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Prepare and Optimization of Cyclobenzaprine Hydrochloride Sustained Release Microspheres

Gokarikaari Navya Sri*, K. Nagasree, P. Laxmi, K. Shravan Kumar

Samskruti College of Pharmacy, Kondapur, Ghatkesar, Medchal, Hyderabad-501301, Telangana, India
***Corresponding E-Mail:** principal.y7@gmail.com*

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ABSTRACT
Cyclobenzaprine, a centrally acting skeletal muscle relaxant used for acute musculoskeletal conditions, suffers from a short half-life and systemic side effects that limit its clinical efficacy, necessitating the development of sustained release formulations. This study aimed to formulate and evaluate Cyclobenzaprine microspheres using ethyl cellulose as the polymeric matrix to achieve controlled drug delivery. Microspheres were prepared through a standardized method, and preformulation studies were conducted on the pure drug to establish its physicochemical characteristics. The prepared formulations (F1, F2, and F3) were evaluated for entrapment efficiency, drug loading, percentage yield, and in vitro drug release profiles. The entrapment efficiency ranged from 34.75% to 87.45%, with drug loading values between 18.10% and 22.65%, and percentage yield varying from 44.8% to 63.2%. In vitro dissolution studies demonstrated controlled release behavior, with F1, F2, and F3 releasing 80.5%, 77.8%, and 72.9% of the drug, respectively, over 8 hours. Among the three formulations, F3 exhibited the most consistent and reliable performance with the highest entrapment efficiency (87.45%), optimal drug loading (22.65%), and the slowest drug release profile (72.9% at 8 hours), indicating superior sustained-release characteristics. These findings suggest that the F3 formulation is promising for further investigation and warrants stability studies, preclinical, and clinical evaluations to confirm its potential as an improved therapeutic option for musculoskeletal disorders.

Keywords: Cyclobenzaprine, ethyl cellulose microspheres, sustained release, controlled drug delivery, entrapment efficiency, drug loading, in vitro dissolution

INTRODUCTION

Cyclobenzaprine

IUPAC Name : dimethyl(3-{tricyclo[9.4.0.0^{3,8}] pentadeca-1(15),3,5,7,9,11,13-heptaen-2-ylidene} propyl) amine.

Molecular formula : $C_{20}H_{21}N$

Molecular Weight : 275.387 g/Mol

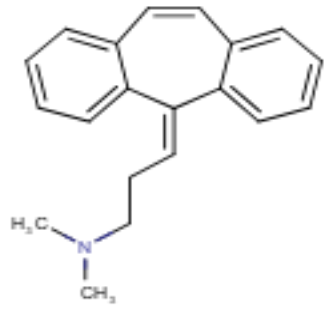

Fig.1: Cyclobenzaprine

Mechanism of Action

- Acts at the **brainstem** to reduce tonic somatic motor activity.
- Does **not act directly on skeletal muscle** or neuromuscular junction.
- Thought to reduce **gamma and alpha motor neuron excitability**, leading to muscle relaxation.

Pharmacokinetics

- **Absorption:** Well absorbed orally
- **Onset of Action:** Within 1 hour
- **Peak Effect:** 3–8 hours
- **Duration:** 12–24 hours (ER formulation provides extended coverage)
- **Protein Binding:** ~93%
- **Metabolism:** Primarily hepatic (CYP1A2)
- **Elimination Half-life:** 18 hours (range: 8–37 hours)
- **Excretion:** Mainly urine as metabolites, small amount in feces

Indications

- Relief of muscle spasm associated with acute, painful musculoskeletal conditions (e.g., back pain, neck strain).
- Typically used **short-term (2–3 weeks)** due to lack of long-term efficacy data.

Dosage

- Immediate release: 5–10 mg orally **three times daily**
- Extended release: 15–30 mg **once daily**
- **Maximum dose:** 30 mg/day (IR) or 30 mg/day (ER)
- **Geriatrics:** Use lower dose due to risk of sedation and anticholinergic effects

Adverse Effects

- **Common:** Drowsiness, dizziness, dry mouth, fatigue, headache, constipation, blurred vision
- **Serious (rare):** Cardiac arrhythmias, serotonin syndrome (if combined with serotonergic drugs), confusion, hallucinations
- **Anticholinergic effects** may be significant in elderly

Contraindications

- Hypersensitivity to cyclobenzaprine or related compounds
- Concomitant use with MAO **inhibitors** (within 14 days) → risk of hyperpyretic crisis, seizures, death
- Hyperthyroidism
- Recent myocardial infarction
- Cardiac arrhythmias, heart block, heart failure

Drug Interactions

- CNS depressants (alcohol, benzodiazepines, opioids): Enhanced sedation
- Tricyclic antidepressants, anticholinergics: Increased side effects
- SSRIs, SNRIs, MAOIs, tramadol, linezolid, St. John's Wort: Risk of serotonin syndrome
- CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin): May increase levels

MATERIALS AND METHODS

Table 1: Materials used

S.No.	Materials	Manufacturer
1.	Cyclobenzaprine	Novertis labs, india.
2.	Ethyl cellulose	Indian research products, Chennai.
3.	Dichloro methane	Spectrum reagents and chemicals pvt, ltd, cochin.
4	Poly vinyl alcohol	Loba chemicals pvt.ltd, Mumbai.
5.	Ethanol	Hong yang chemicals corp.china.

Table 2: List equipment's used

S.No	Equipment	Company
1.	Electronic balance	AND GP-12K
2	FT-IR	Bomem FTIR MB-II
3	Electromagnetic stirrer	Remi magnetic stirrer
4	P^H Meter	ELICO LI 120 P^H Meter
5	Sonicator	LOBO Life 3-5L Sonicator
6	Dissolution apparatus	Electro lab USP XXII
7	UV spectrophotometer	Schimadzu
8	SEM	FEI-Quanta 200F

Preformulation Studies

Preformulation was the first step in the rational development of dosage forms of a drug substance. It can be defined as" an investigation of physical and chemical properties of a drug substance alone and when combined with excipients".

Organoleptic properties

The Organoleptic character of the drug like color, odour and appearance play an important role in the identification of the sample and hence they should be recorded in a descriptive terminology. The results were given in results and discussion section.

Solubility Studies:

It is important to know about solubility characteristics of a drug in aqueous systems, since they must possess some limited aqueous solubility to elicit a therapeutic response. Solubility was carried out in water, ethanol, acetonitrile and other solvents. The results were given in results and discussion section.

Melting point: Melting point of pure Cyclobenzaprine drug was determined by melting point apparatus. The results were given in results and discussion section.

Drug and Excipient Compatibility Study

To investigate any possible interactions between the drug and excipients used, the FTIR spectra of pure Cyclobenzaprine and its physical mixture with ethyl cellulose were carried out using Bomem FTIR MB-II spectrophotometer. The samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 10 Ton/nm^2. The wave number selected ranged between 400 and 4800 cm^{-1}. The results were given in results and discussion section.

Solvent evaporation method:

Cyclobenzaprine microspheres were prepared by solvent evaporation technique. For this, Cyclobenzaprine was dissolved in dichloromethane and then polymer was dissolved in ethanolic solution .Both drug and polymer solution were mixed well to form a uniform solution. The obtained drug and polymer solution was added drop wise to the PVA solution under constant stirring at1500 rpm. The constant stirring using homogenizer at 1500rpm. The beaker and its content were heated at 80^0 c with constant stirring for 1hr until the aqueous phase was completely removed by evaporation. The microspheres formed were collected by whatman filter paper and washed 3 times with distilled water and dried at room temperature for one day.

In vitro release studies

The in-vitro drug release studies were conducted in p^H 6.8 buffer for 8hrs using USP type –II dissolution apparatus under sink conditions. Accurately weighed samples of the microspheres were added to the dissolution medium kept at 37± 0.5^0c .At present time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. After suitable dilution samples were analysed spectrophotometrically at 217nm.

Kinetics analysis of dissolution data:

The release profiles of different batches of microspheres were fitted for different models such as Zero order, First order, Higuchi and Kosmeyer- peppas ploats.

RESULTS AND DISCUSSION

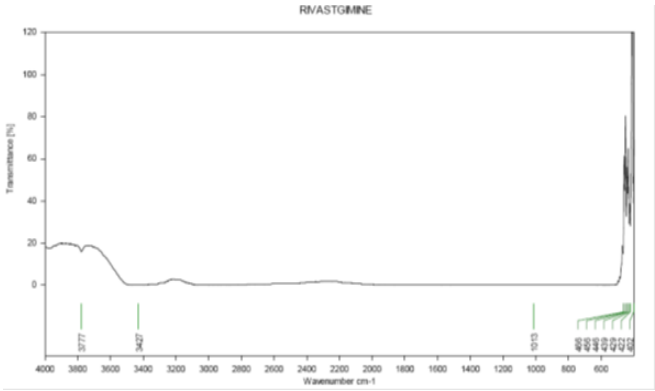

Fig.2: FTIR of Cyclobenzaprine

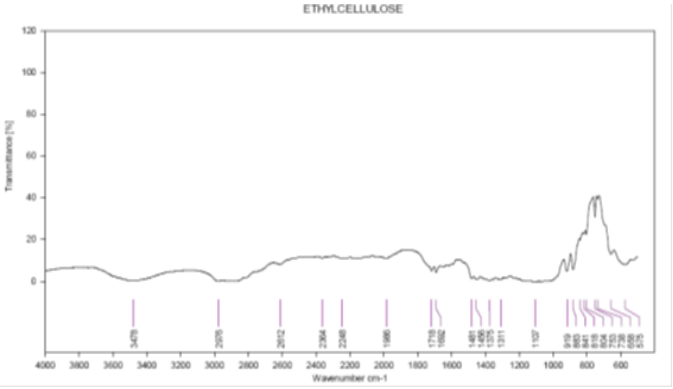

Fig.3: FTIR of Ethyl cellulose

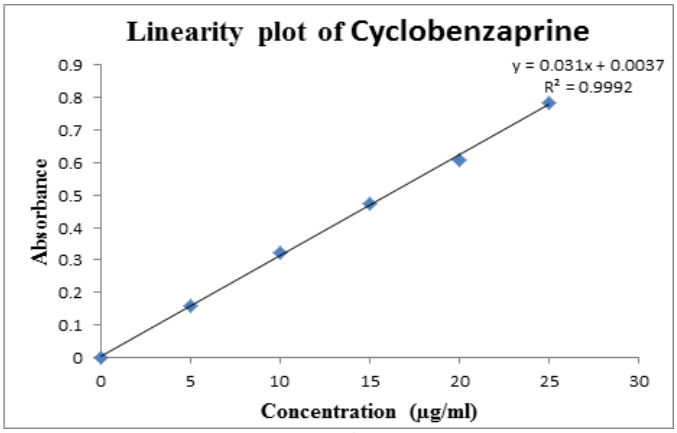

Fig.4: linearity plot of Cyclobenzaprine.

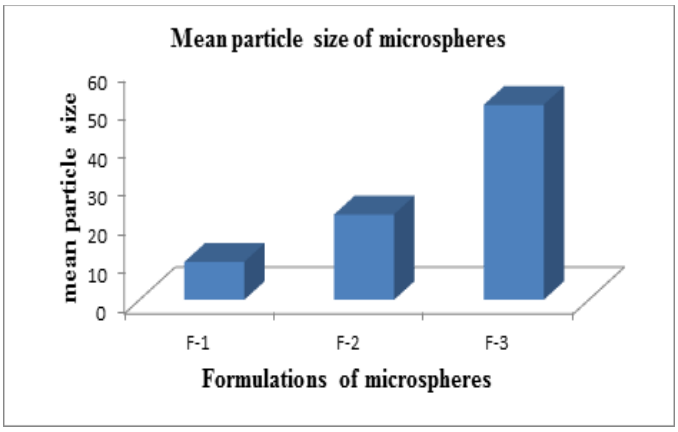

Fig.5: Mean particle size of microspheres

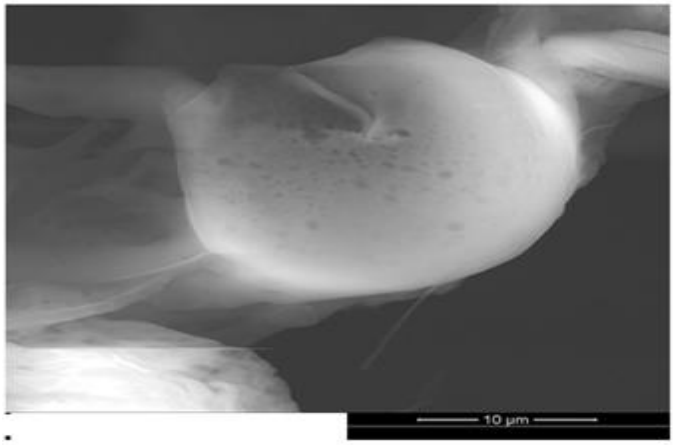

Fig.6: SEM photograph of Cyclobenzaprine microspheres

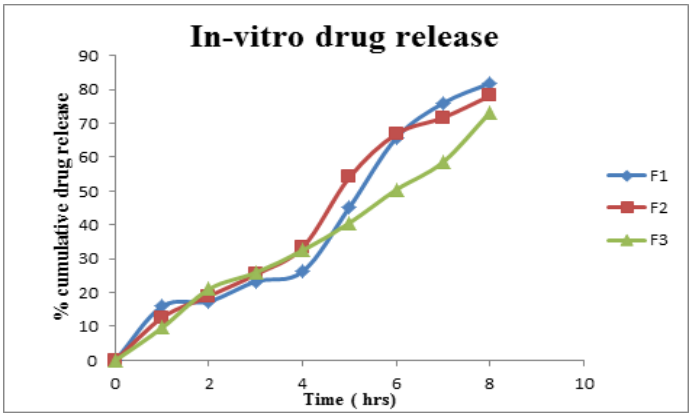

Fig.7: In-vitro drug release Cyclobenzaprine microspheres

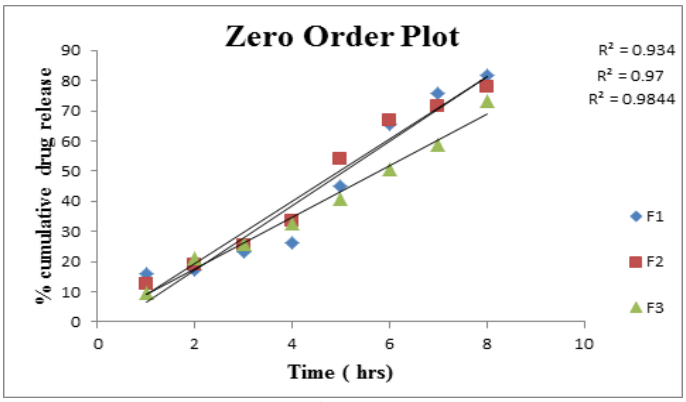

Fig.8: Zero order release of Cyclobenzaprine microspheres

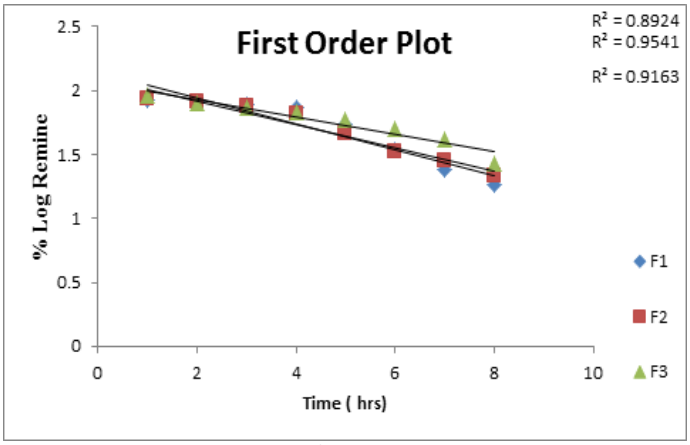

Fig.9: First order release of Cyclobenzaprine microspheres

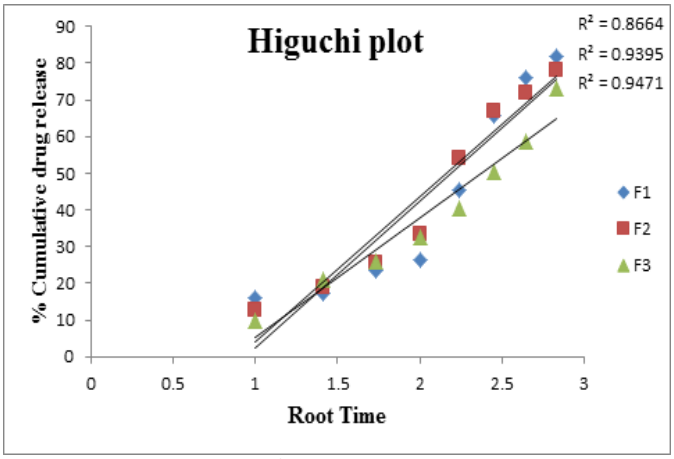

Fig.10: Higuchi plot of Rivastigmine tartrate microspheres

Table 3: Drug release kinetics of Cyclobenzaprine microspheres

Formulations	Zero order R^2	First order R^2	Higuchi plot R^2	Peppas plot		
				R^2	K	N
F_1	0.934	0.892	0.866	0.857	11.387	0.878
F_2	0.970	0.954	0.939	0.960	10.754	0.947
F_3	0.987	0.916	0.947	0.984	9.853	0.918

Table 4: Cumulative drug release of Cyclobenzaprine microspheres

Time (hrs)	% Cumulative drug release		
	F_1	F_2	F_3
0	0	0	0
1	15.97	12.64	9.66
2	17.44	19.01	21.04
3	23.29	25.40	25.93
4	26.24	33.38	32.46
5	45.23	54.09	40.62
6	65.70	66.87	50.41
7	75.98	71.72	58.58
8	81.90	78.16	73.27

CONCLUSION

Microspheres are mono- or multi-nuclear drug delivery systems in which the active pharmaceutical ingredient is embedded within a spherical polymeric matrix. These solid particles, generally ranging in size from 1 µm to 1000 µm, are prepared using biodegradable synthetic polymers or modified natural products such as starches, gums, proteins, fats, and waxes. Microsphere-based formulations offer the advantages of controlled release, improved bioavailability, and site-specific delivery. Cyclobenzaprine is a centrally acting skeletal muscle relaxant structurally related to tricyclic antidepressants. It is primarily prescribed for the management of acute musculoskeletal conditions associated with muscle spasms, pain, and stiffness. However, its short half-life and systemic side effects limit its therapeutic efficiency, creating the need for a sustained release formulation. The entrapment efficiency of the formulations was found to be F1: 34.75%, F2: 60.92%, and F3: 87.45%. The drug loading values were F1: 18.10%, F2: 20.25%, and F3: 22.65%. The percentage yield obtained was F1: 44.8%, F2: 55.7%, and F3: 63.2%. In vitro dissolution studies showed drug release of F1: 80.5%, F2: 77.8%, and F3: 72.9% at the end of 8 hours. Dissolution profile graphs (percentage drug release vs. time) were plotted for all formulations. Among them, F3 demonstrated the most consistent and reliable results. Hence, F3 formulation was considered promising and may be further subjected to stability studies, as well as pre-clinical and clinical investigations.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL: Not applicable

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AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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