ISSN 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF CYCLOBENZAPRINE HYDROCHLORIDE LOADED SUSTAINED RELEASE MICROSPHERES

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Abstract

The purpose of this work was to prepare ustained release microspheres of cyclobenzaprine hydrochloride by solvent evaporation techniques using Eudragit RS 100, Eudragit RS&RL 100 and Ethylcellulose as polymers and yield, particle size, encapsulation efficiencies and in vitro release of the prepared microspheres were evaluated. The results showed that percentage yield, encapsulation efficiencies and particle size were influenced mainly by polymer concentration, type of polymer and stirring speed. From the results of the in vitro study shows that the desired release rate is achieved by CBRS 4, CBRS 12 and CBEC 19 formulations are releasing the drug up to 12 hrs. DSC results showing there is no interaction between drug and polymers. SEM results of optimized microspheres showing discrete, spherical microspheres.

Key Words: cyclobenzaprine hydrochloride , Eudragit RS 100, Eudragit RL 100,Solvent Evaporation.

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INTRODUCTION:

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to the patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as drug carriers. Even today these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription and over the counter drug market place. This type of drug delivery system is known to provide a prompt release of drug. Therefore to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels [1,2].

Microspheres are, in strict sense, spherical empty particles. However, the term microcapsules and microspheres are often used synonymously. The term microcapsule, is defined as a spherical particle with size varying from 50 nm to 2 mm, containing a core substance. In addition, microbeads, beads are the related terms used for microspheres[3,4].

Microsphere is defined as "a monolithic structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles, falling in the size range 1-500 μ^4."Insoluble drug carriers for prolonged and controlled delivery of therapeutic agents in biological system recently have generated interest. Microspheres belong to the same carrier system[5] .

Cyclobenzaprine is a skeletal muscle relaxant and a central nervous system (CNS) depressant. It acts on the locus coeruleus where it results in increased norepinephrine release, potentially through the gamma fibers which innervate and inhibit the alpha motor neurons in the ventral horn of the spinal cord[6] Cyclobenzaprine HCl mean oral bioavailability range from 33-55%.and it is highly bound to plasma proteins. Cyclobenzaprine is extensively metabolized, and is excreted primarily as glucuronides via the kidney.

The present study was preparing sustained release microspheres by solvent evaporation method using Eudragit RS 100, Eudragit RL 100 and Ethylcellulose as polymers.

MATERIALS AND METHODS:

Materials

Cyclobenzaprine Hydrochloride, USP was obtained as gift sample from Vasudha Pharma Pvt Ltd, vengalrao nagar, Hyderabad. Eudragit RS 100 and RL 100 from M/s Rohm pharma, Germany, Ethyl cellulose N50, Petroleum ether, span ether from SD Fine Chemicals, Mumbai. All the reagents were of analytical grade.

Preparation Method of Sustained Release Microspheres

Sustained microspheres containing cyclobenzaprine hydrochloride as a core material were prepared by "Non-aqueous Emulsion Solvent Evaporation" method.

Eudragit Polymers:

The drug was dissolved in polymer solution made by dissolving polymer in 2:1 mixture of acetone and methanol. The above slurry was slowly introduced into 75 ml of light liquid paraffin containing span 80 (0.5%) as surfactant while being stirred at 1100 rpm and 2200 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature. The stirring was continued for three-and-a half (3 ½) to four (4) hours to allow the solvents (acetone, methanol) to evaporate completely and the formed microspheres were collected by filtration. The microspheres were washed repeatedly with n-Hexane and petroleum ether until free from oil. The collected microspheres were dried at room temperature for 24 hours[15].

The schematic representation of formulation of eudragit sustained release microspheres of cyclobenzaprine hydrochloride was shown in Table 1,2&3.

Table 1 Formulation Codes For Eudragit RS Microspheres Prepared at 2200 Rpm Speed.

Formulation code (Eudragit RS)	Ratio of drug polymer (dg:RS)	Speed (rpm)
CBRS 1	1:1	**2200**
CBRS 2	1:2	**2200**
CBRS 3	1:3	**2200**
CBRS 4	1:4	**2200**
CBRS 5	1:5	**2200**
CBRS 6	**1:6**	**2200**

Table 2 Formulation Codes For Eudragit RS & RL Microspheres Prepared at 2200 Rpm Speed

Formulation code (Eudragit RS&RL)	Ratio of drug polymer (dg: RS: RL)	Speed (rpm)
CBRS 7	1:3:1	**2200**
CBRS 8	1:4:1	**2200**
CBRS 9	**1:5:1**	**2200**

Table 3 Formulation Codes For Eudragit RS Microspheres Prepared at 1100 Rpm Speed.

Formulation code (Eudragit RS)	Ratio of drug polymer (dg:RS)	Speed (rpm)
CBRS 10	1:1	**2200**
CBRS 11	1:2	**2200**
CBRS 12	1:3	**2200**
CBRS 13	1:4	**2200**
CBRS 14	1:5	**2200**
CBRS 15	**1:6**	**2200**

ETHYL CELLULOSE POLYMER:

The drug was dissolved in polymer solution made by dissolving polymer in 3:1 mixture of acetone and ethanol. The above slurry was slowly introduced into 75 ml of light liquid paraffin containing span 80 (0.5%) as surfactant while being stirred at 2200 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature. The stirring was continued for three-and-a half (3 ½) to four (4) hours to allow the solvents (acetone, ethanol) to evaporate completely and the formed microspheres were collected by filtration. The microspheres were washed repeatedly with n-Hexane and petroleum ether until free from oil. The collected microspheres were dried at room temperature for 24 hours .

Table 4 Formulation Codes For Ethyl Cellulose Microspheres Prepared at 2200 Rpm Speed.

Formulation code (Ethylcellulose)	Ratio of drug polymer (dg:EC)	Speed (rpm)
CBEC 16	1:1	**2200**
CBEC 17	1:2	**2200**
CBEC 18	1:3	**2200**
CBEC 19	1:4	**2200**
CBEC 20	1:5	**2200**
CBEC 21	**1:6**	**2200**

Evaluation of Sustained Microspheres:

Drug interaction study by Differential Scanning Calorimeter (DSC)

DSC is very useful in the investigation of thermal properties of the microspheres, providing both qualitative and quantitative information about the physicochemical state of drug inside the microspheres. Drug may have been dispersed in the crystalline or amorphous form or dissolved in the polymer matrix during formation of the microspheres. There is no detectable endotherm if the drug is present in a molecular dispersion or solid solution state in the polymeric microspheres loaded with drug.

Yield of sustained microspheres[16,17,18,]

The yield of microspheres was calculated from the amount of microspheres obtained divided by the total amount of all non-volatile components

$$\%\text{Yield} = \frac{\text{Actual weight of the microspheres}}{\text{Total weight of all non-volatile components}} \times 100$$

Particle size and shape[7]

The particle size of the microspheres was measured by optical microscopy. The eyepiece micrometer was calibrated using a stage micrometer and the calibration factor was used further in the calculation of the size of microspheres. The microspheres were finely spread over a slide and visualized under an optical microscope using an eyepiece micrometer. About 50 readings were taken at random and the mean ± standard deviation was calculated. The shape of the microspheres was visualized and the photographs were taken with the aid of a binocular microscope (Quasmo, India, model PZRM 700).

Surface Morphology of the Sustained Release Microspheres

The surface morphology of the sustained microspheres was studied with the aid of a Scanning Electron Microscope (SEM).

Drug entrapment efficiency (DEE)[8]

The amount of drug entrapped was estimated by crushing 50 mg of microspheres using mortar and pestle, and extracting drug with aliquots of 7.4 pH buffer repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using7.4 pH buffer. The solution was taken in a beaker and sonicated in a bath sonicator for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectrophotometrically at 290 nm against an appropriate blank.

The amount of drug entrapped in the microspheres was calculated using the following formula –

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

In vitro drug release study[9,10]

In vitro drug release studies were carried out for all formulations in USP type II dissolution test apparatus (TDT 06P, Electrolab, India).

Microspheres equivalent to 15 mg of cyclobenzaprine hydrochloride were poured into dissolution medium containing 500 ml of pH 7.4 buffer maintained at 37 ± 0.2 º C at a rotation speed of 50 rpm. 5 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions. The necessary dilutions were made with 7.4 pH buffer and the solution was analysed for the drug content spectrophotometrically using UV-Visible spectrophotometer (Model 2210, Chemito, India) at 290 nm against an appropriate blank. Three trials were carried out for all formulations. From this cumulative percentage drug release was calculated and plotted against function of time to study the pattern of drug release. The results are presented in tables and figures.

Mechanism of drug release

The obtained dissolution data was fitted into various kinetic models to understand the pattern of the drug release from sustained microspheres. The models used were zero order (equation 1),first order (equation 2) and Higuchi model (equation 3) and Koresmeyer Peppas model (equation 4).

i) zero order release kinetics:

$$R = Ko\, t \quad \text{-- (1)}$$

R=cumulative percent drug release

Ko=zero order rate constant

ii) First order release kinetics

$$\log C = \log Co - K_1 t / 2.303 \quad \text{-- (2)}$$

where C=cumulative percent drug release

K_1 = first order rate constant

iii)Higuchi model

$$R = K_H\, t^{0.5} \quad \text{-- (3)}$$

Where R = cumulative percent drug relase

K_H = higuchi model rate constant

iv) korsermeyer peppas model:

$$M t / M \alpha = K_k t^n$$

$$\log M t / M \alpha = \log K_k + n \log t \quad \text{-- (4)}$$

where K_k = korsermeyer peppas rate constant

'M t / M α' is the fractional drug release, n = diffusional exponent, which characterizes the mechanism of drug release.

RESULTS AND DISCUSSIONS:

Drug loaded Eudragit RS 100 microspheres (Formulation CBRS 12) showed a broad Sharp peak at 215.5^{o}C as shown in Figure 1. The reduction of height and sharpness of the endotherm peak is due to the presence of polymer in the microspheres. Drug loaded Ethylcellulose microspheres (Formulation CBEC 19) showed a broad Sharp peak at 212.8^{o}C as shown in Figure 1.

The DSC plot of pure cyclobenzaprine hydrochloride shows a sharp endothermic peak near 220.6°C, which is attributed to its melting temperature. The Eudragit, Ethylcellulose microspheres also show the melting point at same temperature indicating no interaction between the drug and excipients**.**

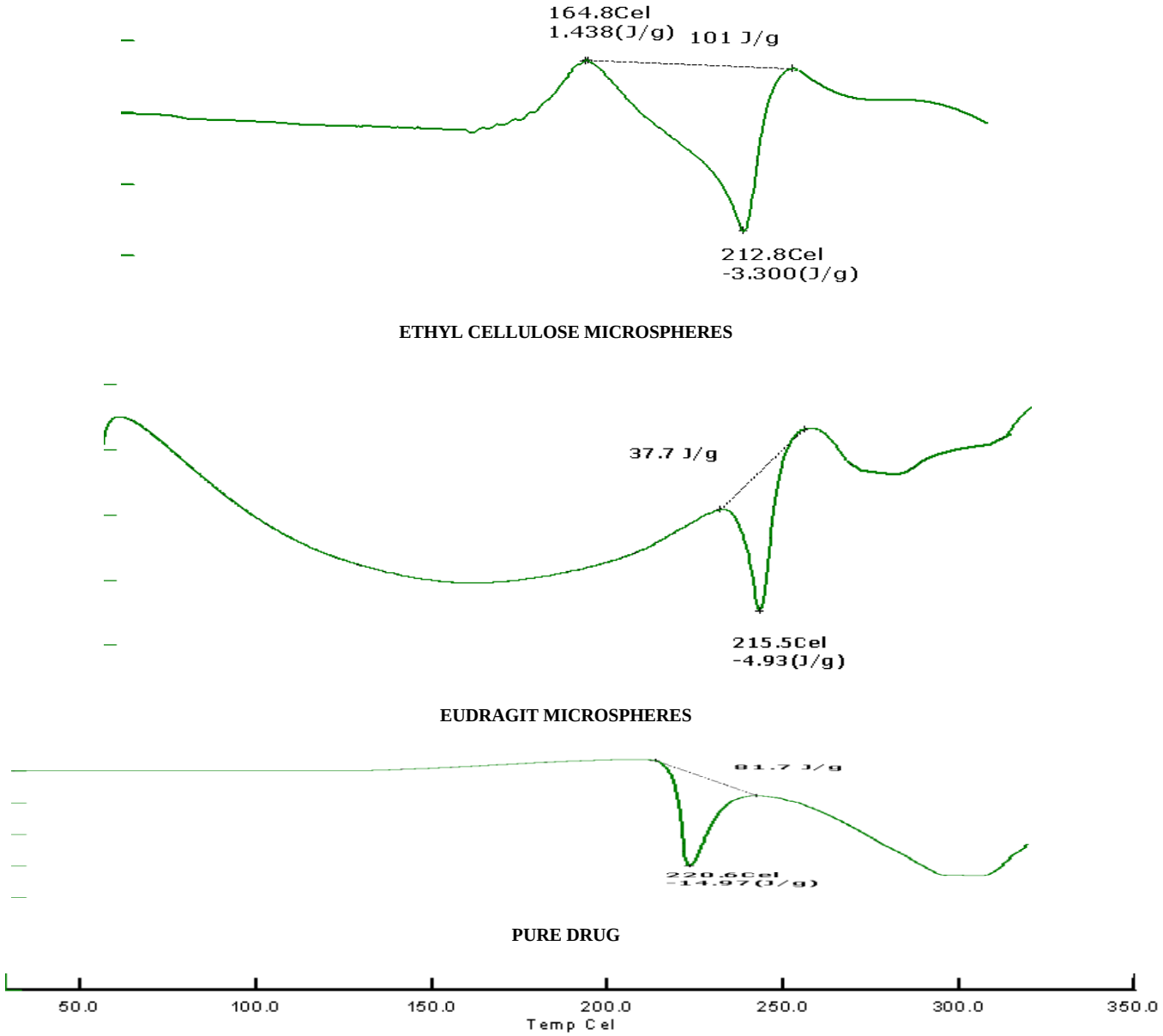


Fig 1 DSC thermogram of pure drug and optimized dosage forms

Formulation and Evaluation of sustained release Microspheres of cyclobenzaprine hydrochloride

Yield of Sustained Release Microspheres

From the table 5 it was observed that yield value was high i.e. more than 93% for drug-polymer ratio of 1:6 for Eudragit microspheres at different speeds, while it is more than 97% for ethyl cellulose microspheres(CBEC 21). This decrease in yield for Eudragit microspheres might be due to, film forming property of Eudragit polymer.

Particle Size and Shape of Microspheres

The formulated microspheres were evaluated for the size with the aid of an optical microscope. From table 6 the mean particle size of the Eudragit microspheres at increasing Eudragit concentrations (*i.e.*, at drug-polymer ratios 1:1 to 1:6) increased from 88.39 to 115 µm at 2200 rpm and from 95.11 to 123.11 µm at 1100 rpm respectively. The mean particle size of the ethyl cellulose microspheres at increasing ethyl cellulose concentrations (*i.e.*, at drug-polymer ratios 1:1 to 1:6) increased from 175.99 to 227.27µm at 2200 rpm shown in table-6. This increase in particle size of the microspheres can be attributed to an increase in viscosity with increasing polymer concentrations, which resulted in larger emulsion droplets leads to the formation of greater microsphere size.

Table 5 Yield of Sustained Release Microspheres

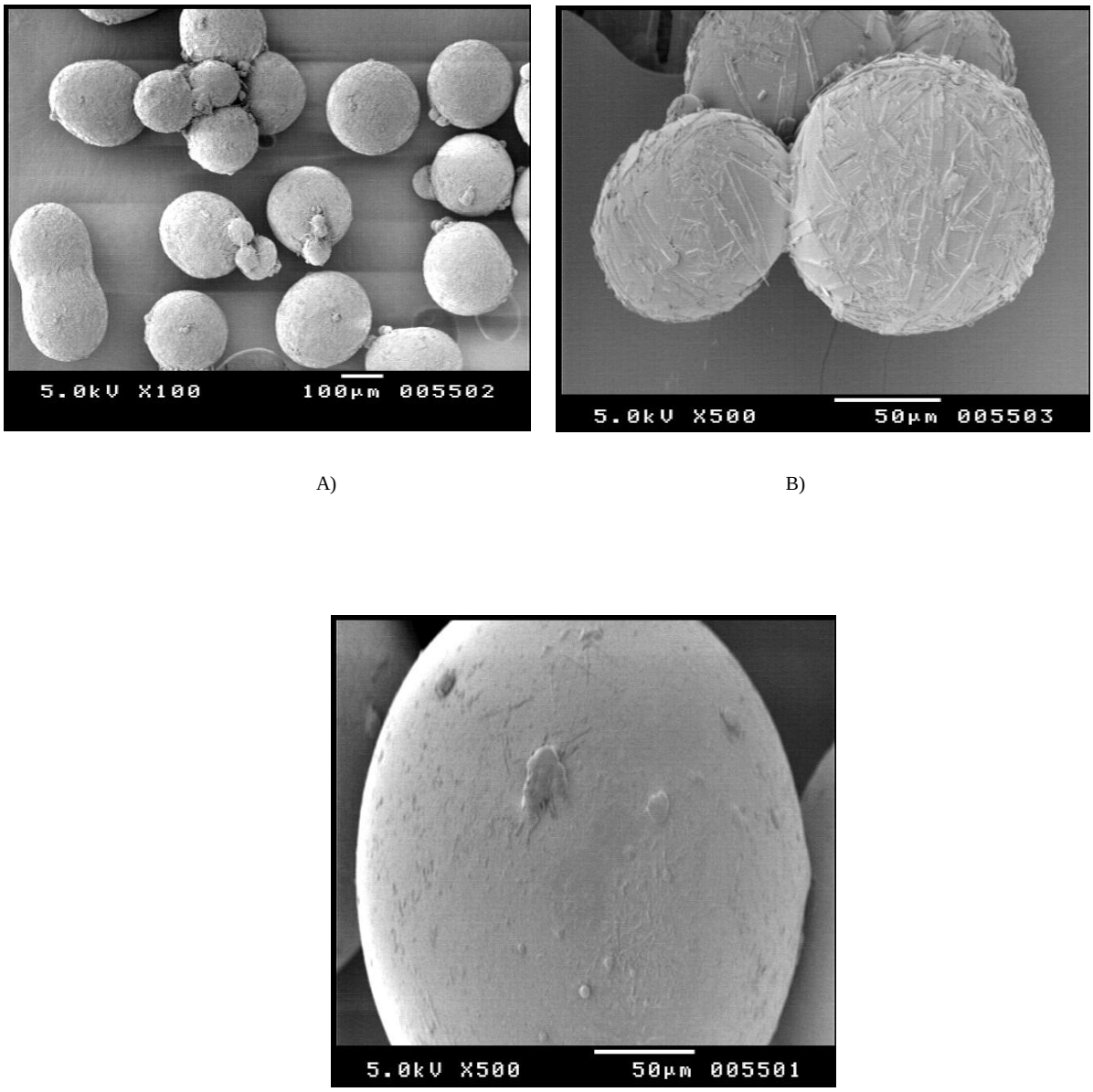
Formulation code	%yield	Formulation code	%yield	Formulation code	%yield
CBRS1 (1:1)	75.85	**CBRS10 (1:1)**	78	**CBEC16 (1:1)**	**93.25**
CBRS2 (1:2)	79.55	**CBRS11 (1:2)**	82	**CBEC17 (1:2)**	**94.33**
CBRS3 (1:3)	88.33	**CBRS12 (1:3)**	86	**CBEC18 (1:3)**	**95.55**
CBRS4 (1:4)	90.69	**CBRS13 (1:4)**	91.33	**CBEC19 (1:4)**	**96.25**
CBRS5 (1:5)	92.79	**CBRS14 (1:5)**	92.77	**CBEC20 (1:5)**	**98.33**
CBRS6 (1:6)	**93**	CBRS15 (1:6)	**93.55**	CBEC21 (1:6)	**97.92**

Table 6 - Particle Size of Sustained Release Microspheres

Formulation code	Particle size (in microns)	Formulation code	Particle size (in microns)	Formulation code	Particle size (in microns)
CBRS 1 (1:1)	88.39	**CBRS 10 (1:1)**	95.11	**CBEC 16 (1:1)**	**175.99**
CBRS 2 (1:2)	93.64	**CBRS 11 (1:2)**	102	**CBEC 17 (1:2)**	**187.84**
CBRS 3 (1:3)	96.72	**CBRS 12 (1:3)**	109.55	**CBEC 18 (1:3)**	**195.55**
CBRS 4 (1:4)	101.44	**CBRS 13 (1:4)**	115.40	**CBEC 19 (1:4)**	**213.66**
CBRS 5 (1:5)	108.25	**CBRS 14 (1:5)**	119.64	**CBEC20 (1:5)**	**221.44**
CBRS 6 (1:6)	**115**	CBRS 15 (1:6)	**123.11**	CBEC 21 (1:6)	**227.57**

Surface Morphology by scanning electron microscopy (SEM)

A SEM photograph of optimized Eudragit microspheres magnification, (CBRS 4) at 100×, (CBRS 12) at 500× magnification, (CBEC 19) at 500× magnification.SEM photographs showed discrete, spherical microspheres shown in figure-2. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of unentrapped drug in dispersion medium.



A) B)

C)

Figure 2 A) CBRS 4 at 100×, B) CBRS 12 at 500× magnification and C) CBEC 19 at 500× magnification.

Drug Entrapment Efficiency of Microspheres

The best drug loading percentage was observed at a drug- Eudragit ratio of 1:4 (CBRS 6 and CBRS 15). The higher percentage of drug loading were 56.67% (CBRS 6) and 63.33% (CBRS 15). For ethyl cellulose microspheres the best drug loading percentage was observed at a drug –ethyl cellulose ratio of 1:6 (CBEC 21) that was 63%. The higher percentage of drug loading 63.00 indicting that by increasing the drug to polymer ratio percentage of drug loading also increased. This may be attributed to the availability of more coat material per drug molecule.

In vitro dissolution studies of cyclobenzaprine microspheres

The results of the in vitro drug release studies were given in the tables 7-10 and figures3-5. From the obtained dissolution data following inferences were made.

The drug release from the 1:1 of Drug: Eudragit RS 100(CBRS 1) at the speed of 2200 rpm showed a burst effect, releasing 63.519 % of the drug within 0.5 hour and overall the release could be sustained only for 7 hours. But the drug release from the 1:1 of drug : Eudragit RS 100(CBRS 10) at the speed of 1100 rpm showed a slow release effect, releasing 44.856%of the drug within 0.5 hrs and overall release sustained up to 9 hrs . This might be due to the more uniform coating of polymer around the microspheres at slow speed.

Although 1: 1 core to coat ratio at 1100 and 2200 speed was not sufficient to retard the drug release for a prolonged period of time up to 12 hrs. On increasing the drug to polymer ratio, the drug release could be prolonged. The 1:4 ratio of drug to Eudragit RS 100 at 2200 rpm speed could sustain the release for 12 hours releasing about 99.247% of the drug. And the 1:3 ratio of drug to Eudragit RS 100 at 1100 rpm speed sustain the release for 13 hrs releasing about 98.802% of the drug .the slow release from 1:3 drug to Eudragit RS 100 polymer at 1100 rpm speed might be due to the more uniform coating of polymer around the microspheres at slow speed . The available literature[11] suggests that the quaternary ammonium groups in RL100 and RS100 are 8.85 - 11.96 % and 4.48 - 6.77 % respectively and they have a profound influence on the permeability of the polymer.

The drug release from ethyl cellulose microspheres were also in same pattern having some burst release pattern when compared to Eudragit polymer. Drug release from 1:1 of drug:ethyl cellulose N50(CBEC16) at the speed of 2200 rpm showed a burst effect, releasing 46.66 % of the drug within 1 hour and overall the release could be sustained only for 7 hours.

The drug release from CBEC16 formulation was only up to 7 hours. So, drug relase from the microspheres will be increased by increasing the core to coat ratio. And when comparing the drug release from increased core to coat ratios formulations drug release retarded up to 13 hrs which was desired for our study. Finally drug release from 1:4 ratio of Drug:Ethyl cellulose N50(CBEC 19) showing sustained release of drug from the microspheres about 12 hours.

Therefore, a high core to coat was essential to prolong the release of the drug from microspheres and this could be achieved by using 1: 3 ratio of drug to RS 100 at 1100 rpm(CBRS 12) ,1:4 ratio of drug to RS 100 at 2200 rpm (CBRS 4)and 1:4 ratio of drug to ethyl cellulose N 50(CBEC 19) at 2200 rpm.

While increasing core to coat ratios of drug and polymers the cumulative % drug release was decreased it was 89.77% for CBRS 6, 70.152 for CBRS 15 and 80.152% for CBEC 21.

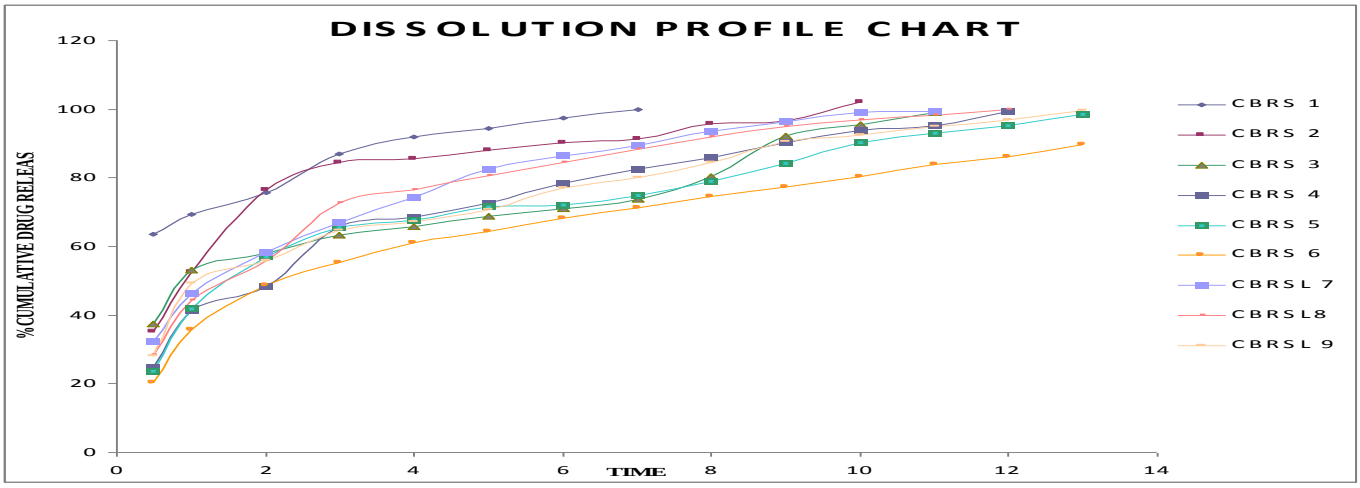


Fig 3 Cumulative percentage drug released Vs Time Curves of eudragit microspheres CBRS 1 – CBRSL 9 in P^H 7.4 buffer.

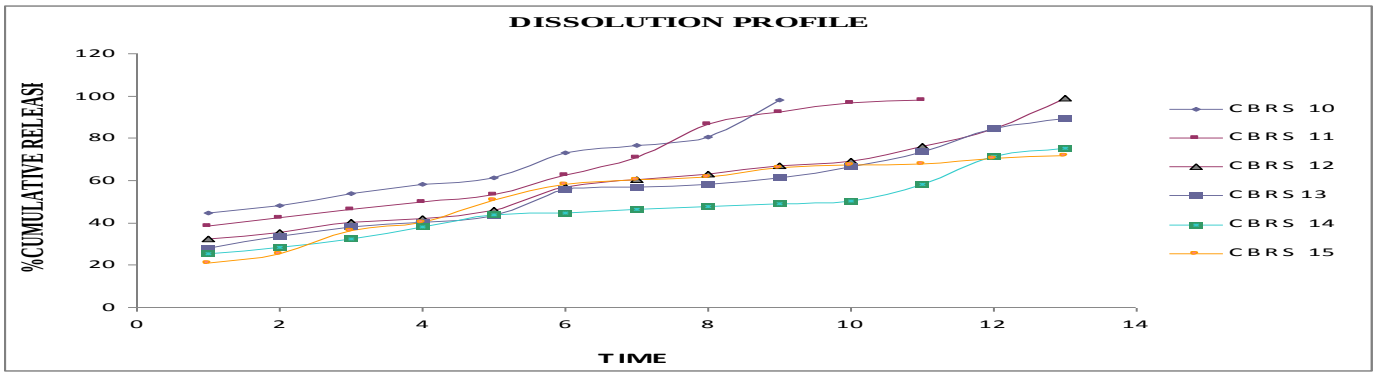


Fig 4 Cumulative percentage drug released Vs Time Curves of eudragit microspheres CBRS 10 – CBRS 15 in P^H 7.4 buffer.

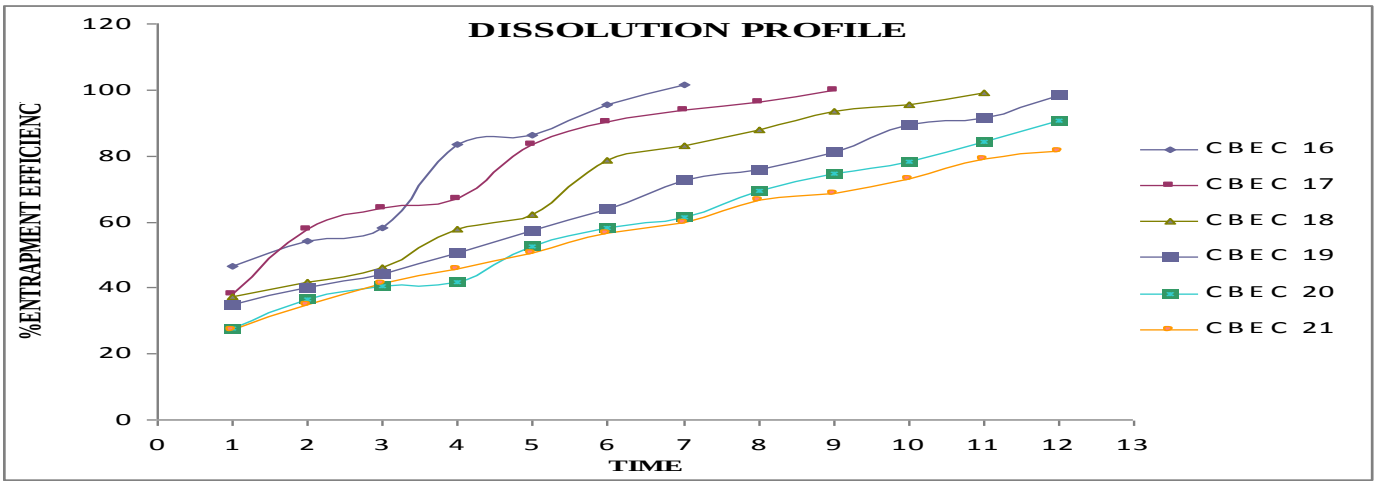


Fig 5 Cumulative percentage drug released Vs Time Curves of Ethylcellulose microspheres CBEC 11 – CBEC 21 in P^H 7.4 buffer.

Table 7 In vitro drug release (dissolution) data for CBRS 1 –CBRS 6 formulations

Cumulative %drug release

TIME (hours)	CBRS 1	CBRS 2	CBRS 3	CBRS 4	CBRS 5	CBRS 6
0.5	63.519	35.185	37.449	24.897	23.663	20.339
1	69.471	52.680	53.109	41.302	41.706	35.658
2	75.628	76.452	57.949	48.339	56.976	48.679
3	86.990	84.521	63.232	65.910	65.546	55.381
4	91.907	85.845	65.664	68.565	67.786	61.105
5	94.432	87.997	68.725	72.674	71.684	64.546
6	97.520	90.159	70.979	78.451	72.105	68.153
7	99.826	91.508	73.656	82.614	74.995	71.123
8	----------	95.743	80.256	85.770	78.929	74.658
9	----------	96.707	92.243	90.177	84.324	77.326
10	----------	101.995	95.451	93.784	90.160	80.256
11	----------	----------	99.087	95.353	93.148	83.945
12	----------	----------	----------	99.247	95.186	86.111
13	----------	----------	----------	----------	98.630	89.777

Table 8 In vitro drug release (dissolution) data for CBRS 7 –CBRS 9 formulations

Cumulative %drug release

TIME (hours)	CBRS 7	CBRS 8	CBRS 9
0.5	32.147	28.395	27.984
1	46.259	44.409	49.962
2	58.321	55.786	55.816
3	66.856	72.579	64.791
4	74.412	76.507	67.026
5	82.589	80.663	70.714
6	86.473	84.429	77.095
7	89.437	88.421	80.015
8	93.633	92.022	84.390
9	96.213	94.819	90.435
10	98.963	97.012	92.397
11	99.458	98.392	94.986
12	----------	99.812	96.801
13	----------	----------	99.548

Table 9 In vitro drug release (dissolution) data for CBRS 10 –CBRS 15formulations

Cumulative %drug release

TIME (hours)	CBRS 10	CBRS 11	CBRS 12	CBRS 13	CBRS 14	CBRS 15
1	44.856	38.547	32.305	27.984	25.206	21.605
2	48.212	42.659	35.585	33.707	28.649	25.233
3	53.849	46.321	40.118	38.023	32.319	36.494
4	58.284	49.865	42.002	40.307	38.066	40.415
5	61.509	53.245	46.160	43.220	43.744	50.737
6	73.198	62.752	57.131	55.820	44.516	58.033
7	76.704	71.111	60.348	56.766	46.320	60.227
8	80.444	86.651	63.170	58.333	47.620	61.814
9	98.196	92.234	67.036	61.141	49.028	66.290
10	----------	96.678	69.071	66.434	50.546	67.293
11	----------	98.233	76.054	73.402	58.244	68.093
12	----------	----------	84.723	84.525	71.233	70.542
13	----------	----------	98.802	89.166	75.197	72.000

Table 10 In vitro drug release (dissolution) data for CBEC 16 –CBEC 21 formulations

Cumulative %drug release

TIME (hours)	CBEC 16	CBEC 17	CBEC 18	CBEC 19	CBEC 20	CBEC 21
1	46.667	38.148	37.222	34.815	27.593	27.222
2	54.074	57.778	41.667	40.185	36.481	35.00
3	58.299	64.023	46.004	44.324	40.584	41.504
4	83.492	66.828	57.823	50.582	41.830	45.715
5	86.181	83.531	62.273	57.231	52.523	50.681
6	95.557	90.161	78.651	63.970	58.160	56.684
7	101.350	93.785	83.031	72.751	61.379	59.717
8	----------	96.289	87.783	75.993	69.410	66.443
9	----------	99.904	93.436	81.261	74.686	68.733
10	----------	----------	95.576	89.303	78.092	72.867
11	----------	----------	99.149	91.609	84.454	79.216
12	----------	----------	----------	98.522	90.085	81.502
13	----------	----------	----------	----------		

Release kinetics

The mechanism of cyclobenzaprine hydrochloride release from microspheres was studied by fitting the data obtained from *in-vitro* release studies into zero-order, first-order, Higuchi's, korsermeyer peppas kinetic models. Obtained values of correlation coefficient are given in Table 11. On application of different release kinetic models mentioned earlier, it was found that optimized formulations showed better fitting with the zero-order release and korsermeyer peppas model.

Table 11 Correlation coefficient values for release kinetics of sustained release microspheres

Formulation code	First-Order	Zero-Order	Higuchi	korsermeyer peppas
CBRS 4	0.8666	0.9139	0.9416	**0.9747**
CBRS 12	0.594	0.9693	0.9416	**0.9505**
CBEC 19	**0.8066**	**0.9956**	**0.943**	**0.9693**

CONCLUSION:

Rationale of the present study was to prevent extensive metabolism of the drug and consequently to increase the oral bioavailability of the drug in the form of sustained release microspheres.

Attempt has been made to prepare sustained release microspheres of cyclobenzaprine hydrochloride, a highly water soluble drug. The microspheres were prepared by solvent evaporation method using Ethylcellulose, Eudragit polymers as retarding polymers and evaluated for parameters like percentage yield, particle size, entrapment efficiency and the effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on evaluated parameters. Microspheres morphology was evaluated by SEM. The yield and entrapment efficiency was high for eudragit microspheres were CBRS 4, CBRS 12 and for Ethylcellulose microspheres was CBEC 19. Particle size, entrapment efficiency and production yield were influenced by the type of polymer, polymer concentration, stirring speed and combination of polymers. *In vitro* dissolution of optimized formulations of various Eudragit, CBRS 4, CBRS 12 and Ethylcellulose, CBEC 19 in pH 7.4 formulations are releasing the drug up to 12 hrs.

According to the results of DSC analysis, no drug interaction occurred with polymers and cyclobenzaprine hydrochloride. And SEM photographs of optimized formulations CBRS 4, CBRS 12 and CBEC 19 showed discrete, spherical microspheres.

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