

# A Review on Formulation and Evaluation of microspheres of cyclobenzaprine HCl- Skeleton muscle relaxant

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**Abstract-** The microsphere has free-flowing powder properties and contains proteins as well as synthetic or natural polymers. This polymer seems to be biodegradable in nature and particles having below 200 µm. Cyclobenzaprine hydrochloride is a sympathomimetic muscle relaxant that has been widely used for the relief of muscle spasms associated with acute, painful musculoskeletal conditions for the past 30 years. It activates the locus cerelus in the brain stem leading to an increased release of nor epinephrine in the ventral horn of the spinal cord & subsequent inhibitory action of nor epinephrine on alpha motor neurons. Cyclobenzaprine related to the first-generation Tricyclic antidepressants. Such Tricyclics including amitriptyline act to inhibit the uptake of nor epinephrine, resulting in increased trans synaptic or epinephrine concentration. They have been shown to exert analgesic effect in chronic nerve & muscle pain. The current goal of this review is to investigate multiple elements of the microparticulate drug-delivery system, such as formulation methods, evaluation, and characterization.

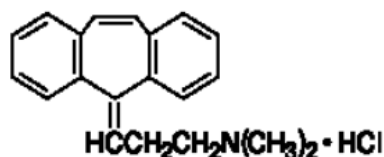
**Key-Words:** Microspheres, Cyclobenzaprine hydrochloride, polymer, solvent evaporation, muscle relaxants, evaluation

## INTRODUCTION

Cyclobenzaprine hydrochloride (CBZ) [3-(5H-dibenzo [a,d] cyclohepten-5-ylidene)-N,N-dimethyl-1- propanamine hydrochloride; CZ] is a well-known centrally acting, skeletal muscle relaxant which acts primarily within the central nervous system at brain stem level. It's bound to the serotonin receptor that reduces muscle tone by decreasing the activity of serotonergic neurons. It undergoes rapid and extensively first-pass metabolism in the gastrointestinal and liver.

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Cyclobenzaprine related to the first-generation Tricyclic antidepressants. Such Tricyclics including amitriptyline act to inhibit the uptake of nor epinephrine, resulting in increased trans synaptic or epinephrine concentration. They have been shown to exert analgesic effect in chronic nerve & muscle pain. Cyclobenzaprine may have a similar effect.



Structure of cyclobenzaprine HCl

For many acute diseases 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 an efficient release of drug. 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.

Microsphere defined as "a monolithic structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion, falling in the size range 1-500 µ.

## TYPES OF MICROSPHERES

### Bio adhesive microspheres

Adhesion is the process of a medication adhering to a membrane using the adhesive properties of water-soluble polymers. Bio adhesion is the attachment of a medication delivery device to a mucosal surface, such as the buccal, ocular, rectal, nasal, etc. Materials that adhere to biological substrates, such as mucosal members, are referred to as having "bio adhesion." The ability of establishing a close and persistent contact at the site of administration exists due to the adhesion of bio adhesive drug delivery devices to the mucosal tissue. By reducing the frequency of delivery, this extended retention time can improve patient compliance

while also enhancing absorption when combined with a controlled drug release. By attaching the drug to a carrier particle, carrier technology provides an intelligent method for drug delivery.

### Floating microspheres

In floating types, the bulk density is less than the gastric contents and hence continues to remain buoyant in stomach without affecting gastric emptying rate. If the system is floating on gastric content, the drug is released slowly at the desired rate, increasing gastric residence and fluctuation in plasma concentration. It also reduces the risk of striking and dose dumping while producing a longer therapeutic efficacy. This is how the drug (ketoprofen) is administered.

### Radioactive microspheres

Radio embolisation therapy microspheres with sizes ranging from 10 to 30 nm are larger than capillaries and are trapped in the first capillary bed when they come into contact. They are injected into the arteries leading to the tumour of interest. As a result, these radioactive microspheres deliver a high radiation dose to the targeted areas while causing no harm to the normal surrounding tissues. It differs from a drug delivery system in that radioactivity is not released from microspheres but instead acts from within a radioisotope typical distance, and the various types of radioactive microspheres are emitters, emitters, emitters.

### Mucoadhesive microspheres

Mucoadhesive microspheres with a diameter of 1-1000nm and made entirely of a mucoadhesive polymer or with an outer layer of it provide additional advantages, such as efficient absorption and improve bioavailability of drugs due to a high surface to volume ratio, much more intimate contact with the mucus layer, and specific targeting of drug to the site of absorption achieved by anchoring plant lectin. Mucoadhesive microspheres can also be adapted to adhere to any mucus layer, including those found in the eye, nasal cavity, urinary tract, and gastrointestinal tract, allowing for both localised and systemic controlled drug release.

### Polymeric microspheres

**Biodegradable polymeric microspheres** Natural polymers like starch are used because they are biocompatible, bioresorbable, and bio adhesive in nature. Because of their high degree of swelling in aqueous medium, biopolymers extend the retention time when in contact with mucous membranes, resulting in gel formation. The rate and extent of release of drug are controlled in a sustained manner by polymer concentration and release pattern. The main disadvantage is that drug loading efficiency of bio - based microspheres in clinical use is complex, making drug release difficult to control.

**Synthetic polymeric microspheres** the interest in synthetic polymeric microspheres is commonly used in medical applications; additionally, they are used as bulking agents, fillers, vascular particles, drug delivery vehicles, and other applications, and have been shown to be safe and biocompatible. However, the main disadvantage of these microspheres is that they tend to migrate away from the injection site, posing a risk of blood clots and further organ failure.

### Materials

Polymers are commonly used as microspheres. They are divided into two types.:

- Synthetic Polymers
- Natural polymers

Synthetic polymers are divided into two types.

#### a) Non-biodegradable polymers

Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

#### b) Biodegradable polymers

Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

**Proteins:** Albumin, Gelatin, Collagen

**Carbohydrates:** Agarose, Carrageenan, Chitosan, Starch

**Chemically modified carbohydrates:** Poly dextran, Poly starch.

### METHODS OF PREPERATION

1. Emulsion solvent evaporation technique
2. Emulsion cross linking method
3. Coacervation method
4. Spray drying technique
5. Emulsion-solvent diffusion technique
6. Multiple emulsion method
7. Ionic gelation
8. Hydroxyl appetite (HAP) microspheres in sphere morphology

### Emulsion solvent evaporation technique

The drug is dissolved in polymer that has previously been dissolved in chloroform in this technique, and the resulting solution is then added to an aqueous phase containing 0.2% sodium PVP as an emulsifying agent. The above mixture was agitated at 500 rpm, and the drug and polymer (eudragit) were transformed into fine droplets that solidified into rigid microspheres by solvent

evaporation. The microspheres were then collected by filtration, washed with demineralised water, and desiccated at room temperature for 24 hours. This method was used to create aceclofenac microspheres.

#### **Emulsion cross linking method**

In this method, the drug was dissolved in an aqueous gelation solution that had been heated for 1 hour at 40°C. The solution was added drop by drop to liquid paraffin while stirring the mixture at 1500 rpm for 10 minutes at 35°C, resulting in a w/o emulsion, which was then stirred for another 10 minutes at 15°C. Thus, the microspheres were washed three times with acetone and isopropyl alcohol before being air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for three hours for cross linking before being treated with 100mL of 10mm glycine solution containing 0.1% w/v of tween 80 at 37°C for ten minutes to block unreacted glutaraldehyde. Gelatin A microspheres are 13 examples of this technique.

#### **Coacervation method**

**Coacervation thermal change:** It was performed by heating a weighed amount of ethyl cellulose in cyclohexane with vigorous stirring at 80°C. The drug was then finely pulverised and vigorously stirred into the above solution, and phase separation was accomplished by lowering the temperature and using an ice bath. The above product was then washed twice with cyclohexane, air dried, and sieved (sieve no. 40) to obtain individual microcapsules.

**Coacervation non solvent addition:** A weighed amount of cross - linking agent was dissolved in benzene containing propylisobutylene in a closed beaker with mechanical stirring for 6 hours at 500 rpm, and the drug was dispersed in it for 15 minutes. Petroleum benzoin is then used to separate the phases. 14 times, with constant stirring. The microcapsules were then drained with n-hexane and evaporated to dryness for 2 hours before being baked at 50°C for 4 hours.

#### **Spray drying technique**

This was used to develop polymeric blended microspheres containing the drug ketoprofen. It entails dispersing the core material in liquefied coating material and then spraying the mixture in the environment for coating solidification followed by rapid solvent evaporation. An organic solution of poly (epsilon caprolactone) (PCL) and cellulose acetate butyrate (CAB) in various weight ratios, as well as ketoprofen, was prepared and sprayed in various experimental conditions to produce drug-loaded microspheres. This is quick, but the crystallinity may be lost due to the rapid drying process.

#### **Emulsion-solvent diffusion technique**

To improve the residence time of ketoprofen in the colon, floating microspheres of ketoprofen were prepared using the emulsion solvent diffusion technique. The drug polymer combination was dissolved in a 1:1 mixture of ethanol and dichloromethane before being added drop by drop to a solution containing sodium lauryl sulphate (SLS). For 1 hour, the solution was stirred at room temperature with a propeller agitator at 150 rpm. As a result, the formed floating microspheres were sanitised and dried at room temperature in a dessicator. The microparticles listed below were sieved and obtained.

#### **Multiple emulsion method**

This technique was used to prepare indomethacin oral controlled release drug delivery. Initially, the powder drug was dispersed in a solution (methyl cellulose), which was then emulsified in an ethyl cellulose solution in ethyl acetate. After that, the microemulsion was re-emulsified in an aqueous medium. During this phase, fractional microspheres were formed under ideal circumstances.

#### **Ionic gelation**

This technique was used to create an alginate/chitosan particulate system for diclofenac sodium release. To a 1.2% (w/v) aqueous solution containing alginate, 25% (w/v) diclofenac sodium was added. To obtain the complete solution, stirring was continued, and it was then added drop by drop to an acetic acid solution containing Ca<sup>2+</sup>/Al<sup>3+</sup> and chitosan. The formed microspheres were kept in the original solution for 24 hours to allow internal gellification, followed by filtering for separation. The drug released completely at pH 6.4-7.2, but it did not release at acidic pH.

#### **Hydroxyl apatite (HAP) microspheres in sphere morphology**

This was used to make microspheres with unusual spheres in sphere morphology. Microspheres were made using an o/w emulsion followed by solvent evaporation. First, an o/w emulsion was created by dispersing the organic phase (NSAIDs with 5% w/w EVA and an appropriate amount of HAP) in the surfactant's aqueous phase. The organic layer was dispersed in the form of small droplets that were surrounded by surfactant molecules, preventing co-solvening and allowing the droplets to remain distinct. The DCM was slowly evaporated while stirring, and the droplets solidified individually to form microspheres.

### **PHYSICOCHEMICAL EVALUATION**

#### **Characterization**

Identification of the nanoparticle's carrier is an important concept that aids in the development of a suitable carrier for protein, drug, or antigen delivery. The microstructures of these microspheres vary. These microstructures govern the carrier's release and stability.

#### **Particle size and shape**

The most common methods for visualising microspheres are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be applied to determine microparticle shape and outer structure. In the case of double-walled microspheres, LM allows for control over coating parameters. The structures of the microspheres can be seen before and after coating, and the

difference can also be measured microscopically. In comparison to the LM, the SEM provides higher resolution. SEM can investigate the surfaces of microspheres and cross-sections of particles.

#### **Electron spectroscopy for chemical analysis**

Electron spectroscopy for chemical analysis can be used to determine the surface chemical properties, atomic composition of the surface, and surface degradation of bio - based microspheres (ESCA).

#### **Isoelectric point**

The micro electrophoresis apparatus is used to determine the isoelectric point by measuring the electrophoretic mobility of microspheres. The electrophoretic mobility of microspheres can be related to their surface charge, ionisable behaviour, or ion absorption nature.

#### **Angle of contact**

The hydration property of a micro particle's carrier is determined by measuring the angle of contact. It determines whether microspheres are water soluble or non - polar in nature. At the solid/air/water interface, the angle of contact is measured.

#### **Drug release**

##### **In vitro methods**

In vitro drug release studies have been used as a quality assurance procedure in pharmaceutical manufacturing, product development, and so on. Sensitive and measurable release data from physiochemically and hydrodynamically defined conditions are required, but no guideline in vitro method has yet to be developed. Depending on the shape and application of the dosage form developed, different workers used apparatus of varying designs and under varying conditions.

##### **Beaker method**

In this method, the dosage form is made to adhere to the bottom of the beaker that included the medium and is uniformly stirred with an overhead stirrer. The volume of medium used in the literature for the research ranges from 50 to 500 ml, and the stirrer speed ranges from 60 to 300 rpm.

##### **Dissolution apparatus**

The rotating elements, paddle, and basket of a standard USP or BP disintegration apparatus were used to study in vitro release profiles. The study's dissolution medium ranged from 100 to 500 ml, and the rotation speed ranged from 50 to 100 rpm.

#### **MICROSPHERES OFFER VARIOUS ADVANTAGES INCLUDING:**

1. Increases patient compliance by lowering the frequency of dosing.
2. Improved systemic absorption despite the first-pass effect because volatility in plasma drug concentration is avoided; continuous drug release maintains a desirable plasma drug concentration.
3. Prolonged gastric retention due to buoyancy.
4. Improved absorption of drugs that dissolve only in the stomach.
5. Prolonged drug release under strict control.
6. Drug delivery to the stomach can be accomplished.
7. Prevention of gastric irritation as a result of the sustained release effect.
8. Short half-life drugs can have a better therapeutic effect.

#### **LIMITATIONS**

Although microparticles have a number of potential benefits, their application may be bounded due to the following factors:

1. A higher dose of fluids in the abdomen is considered necessary for the microparticles to float and function properly.
2. The dosage form must be taken with a full glass of water (200-250 ml).
3. Incompatible with drugs that have a problem with solubility or stability in gastric fluids.
4. First-pass metabolism drugs (metoprolol, etc.) are not suitable.

#### **APPLICATIONS**

##### **1. Microspheres in vaccine delivery**

An ideal vaccine must meet the criteria of efficacy, safety, ease of use, and cost. Biodegradable vaccine delivery systems for parenteral administration may overcome the shortcomings of conventional antibiotics. The interest in intravenous fluid (subcutaneous, intramuscular, and intradermal) carriers stems from the following benefits:

- i. Adjuvant action improves antigenicity
- ii. Antigen release is modulated
- iii. Antigen stabilisation

##### **2. Targeting using microparticulate carriers**

Targeting, or site-specific drug delivery, is a well-known dogma that is gaining widespread attention. The drug's therapeutic efficacy is dependent on its access to and specific interaction including its candidate receptors. The ability to exit the collection in a reproducible, efficient, and specific way is central to drug action via a carrier system.

##### **3. Chemoembolization**

Chemoembolization seems to be an endovascular therapy that consists of selective arterial embolization of a tumour followed by instantaneous or successive local delivery of a chemotherapeutic agent.

##### **4. Imaging**

The range of particle sizes of microparticles is an important aspect when imaging specific sites with radiolabelled microspheres. Particles injected intravenously other than through the portal vein become entrapped in the lungs' capillary bed. Using labelled human serum albumin microspheres, this phenomenon is used for scintigraphic imaging of tumour masses in the lungs.

## 5. Topical porous microspheres

Microsponges are highly permeable microspheres with a plethora of interconnected voids ranging in particle size from 5-300m. As a topical carry system, these microsponges can entrap a broad range of active compounds such as moisturisers, aromas, essential oils, and so on.

**Jani et al. (2019)** Cyclobenzaprine hydrochloride was studied for brain targeted drug delivery in patients with skeletal muscle disorders. The nasal drug delivery system is a potential route for direct drug delivery to the central nervous system via the olfactory region, bypassing hepatic first-pass metabolism and providing a rapid onset of action. If cyclobenzaprine hydrochloride was formulated as a nasal in-situ gel, it would remain in contact with the nasal mucosa for a longer period of time, allowing the drug to be delivered from the nose to the brain via the olfactory region. The in-situ gel was created using a temperature-sensitive approach and either a simple mixing method or a cold method.

**Nikunja B. Pati et al. (2014)** The non-emulsion solvent evaporation method was used to successfully create cyclobenzaprine hydrochloride microspheres. Drug-polymer ratios with polymer matrices influenced microsphere yield, entrapment efficiency, and particle size. For all formulations, yield and entrapment efficiency were nearly identical. It was discovered that as polymer concentration and agitation speed increased, the mean size of the particles and drug release of microspheres decreased. The evaluation of controlled release revealed that almost all formulations' drug release from microspheres followed zero-order release and was a fickian diffusion-controlled process. As a result, the current study demonstrates the versatility of microspheres in delaying drug release. This, in turn, may reduce the amount of dosing, improving patient compliance.

**Koteswara et al (2014)** Controlled release microspheres of the highly water-soluble drug cyclobenzaprine hydrochloride. The microspheres were prepared using a solvent evaporation method with Ethylcellulose and Eudragit polymers as retarding polymers and evaluated for parameters such as percentage yield, particle size, entrapment efficiency, as well as the effect of preparation and process variables such as drug - excipient ratio, speed, polymer type, and polymer combination on evaluated parameters. SEM was used to examine the morphology of the microspheres. The yield and entrapment efficiency for eudragit microcapsules were CBRS 4, CBRS 12, and CBEC 19 for ethylcellulose microspheres. The type of polymer, polymer concentration, agitation speed, and polymer mixture all had an effect on particle size, entrapment efficiency, and production yield. In vitro dissolution of numerous Eudragit, CBRS 4, CBRS 12, and Ethylcellulose preparations.

**Rajendra Messa et al (2014)** Cyclobenzaprine hydrochloride, a muscle tissue relaxant that relieves local muscle spasms without interfering with muscle, was chosen as the drug because it initiates rapid and extensive metabolism, causing a low oral bioavailability.

## CONCLUSION

In comparison to other types of drug delivery systems, microspheres are a very good option for drug delivery systems because they have the advantages of improving clinical compliance and specificity of targeting. For low back pain caused by muscle spasm, analgesic pain relief may be coupled with a muscle relaxant. The most recent is cyclobenzaprine hydrochloride. These investigations lead to an intriguing and therapeutically beneficial sublingual cyclobenzaprine HCl product in the form of a nanoparticulate system for the rapid relief of pain and migraine. Microspheres not only deliver drugs, but they also play an important role in imaging tumours, detecting biomolecular interactions, and treating cancer, and thus in the next generation, microspheres will play an important part in the development of the medical field.

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