MICROSPHERE: A NOVEL TOOL FOR CONTROLLED DRUG DELIVERY

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ABSTRACT

The aim of this review article is to highlight recent advancements of Microsphere as a technique of drug delivery to a specific target site of action. Microsphere as transporters of drug are developed to deliver therapeutic agents to the target site of action in a sustained or controlled release manner. Microsphere are also referred to as coated granules, pellets or seeds, microsperules, and spansules and are mainly used in medicine as drug carriers. Many aspects of Microsphere and their recent advancements including the need for natural or biodegradable polymers to produce maximum therapeutic effect with minimum toxicity are reviewed. Diverse microsphere applications are used because of its controlled release rate of encapsulated drug over a period of hours to months. Microencapsulation provides an active protection of the encapsulated drug against degradation before it reaches the target site of action. Pre-programmed drug release profiles can be generated to match the therapeutic needs of the patient. Applications include targeting using microparticulate carriers, vaccine delivery, monoclonal antibody mediated Microsphere targeting, chemoembolization, imaging, topical porous Microsphere, surface modified Microsphere, vast advancements in biotechnology, gene delivery, intratumoral and local drug delivery, intramuscular, intravenous, intra-arterial, oral, nasal, buccal, transdermal, colonic and gastrointestinal drug delivery. Microsphere or micro-particles manufactured by an appropriately selected method can be evaluated qualitatively and quantitatively by Scanning electron microscopy (SEM), X-Ray diffraction (XRD), Differential Scanning Calorimetry
Gupta et al. World Journal of Pharmacy and Pharmaceutical Sciences

(DSC), Fourier Transform Infrared Spectroscopy (FT-IR), Ultraviolet-visible (UV) Spectroscopy, In vitro and In vivo drug release studies.

KEYWORDS: Microsphere, Microencapsulation, Drug delivery system, Controlled drug delivery, Target site, Therapeutic efficacy.

INTRODUCTION
The first microencapsulation procedure was published by Bungenburg de Jong and Kaas in 1931, which dealt with the preparation of gelatin Microsphere by the coacervation process.[1] Other methods of microsphere preparation are single emulsion, multiple emulsion, polymerization, phase separation or coacervation, spray drying and solvent extraction method. Microsphere are generally free flowing powders consisting of one or more drug(s) entrapped in a coating of natural or synthetic polymer(s) as shown in Figure 1. The core may also be denoted as the nucleus and the coating as the wall or shell. Microsphere used in medicine are predominantly spherical, small particles with a particle size ranging from 1-1000 µm.[2] Microparticles are irregularly shaped Microsphere. Products less than 1µm are nanospheres. Microencapsulation is an important strategy used in the application of medicine, to deliver required therapeutic agents to the specific target site of action in a sustained drug release profile. Advancement in pharmaceutics, genomics, biotechnology and combinational chemistry will progressively lead to an extensive range of new, potent, highly specific and effective therapeutic outcome for patients. Drugs with very short biological half-lives require frequent dosing to maintain an adequate therapeutic level. This implies that microencapsulation will be a desirable formulation for such drugs. Patient compliance and drug stability will also be enhanced by the medium of Microsphere. The various methods (as stated in the abstract) used in the formulation of Microsphere will be outlined in this article. Polymers used for microencapsulation can be natural or synthetic. Natural polymers include proteins, carbohydrates or chemically modified carbohydrates. Synthetic polymers can be biodegradable or non-biodegradable. Biodegradable polymer Microsphere are most commonly used because of its numerous advantages. Microsphere encapsulate many types of drugs and are generally biocompatible with high bioavailability. Glass, polymer and ceramic Microsphere are available commercially.[2] The pharmaceutical characteristics and consideration of Microsphere are outlined in table 1 below. The tissue distribution, cellular interaction, metabolism and clearance kinetics of the drug are highly dependent on the nature of the drug carrier. Optimization of process parameters used in the manufacturing of
Microsphere as drug delivery devices will aim to deliver therapeutic agent(s) in the required quantity, at the appropriate time intervals and to the appropriate location in the body or administered directly at the target site of action (localized) to increase drug efficacy, patient compliance with minimal adverse effects. Microsphere can therefore alter the in vivo mechanism of action of drug, pharmacokinetic and pharmacodynamics profile enabling controlled drug release.

![Diagram of Microsphere Structure](image)

**Fig1: Structure of spherically shaped microsphere**

<table>
<thead>
<tr>
<th>Property</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Diameter, Uniformity/Distribution</td>
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<tr>
<td>Composition</td>
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<td>Surface Chemistry</td>
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</tr>
<tr>
<td>Special Properties</td>
<td>Visible dyes,fluophore, Super-Paramagnetic</td>
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**Table 1: Properties of Microspheres**

**MATERIALS**

Materials required for microsphere formulations include drug, polymer, solvent, plasticizer, surfactant, channeling agent, waxy sealant, crosslinking agent, anti-tack agent, dispersed solid(s) including colorants, opaquant-extenders, and fillers. The nucleus of Microsphere may contain one or more drug either alone or in combination with appropriate additives to form a liquid or solid phase. Solid cores are more frequently used than liquid cores. The solvent properties of such liquids will critically influence the rate of drug release and the selection of coating materials, which should not be significantly affected by the vehicle over the shelf life of the product.[3] For drugs having high hydrophilicity and known bioavailability, problems associated with low rates of dissolution, decrease in particle size of suspended drugs may be important in enhancing in vivo absorption. Smaller Microsphere have faster rate of drug release compared to larger Microsphere, because of increased surface area per unit volume or
weight of core material. The density of the core is important in controlling the transit time in the GI tract.

**Polymers** are classified into three types.

1. **Synthetic** polymers are biodegradable or non-biodegradable. Biodegradable polymers include lactides, glycolides and their co-polymer, poly-anhydrides, poly alkylcyano-acrylates. Non-biodegradable Microsphere include polymethyl-methacrylate (PMMA) and epoxy polymers. Synthetic polymers are frequently used in parenteral administration. For non-biodegradable polymers, the drug carrier remaining in the body after the drug is completely released will lead to a greater risk of carrier toxicity. This implies that biodegradable drug carriers are more suitable for parenteral administration, since it degrade in the body to non-toxic substances.

2. **Natural** polymers include proteins, carbohydrates and chemically modified carbohydrates. Proteins include albumin, gelatin and collagen. Carbohydrates used as polymers included agarose, carrageenan or chitosan.

3. **Semisynthetic** polymers are chemically modified carbohydrates include poly-dextran and poly-starch.

**Solvents**

Polymers are usually applied to cores forming the nucleus of Microsphere by using a suitable organic or inorganic solvent system. This dissolves the polymer and disrupts the cohesive force between the polymer molecules. The more crystalline a polymer is, the greater will be its cohesive force and consequently it will be more difficult to dissolve in a solvent system.

**DRUG LOADING AND DRUG RELEASE KINETICS**

**Drug Loading**

Active components are loaded in the core of Microsphere during the initial preparation and by incubation at approximately 28°C. During incubation, the drug if soluble in the solvent or water will be dried and can be loaded over the formed Microsphere. This implies that washing the formed microsphere is an important step to remove any solvent from the surface of formed Microsphere. Solvents selected should be non-toxic and highly volatile. Drugs that are soluble in water can remain on the surface of the Microsphere even after washing with distilled water. The active components (drug) can be loaded by means of physical entrapment, chemical linkage or surface adsorption. Entrapment largely depends on the method of preparation and the nature of the drug or polymer. Maximum loading can be
achieved by incorporating the drug during the time of preparation, presence of additives (e.g., cross-linking agent, surfactant, stabilizers, etc.) heat of polymerization and agitation intensity.\[4\]

**Drug Release Kinetics**

Release of the active constituent is an important consideration for Microsphere. Drug release profile depends on the nature and physicochemical properties of both drug and polymer used in microsphere preparation. The release of drug from both biodegradable and non-biodegradable Microsphere is influenced by the structure or micromorphology and properties of drug carrier or polymer. Drugs can be released through the wall of the Microsphere either by diffusion, erosion or osmosis.

1. **Diffusion**

Water diffuses into the Microsphere when it is in contact with aqueous fluids in the gastrointestinal tract. This results in drug dissolution and the drug then diffuses across the release coat (polymer) to the exterior.\[5\]

2. **Erosion**

Some coating material can erode gradually with time, thereby releasing the drug contained within the particle. In polymer erosion, the loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with changes in the microstructure of the carrier as water penetrates within it, leading to the plasticization of the matrix.\[5\]

3. **Osmosis**

In allowing water to enter into the microsphere under the appropriate conditions, osmotic pressure can build up within the interior of the particle. The drug is forced out of the particle into the exterior as water diffuses into the core through the polymeric coating material, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by three factors: the macromolecule or polymer ratio, the particle size of the dispersed macromolecule, and the particle size of the Microsphere.\[5\]

**APPLICATIONS IN DRUG DELIVERY SYSTEM**

Pharmaceutical applications in drug delivery system include

1. Ophthalmic drug delivery
2. Gene delivery
3. Intratumoral and local drug delivery
4. Oral drug delivery
5. Nasal drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Vaginal drug delivery
9. Transdermal drug delivery
10. Colonic drug delivery
11. Multiparticulate drug delivery system
12. Conversion of oil and liquid to solid for ease of handling
13. Taste and odor masking
14. To delay volatilization
15. Safe handling of toxic substances

Other microencapsulation applications include adhesives, pharmaceuticals, cosmetics, nutraceuticals, sealants, industrial chemicals, food additives, flavors and essence, pesticides and herbicides and agrochemicals. Table 1 is a summary literature review of formed Microsphere and its applications. Core materials are also microencapsulated in a controlled release formulation for the following reasons.

1. To mask the bitter taste of drugs like Paracetamol and Nitrofurantoin etc.
2. To reduce gastrointestinal irritation
3. Conversion of liquid to pseudo-solid for easy handling and storage
4. To reduce odor and volatility
5. To protect core materials against atmospheric effects including UV, heat, oxidation, acids and bases
6. Improved shelf life by preventing degradative reactions (dehydration and oxidation)
7. For the enhancement of visual and marketing aspect of drug formulation

**ENCAPSULATION EFFICIENCY**

The encapsulation efficiency of microparticles or microsphere depends on various factors including drug concentration, polymer concentration, solubility of polymer in solvent, rate of solvent removal and solubility of organic solvent in water.\(^6\)

**MICROCAPSULES MORPHOLOGY**

The Microsphere morphology is determined by the disposition of the shell and the core material or nucleus.
a. **Mononuclear** microcapsules contain a shell around the nucleus.

b. **Polynuclear** capsules have more than one cores enclosed within the shell.

c. **Matrix encapsulation** is when the core material (nucleus) is distributed homogenously into the shell material.

Microcapsules can also be mononuclear with multiple shells or they may form clusters of microcapsules as shown in figure 2.

![Mononuclear, Polynuclear, Matrix](image)

**Fig 2: Morphology of Microcapsules**

**Advantages of Microsphere**

1. Microsphere facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue.

2. They provide protection of unstable drug before and after administration, prior to the availability at the site of action.

3. They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug. They enable controlled release of the drug. Examples include narcotics, antagonist and steroid hormones.

![Scanning Electron Microscopic Image of Imuran Microsphere](image)

**Fig. 3: Scanning Electron Microscopic Image of Imuran Microsphere**
METHODS FOR MICROSPHERE PREPARATION

Emulsion Polymerization
In this technique, the monomer is added drop wise while stirring the aqueous polymerization medium that consists of the material to be encapsulated (core material) and an appropriate emulsifier. When polymerization begins, the originally produced polymer molecules precipitate in the aqueous medium to form primary nuclei. As the polymerization progresses, the nuclei grow steadily and instantaneously entrap the core material to produce the microparticle. Lipophilic materials either insoluble or partially soluble in water are more appropriate for encapsulation using this method.[7]

Interfacial Polymerization
This technique involves the poly-condensation or condensation polymerization of two complementary monomers at the interface of a two-phase system. The two-phase system is mixed under carefully controlled conditions to form small droplets of one phase (dispersed phase) in another phase (continuous phase / suspension medium). The material to be encapsulated must be selected so that it can be present (dissolved or dispersed) in the droplets. It is also necessary to use a minute quantity of an appropriate stabilizer to prevent droplet coalescence or particle coagulation during the poly-condensation process and capsule formation. Interfacial poly-condensation can be utilized to produce both monocore and matrix type microcapsules, depending on the solubility of the poly-condensate in the droplet phase. If the polymer is soluble in the droplet phase, then matrix-type microcapsules are formed. On the other hand, if the polymer is not soluble, it precipitates around the droplets and leads to the formation of mono core-type microcapsules. The formulation of Microsphere by interfacial poly-condensation is applicable when there is large number of polymers.[8]

Supercritical Fluid Technique
Supercritical fluids are highly compressed gases that possess several advantageous properties of both liquid and gases. Widely used gases are supercritical carbon dioxide, alkanes and nitrous oxide. These gases are readily available, highly pure and cost effective. It has found applications in encapsulating active ingredients by polymers.[9]

In Situ Polymerization
In situ polymerization is similar to interfacial polymerization because the capsule shell formation occurs when polymerization monomers are added to the encapsulation reactor. In this procedure, reactive agents are not added to the nucleus or core material. Formation of an
interface between the disperse core material and the continuous phase result in polymerization. Primarily, a low molecular weight pre-polymer is formed. As time increases, the pre-polymer grow in size, depositing material on the surface of the dispersed core by generating a solid capsule shell. Water-immiscible liquid and polymer dispersion at acidic pH of urea with formaldehyde in aqueous media are used to form the capsule shell in in situ polymerization.\[10\] Wang et al. prepared carboxyl-functionalized magnetic Microsphere by in situ polymerization of styrene and methacrylic acid.\[11\]

**Spray Drying and Spray Congealing**

Spray drying or spray congealing techniques is established by drying the mist of the polymer and the drug in air. Spray drying is the removal of the solvent and spray congealing involves the cooling of the solution. Initially, the polymer is dissolved in an inappropriate organic volatile solvent such as dichloromethane or acetone. The solid drug is then dispersed in the polymer solution under high-speed homogenization. This is followed by atomization in a stream of hot air, which leads to the formation of small droplets in a fine mist from which the solvent evaporates instantaneously, resulting in the formation of Microsphere. Microsphere are then separated from hot air by means of the cyclone separator, while the traces of solvent are removed by vacuum drying. The water-soluble natural polymers, such as starch, gum arabic, chitosan, gellan, and sodium alginate, are frequently used as the wall forming materials \[10\]. The ketoprofen loaded Microsphere with a polymeric blend was prepared by the spray drying technique. Solidification was accomplished by rapid evaporation of the solvent in which the coating material was solubilized. Organic solutions of two polymers, cellulose acetate butyrate and poly (epsilon) caprolactone, in different weight ratios and ketoprofen were prepared and sprayed in different experimental conditions, producing drug-loaded Microsphere.\[11\]

**Single Emulsion Technique**

Microsphere of natural polymers are prepared using the single emulsion technique. The natural polymers are dissolved in aqueous medium and the subsequent is then dispersed in a non-aqueous medium such as oil. This is followed by, cross-linking of the dispersed globules, which is carried out by means of heat or chemical cross-linkers. The chemical cross-linking agents used include glutaraldehyde, formaldehyde, di-acid chloride, etc. The cross-linking process forms small, discrete particles, which are then subjected to centrifugation, washing, and separation.\[12\] Bayomi investigated emulsion cross-linking technique using mineral or
vegetable oil as the oil phase and a drug polymer solution as the aqueous phase in a simple and widely used method for the preparation of NSAIDs. Cross-linking can be achieved by chemical agents or heat. Viscosity of the oil phase, concentration of the cross-linking agent, duration of cross-linking, etc., are the different parameters that affect the release rate and entrapment efficiency. Gelatin Microsphere of ketorolac tromethamine for intranasal systemic delivery were developed using the emulsification cross-linking technique. The drug was dispersed in the polymer gelatin and formulated into a water/oil emulsion with liquid paraffin, using glutaraldehyde as a cross-linking agent.[13]

**Double Emulsion Method**

The double-emulsion method used for the preparation of Microsphere involves the formation of double or multiple emulsions of water and oil. Natural and synthetic polymers are used in this method. The aqueous drug solution is dispersed in a lipophilic organic continuous phase. The continuous phase generally consists of the polymer solution that eventually encapsulates the drug contained in the dispersed aqueous phase. The primary emulsion is then subjected to homogenization or sonication before addition to the aqueous solution, resulting in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction.[14] One formulation by this method was a controlled-release drug-delivery system for indomethacin.[15]

**Emulsion Cross-Linking Technique**

Microsphere formation by this procedure involves scattering / dispersion of an aqueous solution of the polymer containing core material in an immiscible organic solvent (suspension/dispersion medium) in the form of small droplets. The suspension medium contains a suitable stabilizer to maintain the individuality of the droplet/microcapsules. The droplets are subsequently hardened by covalent cross-linking and are directly converted to the corresponding microparticles. The cross-linking process is accomplished either thermally or by the use of a cross-linking agent (e.g., formaldehyde, terephthaloyl chloride, etc. Emulsion cross-linking is a useful method that can be adapted for microencapsulation of soluble, insoluble, liquid, or solid materials, and for the production of both micro- and Nano capsules.[16] Kumbar et al. encapsulated diclofenac sodium into cross-linked chitosan microspheres and investigated the effect of the cross-linking agent. Microsphere of chitosan cross-linked with three different cross-linking agents (glutaraldehyde, sulfuric acid, and heat treatment) were prepared to encapsulate diclofenac sodium.[17]
**Solvent Evaporation/Extraction**

In this process, the polymer is dissolved in a volatile organic water-immiscible solvent such as dichloromethane or chloroform which allows the core material to be dissolved or dispersed. The resulting solution is then added drop-wise to a stirring aqueous solution with an inappropriate stabilizer such as polyvinyl alcohol to produce small polymer droplets enclosing encapsulated material. Hardening of the formed Microsphere can be achieved by solvent extraction or evaporation. Solvent evaporation produces microparticles with lower porosities than microparticles formed by solvent extraction.[12] Palmieri et al. produced ketoprofen microparticles using the solvent evaporation method at 15°C in order to avoid the formation of semisolid particles.[18, 19]

**Coacervation Phase Separation**

This method is widely used for the gelatin and gelatin-acacia, cellulose derivatives and synthetic polymer based microsphere formulation. This type of preparation is separated into simple and complex coacervation processes. Simple coacervation incorporates a single polymer and complex coacervation involves two oppositely charged polymeric materials such as gelatin and acacia, which are both soluble in aqueous media. Vanessa prepared chitosan Microsphere using the simple coacervation method and cross-linking using epichlorohydrin or glutaraldehyde for the controlled release of diclofenac sodium.[20-22]

**Fluidized Bed Coating**

This method is used to encapsulate pharmaceuticals consisting of solid core materials including liquids absorbed into porous solids. Solid particles are suspended by a jet of air and then covered by a spray of liquid coating material. The formed microparticles are then transferred to a place where the coating is solidified by cooling or solvent vaporization. The process of suspending, spraying, and cooling is repeated until the capsule walls are of the desired thickness.[23,24] Silva researched the dissolution process of sodium diclofenac granules coated with a polymeric suspension of EUDRAGIT L-30D-55 by fluidized bed.[25]

**Melt Solidification**

Biodegradable microparticles are also produced by the solidification of molten polymer droplets or by polymer precipitation. A dispersion of the drug in molten polymer is stirred in silicone oil to produce small droplets of the polymer drug mixture. This mixture is then cooled and the resulting solidified microcapsules are separated from the oil. Paradkar et al. developed the melt-solidification technique to obtain sustained-release waxy beads of...
flurbiprofen.\cite{26}

**Polymer Precipitation**

In this process, an aqueous solution of polymer containing the selected drug is added drop wise into a stirred solution, which acts as the precipitating medium. In this method, the polymer droplets precipitate instantaneously and are thus transformed into the drug-loaded microparticles.\cite{27} Swati sashmal designed and evaluated flurbiprofen nanoparticles with a suitable size range. This study depended upon the feasibility and suitability of the aqueous polymeric drug-delivery system, using a statistical design to develop a clinically useful nanoparticle system with targeting potential.\cite{28}

**Centrifugal Extrusion Process**

This method involves liquids that are encapsulated using a rotating head containing concentric nozzles. In this process a jet of core liquid is surrounded by a sheath of wall solution or melt. As the jet moves through the air, it breaks into droplets of core, each coated with the wall solution. While the droplets are in flight, a molten wall may be hardened or a solvent may be evaporated from the wall solution. A high number of microparticles can be produced per nozzle per hour per head.\cite{29} Varshosaz developed piroxicam enteric-coated pellets using nonpareil seeds in the powder-layering technique to minimize the drug’s gastrointestinal adverse effects.\cite{29}

**Vibrational Nozzle Process**

Core-shell encapsulation or micro-granulation (matrix-encapsulation) can be done using a laminar flow through a nozzle and an additional vibration of the nozzle or the liquid. Liquids with limited viscosities (0–10,000 mPa) have been effective in using this method and can be in the form of solutions, emulsions, suspensions, melts, etc. Solidification can be done according to the gelation system used, with an internal gelation (e.g., sol-gel processing, melt) or an external (additional binder system, e.g. in a slurry). The process works very well for generating droplets between applications, as the size of the droplets depends on the size of orifice and the vibration speed of the nozzle.\cite{30,31}

**Ionotropic Gelation Technique**

This technique is defined as a physicochemical process of micro-droplet hardening by chelation of polyelectrolyte with polyvalent ions. Such a chelation results in cross-linking the polyelectrolyte molecules while forming a shell in the form of a polymeric gel. The most
widely used system is based on gelation of aqueous sodium alginate, gellan, or carrageenan solutions by the addition of divalent cations such as calcium chloride, barium chloride, or potassium chloride, which induces the cross-linking of the polymers and instantaneously forms discrete, solid micro-particles. In this method, strong, spherically shaped, narrow high-yield microparticles are formed and used as the carriers of many NSAIDs drug to minimize dose-related ad- verse effects and prolong the drug-release potential.[31,32]

CONCLUSION
Microsphere is currently providing a vast number of applications in the field of medicine and drug delivery system. Targeted drug delivery include; Microsphere in vaccine delivery, monoclonal body anti-mediated Microsphere, chemoembolization, imaging, topical porous Microsphere, surface modified Microsphere, gene delivery, intra-tumoral, oral, nasal, buccal and gastrointestinal drug delivery, transdermal, colonic and multiparticulate drug delivery system. By using various strategies, Microsphere will continue to advance as a novel drug delivery system particularly in cell sorting, diagnostics and genetic engineering. This article demonstrates that Microsphere is an effective transporter of drug and highly useful in medicine as a drug delivery system.

REFERENCES


