



A REVIEW ON MICROSPHERES PREPARATION AND EVALUATION METHODS AND DRUG PROFILE OF BENAZEPRIL ROLE IN LOWERING BLOOD PRESSURE

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ABSTRACT

Microparticles are designed to control drug release into the skin to ensure that the drug remains localized at the application site. It act as reservoir releasing an active ingredient over an extended period of time maintaining effective drug concentration in the skin and at the same time, reduces the undesired side effects. Oral controlled drug delivery system is designed to achieving more predictable and increased bioavailability, thereby obtaining a maximum therapeutic effect. The design of oral dosage pharmaceutical formulation, empty the process can last from a few minutes to 12 hours. The Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in stomach or upper part of small intestine. Thus placement of drug delivery system in a specific region of the GI tract offers a numerous advantages especially to the drugs having narrow absorption window, stability problem in intestine, poor solubility in alkaline PH, local activity of in stomach and property to degrade in colon. Therefore the design of a sustained release preparation requires both prolongation of gastrointestinal transit of dosage form as well as controlled drug release. Benazepril is a class of medications called angiotensin-converting enzyme inhibitors. It acts by decreasing certain chemicals that tighten the blood vessels, so blood flows more smoothly. Benazepril is used in combination with other medications to lower the high blood pressure.

KEYWORDS: Microparticles, colon, oral dosage pharmaceutical formulation, bioavailability, benazepril, blood pressure.

INTRODUCTION

Microspheres are characterized as solid, approximately spherical particles with a diameter having between 1–1000µm, including dispersed drugs in certain solution or microcrystalline shape. Medication is transmitted in from gastrointestinal tract and also has a short half-life is immediately destroyed from circulatory system in the blood.^[1-2]

Criteria for the Preparation of microspheres

- Preparation of microspheres should satisfy certain criteria:
- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a

wide time scale.

- Biocompatibility with a controllable biodegradability and
- Susceptibility to chemical modification.

Types of microspheres

Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio-adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by

smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.

The different types are.

Therapeutic magnetic microspheres: Are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

Diagnostic microspheres: Can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.^[3-8]

Radioactive microspheres

Radio embolisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets trapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these condition radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres. Biodegradable polymeric microspheres Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio-adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymers and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment. Synthetic polymeric microspheres The interest of synthetic polymeric

microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantages of these kinds of microspheres are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.^[9-13]

Different methods of manufacturing of microspheres

Spray Drying Technique

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 μ m. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions this process is rapid and this leads to the formation of porous micro particles.

Solvent Evaporation Technique

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is dispersed in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix-type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.^[14-19]

Wet Inversion Technique

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyphosphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglycidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of Chitosan solution microspheres.

Hot Melt Microencapsulation

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μ m. The mixture is suspended in a non-miscible solvent

(like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. poly anhydrides. Microspheres with diameter of 1-1000 µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.^[20-22]

Polymerization techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

- Normal polymerization
- Interfacial polymerization.

Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the

formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.^[23-26]

Emulsion Solvent Evaporation Technique

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (Eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hours.

Coacervation Method

Coacervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80°C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule. Coacervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for 6 hour at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin 5 times with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hours and then in oven at 50°C for 4 hour.

Ionic Gelation Method

Alginate/chitosan particulate system for Nateglinide release was prepared using this technique. Different % (w/v) of Nateglinide was added to 2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca²⁺ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 6 hours and 24 hours for internal gellification followed by filtration for separation. The complete release was obtained at pH 7.4 but the drug did not release in acidic pH.

Preparation of Microspheres by Thermal cross-linking

Citric acid, as a cross-linking agent was added to 30 ml of an aqueous acetic acid solution of chitosan (2.5% wt/vol) maintaining a constant molar ratio between chitosan and citric acid (6.90×10⁻³ mol chitosan: 1 mol citric acid). The chitosan cross-linker solution was cooled to 0°C and then added to 25 ml of corn oil previously maintained at 0°C, with stirring for 2 minutes. This emulsion was then added to 175 ml of corn oil

maintained at 120°C, and cross linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried and sieved.^[27-28]

Polymers used in microspheres

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. These materials include the polymers of natural and synthetic origin and also modified natural substances. Synthetic polymers employed as carrier materials are methyl methacrylate, acrolein, lactide, glycolide and their copolymers, ethylene vinyl acetate copolymer, polyanhydrides, etc. The natural polymers used for the purpose are albumin, gelatin, starch, collagen and carrageenan.

Classification of polymers

Synthetic Polymers: divided into two types;

Non-biodegradable- Acrolein, Glycidyl methacrylate, Epoxy polymers, etc.

Biodegradable- Polyanhydrides, Polyalkyl cyanoacrylates Lactides and glycolides and their copolymers.

Natural materials

Obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins (albumin, gelatin, collagen)

Carbohydrate (starch, agarose, carrageenan)

Chemically modified carbohydrates [poly (acryl dextran), Poly (acryl starch)]

Ideal characteristics of Carrier

Carrier provides longer duration of action to drug molecule.

It provides stability to the drug molecule.

It provides protection to drug.

It provides water solubility.

It provides sterilizability to drug.

Applications of microspheres

Pharmaceutical applications in drug delivery system

Ophthalmic drug delivery

Polymer exhibits favourable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydrogels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery such as suspensions or ointments, ophthalmic chitosan gels containing Paclitaxel were obtained by casting method with high loading efficiencies and the chemical integrity of molecule was unaltered during preparation according to study.

Oral drug delivery

The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The

results indicated that a film composed of a 1:0.5 drug polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications.

Nasal drug delivery

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer based drug delivery systems such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, and chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of Vancomycin hydrochloride.

Gastrointestinal drug delivery

Polymer granules having internal cavities prepared by deacidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastro retentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 hours e.g., Metoclopramide and glipizide loaded chitosan microspheres.^[29-30]

Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies (Mabs) targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting at specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be used to target microspheres loaded bioactive molecules to selected sites by means of covalent coupling. The free amino groups, aldehyde groups, or hydroxyl groups on the external surface of the microspheres can be linked to the antibodies.

Microspheres in vaccine delivery

The prerequisite of a vaccine is protection against microorganism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, convenience in application and cost. The aspect of safety and minimization of side effect is a complex issue. Biodegradable delivery systems for vaccines that are given by iv route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies because they offer specific advantages including:

- Modulation of antigen release.
- Improved antigenicity.
- Stabilization of antigen.

Colonic drug delivery

Polymer has been used for the specific delivery of insulin to the colon. The chitosan capsules were coated with enteric coating (Hydroxy propyl methyl cellulose phthalate) and contained, apart from insulin, various additional absorption enhancer and enzyme inhibitor. It was found that capsules specifically disintegrated in the colonic region. It was suggested that this disintegration was due to either the lower pH in the ascending colon as compared to the terminal ileum or to the presence bacterial enzyme, which can degrade the polymer.

Per oral drug delivery

As polymer and most of its derivatives has a mucoadhesive property, a presystemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many per orally given peptide drugs, such as insulin, calcitonin, and busserelin. Unmodified chitosan has a permeation-enhancing effect for peptide drugs.

Gene delivery

Gene delivery systems include viral vectors, cationic liposomes, poly cation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used *in-vivo* they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications.^[31-32]

Compression evaluations

Micromeritic Studies

The prepared microspheres are characterized by their micromeritic properties such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose.

Determination of angle of repose

Angle of repose is an indication of the frictional forces excited between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontal plane

$$\tan \theta = h/r$$

Where, θ = the angle of repose

h = height of the heap of the powder r = radius of the heap of the powder

Table 1: Angle of repose.

Sl. No	Angle of Repose (θ)	Type of Flow
1.	< 20	Excellent
2.	20-30	Good
3.	30-40	Passable
4.	>40	Very poor

Method

Weighed quantities of powder (mix blend) were poured through the funnel from the fixed height onto the graph paper. The height of the heap was measured. The circumference of the heap was marked by pencil. The area of the circle formed was calculated on the basis of large squares and small squares present inside the circle and angle of repose was then calculated on the parameter "r" which was found out from the area of circle.

Determination of Bulk Density and Tapped Density

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the Initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following formulae:

$$\text{Bulk density} = W / V_O$$

$$\text{Tapped density} = W / V_F$$

Where, W = weight of the granules,

V_O = initial volume of the granules, V_F = final volume of the granules.

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \text{Tapped density} / \text{Bulk density}$$

Table 2: Hausner's ratio.

Sl. No	Hausner's ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive flowing

Compressibility index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$\text{CI} = (\text{Tapped Density} - \text{Bulk Density}) \times 100 / \text{Tapped Density}$$

Particle Size Determination: The particle size of the microspheres was determined by using optical microscopy method. Approximately 100 microspheres were counted for particle size using a calibrated optical microscope.

Morphological Study using SEM

The morphological study was carried out by Scanning Electron Microscope (SEM). Microspheres were scanned and examined under Electron Microscope connected with Fine coat, JEOL JFC-1100E Ion sputter. The sample was loaded on copper sample holder and sputter coated with carbon followed by Gold.

Percentage Yield

The prepared microspheres of all batches were accurately weighed. The measured weight of prepared microspheres was divided by the total amount of all the excipients and

drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres.

Drug Entrapment

Microspheres equivalent to 40 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100 mL volumetric flask and the volume was made up using 0.1N HCl (pH-1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically at 258 nm against appropriate blank.

Stability Studies

Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity.

Table 3: Drug substances intended for normal storage.

Study	Storage conditions	Minimum period of time
Long term	25°C ±2 °C/60% RH±5% RH	12 Months
Intermediate Accelerated	30 °C±2 °C/65% RH±5% RH	6 Months
	30 °C±2 °C/65% RH±5% RH	6 Months
	40 °C±2 °C/65% RH±5% RH	6 Months

Drug profile of Benazepril hydrochloride

Chemical Name: 3-[[1-(ethoxy-carbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-1-acetic acid monohydrochloride.

IUPAC Name: Benazepril

Molecular Weight: 460.96 g/mole

Molecular Formula: C₂₄H₂₈N₂O₅ •HCl

Description

Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazeprilat, the active metabolite of benazepril, is a non-sulphydryl angiotensin-converting enzyme inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Dosage form: Benazepril is supplied as tablets containing 5 mg, 10 mg, 20 mg, and 40 mg for oral administration.

Mechanism of Action

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Pharmacokinetics

Following oral administration of Lotensin, peak plasma concentrations of benazepril are reached within 0.5-1.0 hours. The extent of absorption is at least 37% as determined by urinary recovery and is not significantly

influenced by the presence of food in the GI tract. Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat. Peak plasma concentrations of benazeprilat are reached 1-2 hours after drug intake in the fasting state and 2-4 hours after drug intake in the non fasting state. The serum protein binding of benazepril is about 96.7% and that of benazeprilat about 95.3%, as measured by equilibrium dialysis; on the basis of in vitro studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, or concentration (over the concentration range of 0.24-23.6 µmol/L).

Benazepril is almost completely metabolized to benazeprilat, which has much greater ACE inhibitory activity than benazepril, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of Lotensin can be recovered in the urine as unchanged benazepril, while about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide.

Pharmacodynamics

Single and multiple doses of 10 mg or more of Lotensin cause inhibition of plasma ACE activity by at least 80%-90% for at least 24 hours after dosing. Pressor responses to exogenous angiotensin I were inhibited by 60%-90% (up to 4 hours post-dose) at the 10-mg dose.

Dosage and administration

In Hypertensive adults

The recommended initial dose for patients not receiving a diuretic is 10 mg once a day. The usual maintenance

dosage range is 20-40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited.

Pediatrics

In children, doses of Lotensin between 0.1 and 0.6 mg/kg once daily have been studied, and doses greater than 0.1 mg/kg were shown to reduce blood pressure. Based on this, the recommended starting dose of Lotensin is 0.2 mg/kg once per day as monotherapy. Doses above 0.6 mg/kg (or in excess of 40 mg daily) have not been studied in pediatric patients³³.

For Hypertensive Patients with Renal Impairment:

For patients with a creatinine clearance <30 mL/min/1.73 m (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg Lotensin once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg.

Overdosage: Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension.^[34-38]

Side effects: The most common side effects patients experience are a headache or a chronic cough. The chronic cough develops in about 20% of patients treated, and those patients that experience it find it develops after a few months of use. Anaphylaxis, angioedema, and elevation of potassium levels are more serious side effects that can also occur.

Contraindications: Benazepril should be discontinued during pregnancy, as it can harm the fetus.

CONCLUSION

Microspheres are spherical and empty particles. The microspheres and microencapsulation are used synonymously. Spheres and spherical particles are also used for a rigid morphology. The microspheres are free flowing powders consist of proteins which are biodegradable in nature and ideally have a particle size less than 200 micrometer.^[39-40] The solid biodegradable microspheres incorporate a drug dissolved throughout particle matrix have the potential for the controlled release of the drug. The drug absorption in the gastrointestinal tract varies with presence of several factors and prolongs the gastric retention of the dosage form that extends from the time for drug absorption. The microspheres prepared by ionotropic gelation technique promises to be potential approach for gastric retention. The proper selection of drug and following designed protocol procedures would show better drug release action at the targeted site in the body.

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