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Review Article

A Review on Methods of Preparation of Mucoadhesive Microspheres

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Abstract
Microspheres are characteristically free flowing powders consisting of proteins or syntheticpolymers having a particle size ranging from 1-1000 µm. The range of Techniques for thepreparation of microspheres offers a Variety of opportunities to control aspects of drugadministration and enhance the therapeutic efficacy of a given drug. There are variousapproaches in delivering a therapeutic substance to the target site in a sustained controlledrelease fashion. One such approach is using microspheres as carriers for drugs also knownas microparticles.Mucoadhesion is topic of current interest in the design of drug delivery system.Mucoadhesive microsphere exhibit a prolonged residence time at the site of application and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved or better therapeutic performance of drug. Mucoadhesive drug delivery systems promises several advantages that arise from localization at a given target site, prolonged residence time at the site of drug absorption and an intensified contact with the mucosa increasing the drug concentration gradient. Hence, uptake and consequently bioavailability of the drug is increased and frequency of dosing reduced with the result that patient compliance is improved. In recent years such Mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal for either systemic or local effects. The principles underlying the development of Mucoadhesive microsphere and research work carried out on these systems are reviewed here.

Keywords: Mucoadhesive microsphere, Methods of preparation of mucoadhesive microspheres,
Controlled drug delivery

Introduction
Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles. A primary object of using mucoadhesive formulations orally would achieve a substantial increase in the length of stay of the drug in GI tract Stability problem in the intestinal fluids can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved. Mucoadhesive microsphere carrier systems are made from the biodegradable polymers in sustained drug delivery.

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Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems[2,3]. Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using assorted polymers. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane[4]. This can be achieved by coupling bio adhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres haveadvantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site[5,6].

To overcome the relativity short GI time and improve localization for oral controlled or sustained release drug delivery systems. The polymers which adhere to the mucin epithelial surface are effective and lead to significant improvement in oral drug delivery based on this three broad categories. Polymer that becomes sticky when placed in water and owes their bio adhesion to sickness. Polymers that adhere through non- specific, non-covalentinteraction are primarily electrostatic in nature. Polymer that binds to specific receptor site on the cellvalerate[7]. Microspheres of biodegradable and non-biodegradable polymers have been investigated for sustained release. An important requirement of polymers is that degradation products should be non toxic because such products eventually enter systemic circulation or result in tissue deposition.The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body.

However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastro-intestinal tract. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity. Microspheres are the carrier linked drug delivery system in which particle size is ranges from (1-1000 µm) range in diameter having a core of drug and entirely outer layers of polymers as coating material[8]. However, the success of these microspheres is limited due to their short

residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site[9,10].

Mucoadhesion / Bio adhesion

Mucoadhesive drug delivery system are the systems which utilizes the property of bio adhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time. The term mucoadhesion was coined for the adhesion of the polymers with the surface of the mucosal layer[11]. Bioadhesions are a phenomenon in which two materials at least one of which is biological and are held together by means of interfacial forces [12]. In biological systems, bio adhesion can be classified into 3 types:

1. Adhesion between two biological phases, for example, platelet aggregation and wound healing.

2. Adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio film formation on prosthetic devices and inserts.

3. Adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

For drug delivery purposes, the term bio adhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion / mucoadhesion as the interaction between a mucin surface and asynthetic or natural polymer. [13] In bio adhesion, the polymer is attached to the biological membrane.

MECHANISM OF MUCOADHESION

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. A General Mechanism of Mucoadhesion Drug Delivery system is show in Figure 1. Penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane (interpenetration, figure 2 shows the mechanism of mucoadhesion[14]:

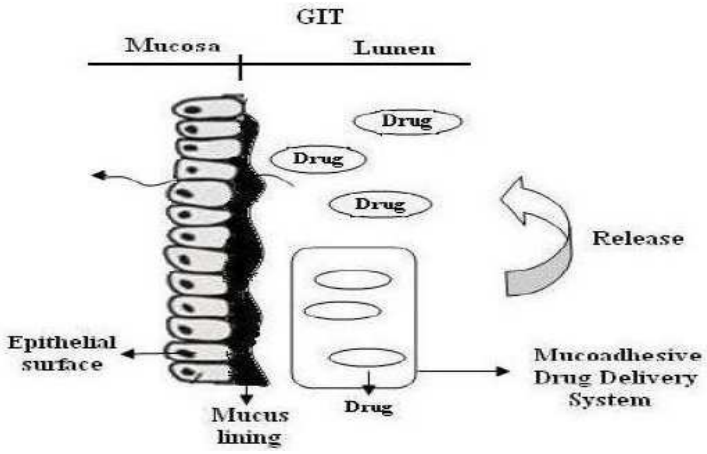


Figure 1.Mechanism of Mucoadhesion.

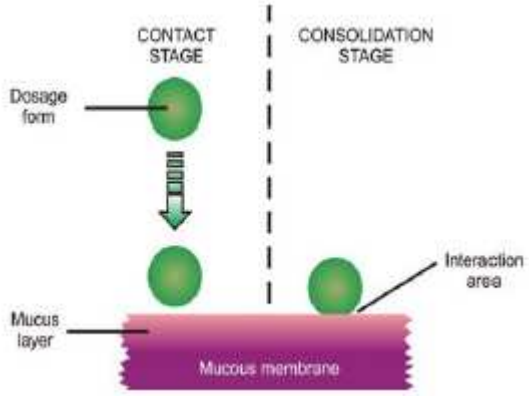


Figure 2: Mechanism of Mucoadhesion.

Advantages of mucoadhesive microspheres drug delivery system[15,16]

(1) As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.

(2) The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract.

(3) Increased residence time combined with controlled API release may lead to lower administration frequency.

(4) Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability.

(5) Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.

(6) Better patient compliance and convenience due to less frequent drug administration.

(7) Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption.

(8) Prolonged and sustained release of drug.
(9) Maintenance of therapeutic plasma drug concentration.
(10) Better processability (improving solubility, dispersibility, flowability).
(11) Increased safety margin of high potency drugs due to better control of plasma levels.
(12) Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.

METHODS OF PREPARATION OF MUCOADHESIVE MICROSPHERES:

Mucoadhesive microspheres can be prepared using any of the following techniques.

Air suspension:

This process consists of the dispersing of solid particles of core materials in a supporting air stream and the spray coating of the air suspended particles.

Coacervation:

This process consists of mainly three steps carried out under continuous agitation. Formulation of three immiscible chemical phases, deposition of coating, rigidization of the coating. Three immiscible phases include a liquid manufacturing vehicle, a core material phase and a coating material phase. The core material is dispersed in a solution of the polymer, the solvent for the polymer being the liquid manufacturing vehicle phase. Microspheres can be prepared by changing the temperature of the polymer solution, By adding salt, Using a non solvent, and also by the addition of an incompatible polymer to the polymer solution and polymer-polymer interaction.[17]

Pan coating:

In this process, the coating material is applied as solution or as atomized spray to the desired solid core material in the coating pan. Warm air is passed over the coated materials to remove the coating solvent.

Solvent evaporation:

This process is 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 disperse 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 solvent evaporation technique is shown in Figure 3. 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. [18]

Spray Drying

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 1-100µm . 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 shown in Figure 4.

Multiple emulsion polymerization technique:

Multiple emulsion method involves formation of (o/w) Primary emulsion (non aqueous drug solution in polymer solution) and then addition of primary emulsion to external oily phase to form o/w/o emulsion followed by either addition of cross linking agent (glutaraldehyde) and evaporation of organic solvent. This method of preparation is ideal for incorporating poorly aqueous soluble drug, thus enhancing its bioavailability. The microspheres prepared by multiple emulsion technique make the poorly aqueous soluble drug such as ketorolactromethamine more bioavailable.[19,20]

Solvent extraction

Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such asisopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for then microspheres. One variation of the process involve direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

Wet Inversion Technique

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyposphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglysidyl ether. Microspheres were then washed and freeze dried.

Changing the pH of the coagulation medium could modify the pore structure of CS microspheres.[21,22]

Figure 3 Steps involved in solvent evaporation method

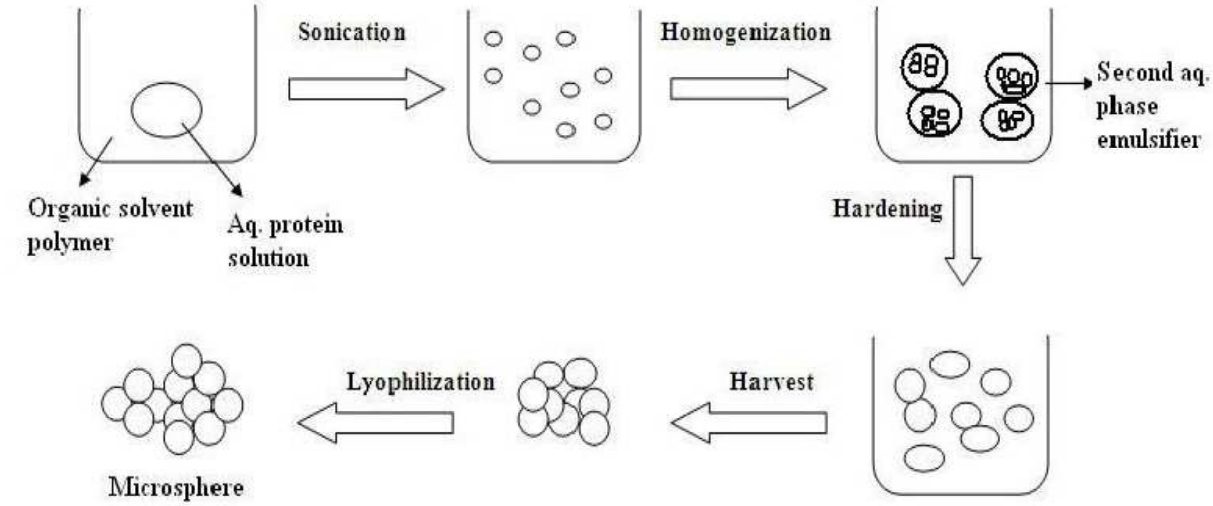
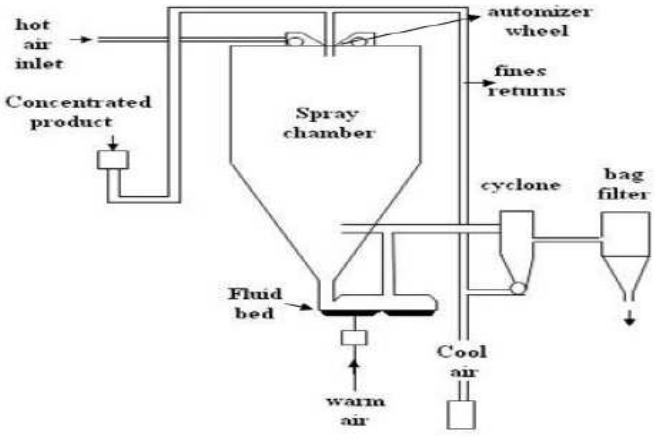


Figure 4. Spray drying method for preparation of microsphere Solven



Complex Coacervation

CS microparticles can also prepare by complex co acervation, Sodium alginate, sodium CMC and sodium polyacrylic acid can be used for complex coacervation with CS to form microspheres. These microparticles are formed by interionic interaction between oppositely charged polymers solutions and KCl& CaCl2 solutions. The obtained capsules were hardened in the counter ion solution before washing and drying.

Hot Melt Microencapsulation

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less then 50 µm. 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.* polyanhydrides. 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. [23]

Figure 5: Microsphere preparation by multiple emulsion method.

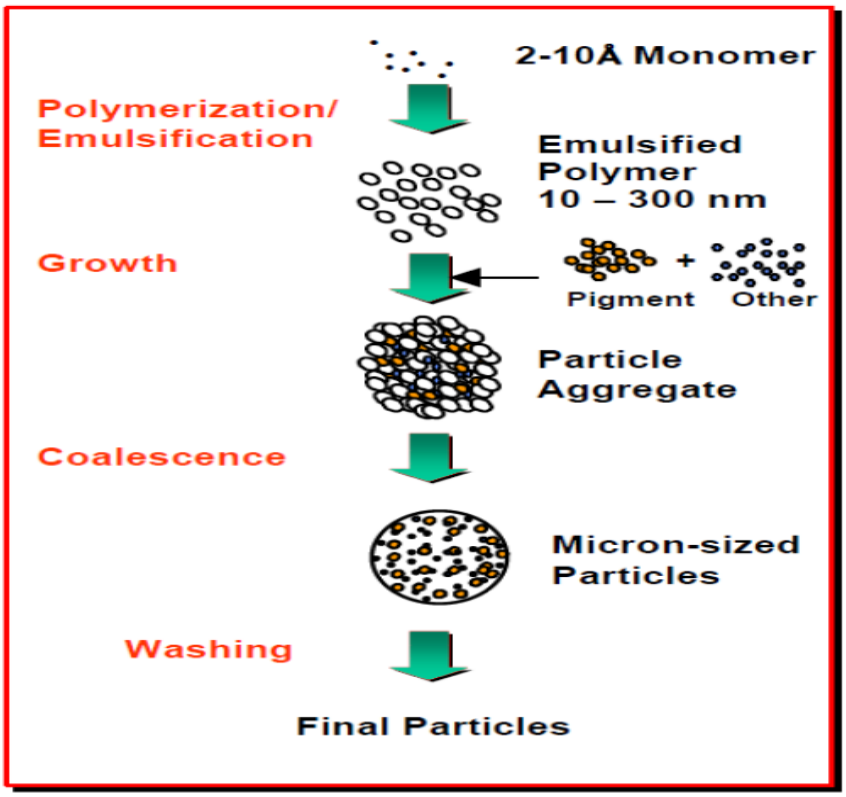
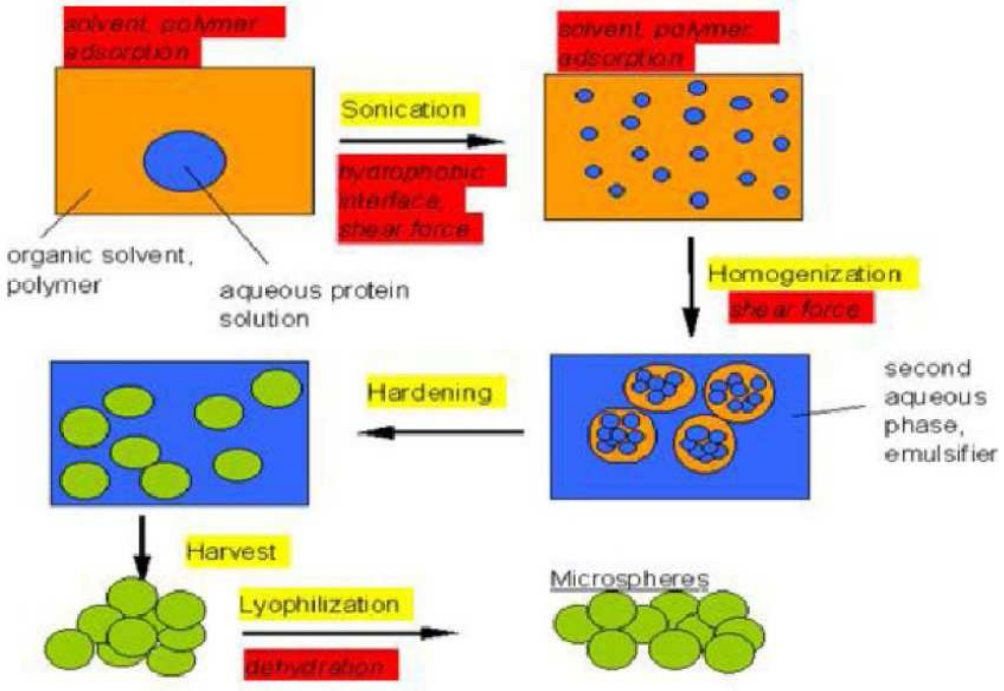


Fig. 6: Solvent Extraction Method



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 molchitosan: 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.

Preparation of Microspheres by Glutaraldehyde crosslinking
A 2.5% (wt/vol) chitosan solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous phase (125 mL) consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 containing 0.5% (wt/vol) Span 85 to form a water in oil (w/o) emulsion. Stirring was continued at 2000 rpm using a 3- blade propeller stirrer (RemiEquipments, Mumbai, India). A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% vol/vol) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60°C-80°C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were then finally dried in a vacuum desiccators.

Preparation of microspheres by Tripolyphosphate
Chitosan solution of 2.5% wt/vol concentration was prepared. Microspheres were formed by dropping the bubble-free dispersion of chitosan through a disposable syringe (10 mL) onto a gently agitated (magnetic stirrer) 5% or 10% wt/vol TPP solution. Chitosan microspheres were separated after 2 hours by filtration and rinsed with distilled water, then they were air dried.[24,25]

Preparation of Microspheres by Emulsification and Ionotropic gelation by NaOH
Dispersed phase consisting of 40 mL of 2% vol/vol aqueous acetic acid containing 2.5% wt/vol chitosan was added to the continuous phase consisting of hexane (250 mL) and Span 85 (0.5% wt/vol) to form a w/o emulsion. After 20 minutes of mechanical stirring, 15 mL of 1N sodium hydroxide solution was added at the rate of 5 mL per min at 15-minute intervals. Stirring speed of 2200 rpm was continued for 2.5 hours. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air dried. [26,27]

Preparation of Ethylcellulose Microspheres
A solution of Ethylcellulose in acetone was added to liquid paraffin containing emulgent (Span 85) while stirring at a speed of 1500 rpm. The emulsion was stirred for 5 to 6 hours at 25°C to 30°C. Subsequently, a suit able amount of petroleum ether was added to the dispersion, filtered, and dried at ambient temperature. The resultant microspheres were washed with water followed by petroleum ether to remove traces of liquid paraffin. The microspheres were desiccated under vacuum. [28]

Conclusion

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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