability and bioequivalence study. This would yield a lower average maximum plasma concentration and results in a lower incidence of intermittent concentration dependent adverse drug reactions and producing a sufficient effective pharmacologic response.

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REFERENCES

1. Chein, Y. W. Oral Drug Delivery and Delivery systems. In, Novel drug delivery systems, Vol. 50, Marcel Dekker, Inc., New York; 1992. 50: 139-177.
2. J. Siepmann et al. (eds.), Fundamentals and Applications of Controlled Release Drug Delivery, Advances in Delivery Science and Technology, DOI 10.1007/978-1-4614-0881-9_2, # Controlled Release Society 2012
3. Abhilash AS, Jayaprakash S, Nagarajan M and Dhachinamoorthi D. Design and evaluation of timolol maleate ocuserts. Indian J Pharm Sci. 2005;67(3):311-314.
4. Agarwal SP, Vasudha S and Anitha P. Spectrophotometric determination of atenolol and timolol dosage forms via charge-transfer complexation. Indian J Pharm Sci.1998;53-55.
5. Amelia A and Vikram K. Design and evaluation of matrix-based controlled release tablets of diclofenac sodium and chondriotin sulphate. AAPS PhramSciTech. 2007;8(4):E88.
6. Atul K, Ashok KT, Narendra KJ and Subheet J. Formulation and in vitro in vivo evaluation of extended-release matrix tablet of zidovudine: Influence of combination of hydrophilic and hydrophobic matrix formers. AAPS Pharm Sci Tech. 2006;7(1):E1.
7. Basak SC, Jayakumar Reddy BM and Lucas Mani KP. Formulation and release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. indian J Pharm Sci. 2006;594-597.
8. Gautam S, Mahaveer S; review: in-vitro drug release Characterization models I.J of Pharma. Studies and Research Vol. II, Issue I,2011;77-84
9. Fedan, J.S., Anticoagulant, antiplatelet, and fibrinolytic (thrombolytic) drugs. In C.R. Craig & R.E. Stitzel (Eds.), Modern pharmacology with clinical applications (6th ed., Lippincott Williams and Wilkins, pp. 269–278);2003.
10. Dilip M. P, Theory of Granulation' Handbook of Pharmaceutical Granulation Technology, Marcel Dekker INC, New York, 1997: 7-13.
11. Leon L, Herbert A. L, and Joseph L. K, "Tablets", The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese publishing house, Bombay,1991: 320-321.
12. Iveson, S.M., Litster, J.D., Hapgood, K. and Ennis, B.J., Nucleation, Growth and Breakage Phenomena in Agitated Wet Granulation Processes: A Review, Powder Technology, 2001;117, 3-39.

13. Banker GS, Anderson NR. Tablets; Lachman L, Lieberman HA, Kanig J L, editor. The Theory and Practice of Industrial Pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1986. p. 293-335.