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Review Article

Microspheres as Drug Carriers: Applications and Innovations in Novel Drug Delivery Systems

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ABSTRACT

Microspheres are rounded, multi-particulate drug delivery systems between 1µm and 1mm that are used to control drug release. Microspheres are biodegradable polymeric microspheres based on natural or synthetic polymers. They possess merits like superior therapeutic activity, increased bioavailability, lowered toxicity, and decreased drug degradation. Microspheres permit sustained drug release, lowering the frequency of administration, and are suitable for site-specific delivery, for instance, in gastrointestinal tissue. Microspheres have various therapeutic properties such as bioadhesive, floating, radioactive, magnetic, and polymeric functionalities. Bioadhesive microspheres increase drug retention in the mucosal surfaces, while magnetic microspheres enable the delivery of drugs at a localized site through the application of an external magnetic field. The preparation methods differ depending on drug characteristics; solvent evaporation, ionic gelation, and spray drying are the most used. Spray drying is efficient for encapsulating hydrophobic drugs, while double emulsion is appropriate for hydrophilic drugs such as peptides and vaccines. Characterization techniques such as particle size analysis, surface topography, determination of drug content, and evaluation of entrapment efficiency guarantee microsphere optimization. They have uses beyond pharmaceuticals in diagnostics and industrial applications. Microspheres promise new therapeutic approaches with advancement in polymer sciences in the form of vaccines, gene therapy, and anticancer treatments. This review emphasizes the benefits, categorization, preparation, and therapeutic uses of microspheres in contemporary drug delivery systems.

Keywords: Therapeutic Drug, Entrapment Efficiency, Microspheres, Determination, Preparation, Bioadhesive.

1. INTRODUCTION:

Microspheres are spherical shaped, solid particles limited in size between 01 to 100 µm up to 1mm in size, which can be produced from proteins or manmade polymers. Their small size and rheological characteristics allow them to be injected with an 18–20 G needle and achieve better local controlled drug delivery than traditional therapies (1,2). The drug is frequently incorporated within the polymer web and its subsequent release rates are controlled by the degradation or dissolution of the matrix in most cases where kinetics proceeds by first-order reactions (3). Microspheres can form two types, solid microspheres and hollow microspheres each having their respective uses. Therefore, solid microspheres can control a slow release of a drug, this is explained by the works that involved galantamine or diltiazem microspheres (4,5). On the other hand, microspheres with no core are employed in gastro- retentive system to prolong the time taken by a drug to pass through the stomachs (6).

Microspheres are widely used in drug delivery to improve solubility in salbutamol sulfate microspheres and for coating of drugs that have untoward taste such as ibuprofen as investigated(7). For drug delivery, biodegradable

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polymers including poly (lactic-co-glycolic acid), natural polymers such as gelatin & alginate are often used, the natural polymers has good biocompatibility and variable degradation profiles (8). The microsphere system also helps to reduce the doses of drugs given to the body, lower side effects as well as sustain drug levels in the body to prevent problems such as antimicrobial resistance (9,10). Some of the observed latest developments in the area of polymer science have led to the development of bioadhesive microspheres and well defined controlled drug delivery systems enabling the release of the drug for optimum time at the intended site within gastro-intestinal tract (11).

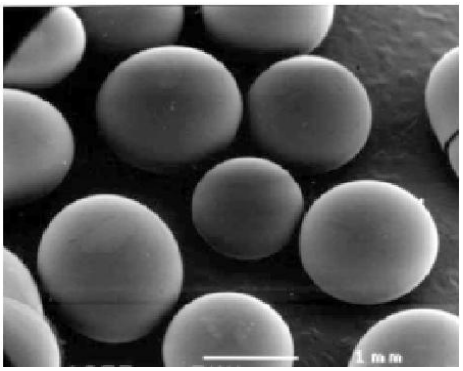

Fig 1: Microspheres

2 ADVANTAGES OF MICROSPHERES

1. Provide pre/post administration protection for the non-stable drug.
2. They reduced concentration of drug at site Other than the tissue or the target organ.
3. Reduces dose and toxicity.
4. Reduces the particle size to improve the dissolution of poorly soluble drugs.
5. Give Constanta and Prolonged therapeutic effect.
6. Less irritable stomach.
7. Improve bioavailability
8. Long biological half-life (12).

3 DISADVANTAGES OF MICROSPHERES

1. The changeovers from the formulations in releases.
2. Nature of the controlled dosing outflow by cross loading is releases that are not analogous to a number of factors such as diet and transfer levels through gut.pdf.
3. The rate of discharge differs between one dose to another.
4. Release control formulations are generally characterized by high dose loading and thus any deficit in quality of the release profile of the drug substance may result in.
5. None of these dosages should be crushed or chewed
6. Potentially dangerous(13).

3 MATERIALS INCORPORATED WITHIN THE FORMULATION OF MICROSPHERE

In the formulation of microsphere mainly used a One approach to counteracting this problem has been the use of microspheres, commonly formulated with a conjugate such as Avec an increasing number of clinical applications along with the goals of providing a targeted drug delivery and a high sensitivity, microspheres have mostly been formulated with an aqueous conjugate such as Ave.The most commonly used microsphere in R&D applications is an aqueous conjugate microsphere used of polymers they can be categorised as follows.

1. Synthetic Polymers
2. Natural polymers

3.1. Synthetic polymers are categorized in two

3.1.1 Non-biodegradable polymers

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Example- Poly methyl methacrylate (PMMA), glycidyl methacrylate epoxy polymers & Acrolein Glacial acrylic acid

3.1.2 Biodegradable polymers

Example- Glycolides and their co polymers, Poly anhydrides, Poly alkyl cyano acrylates, Lactides

3.2 Natural polymers-

They are derived from various storages such as protein, carbohydrates and chemically like modified carbohydrates. They also used like a protein. Such protein includes albumin, gelatin, and collagen, there are some natural biopolymers such as nogallose, Chitosan galactan of Agar, Agarose, Carrageenan, Starch. Substances obtained from chemically altered carbohydrates that are used like Poly starch, Poly dextran,

4 TYPES OF MICROSPHERES

4.1 Bioadhesive Microspheres: These microspheres remain bound to mucosal membranes (such as oral, ocular, nasal, and rectal), using water soluble polymers to enhance drug stay time and bioavailability at the site of absorption. Bioadhesive systems can enhance therapeutic effectiveness by providing prolonged drug exposure at targeted locations (14).

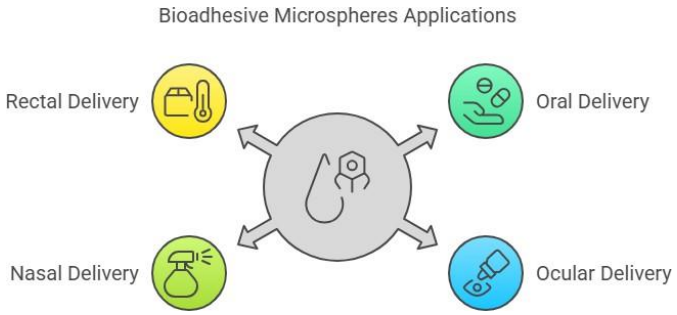

Fig 2: Bioadhesive Microspheres

4.2 Mucoadhesive floating microspheres:

Mucoadhesive floating microspheres or opaque hollow microspheresare targeted for gastroretentive systems. Due to their low density they float in the gastric fluids thus enhancing retention in the stomach in addition to facilitating controlled release of the drug. This system is particularly good for drugs such as ketoprofen, because it decreases dosing and plasma levels variation (15).

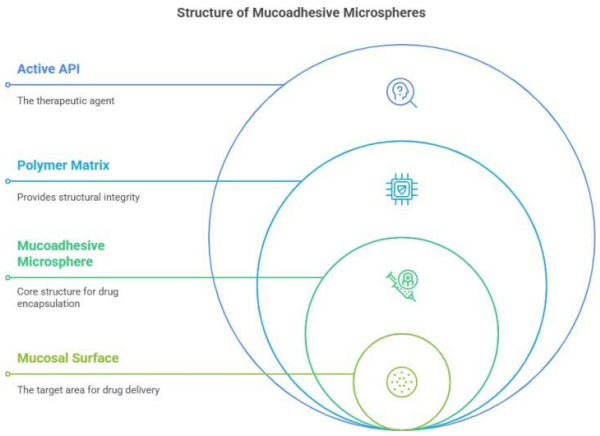

Fig 3: Mucoadhesive floating microspheres

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4.3 Radioactive:

These microspheres are involved in radioembolization therapy where high amounts of radiation are channeled to growths without much influence on other nearby tissues. Depending on the class of the emitted radiation, alpha, beta, gamma, they are usually administered in arteries that feed the tumor through radiation therapy (16).

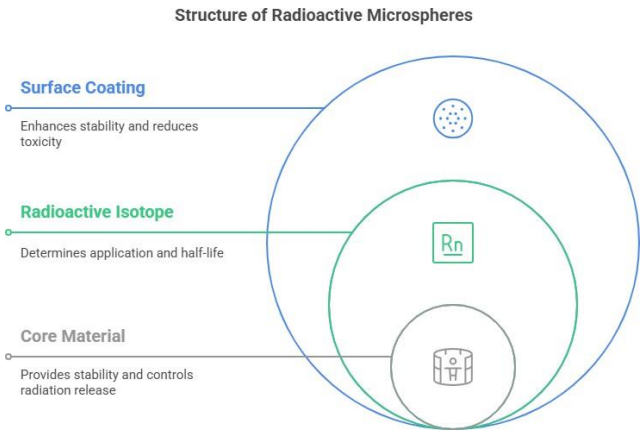

Fig 4: Radioactive microspheres

4.4 Magnetic Microspheres:

It's a delivery system that is very crucial.Which localizes the drug to the disease site. In this largerAmounts of circulating drug can be replenished withReduced amount of the drug magnetically targeted MagneticCarriers respond magnetically to a magnetic field.from incorporated materials, which are applied to magneticMicrospheres of chitosan, dextran, etc. The heterogeneoustypes are(17)

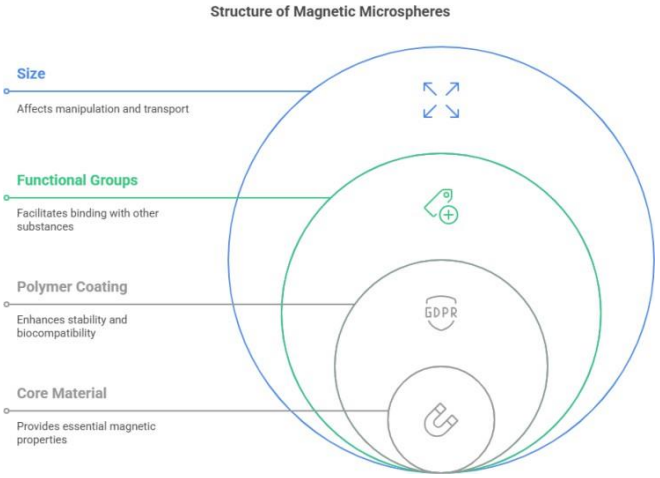

Fig 5: Magnetic Microspheres

a) **Therapeutic magnetic microspheres:** These are combined withDeliver chemotherapeutic agent to liver tumour. Drugs like proteins & peptides, it may be targeted by this system.
b) **Diagnostic microspheres:** They can be applied to imaging Liver metastases and may be used to also discriminate bowel loops from other abdominal structures by forming Nano-sized particles of supramagnetic iron oxides (18).

4.5 Polymeric Microspheres

Microspheres are further divided into:

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a) **Biodegradable Polymeric Microspheres**: These are microspheres prepared from natural polymers such as starch and are biodegradable, biocompatible and bioadhesive that provides improved mucosal Fortune. They are intended for prolonged drug delivery with variable drug release kinetics being sometimes rather difficult to manage (19).
b) **Synthetic Polymeric Microsphere** is widely used in clinical applications as drug delivery vehicles, fillers, and embolic particles. They are safe and tend to be compatible with tissue; however, they have the propensity to migrate away from the injection site and cause complications such as embolism (20).

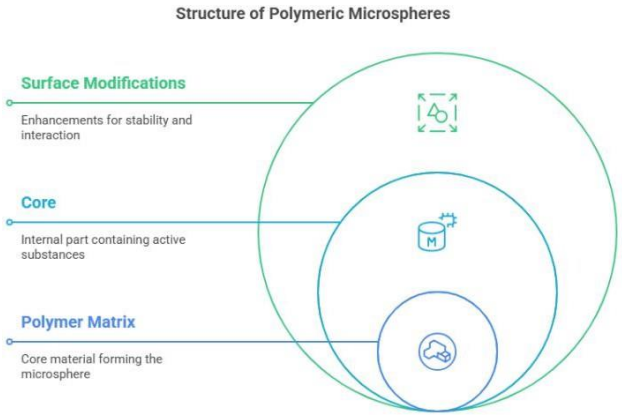

Fig 6: Polymeric Microspheres

5 METHOD OF PREPARATION:

5.1 Spray drying and spray congealing: Spray drying involves dispersion of the drug-polymer solution into hot air where by solvent rapidly evaporates and forms microspheres, usually in sizes between 1-100 µm. It allows for rapid drying with high encapsulation efficiency though sometimes this has to come at the expense of crystallinity. This method is highly utilized with drugs like penicillin and thiamine mononitrate due to the efficient operation under aseptic conditionsion. Solvent Evaporation The single emulsion method comprises dissolving a polymer in an organic solvent followed by dispersion of the organic droplets within an immiscible aqueous phase through the action of a stabilizer like polyvinyl alcohol, PVA. Agitating the system would lead to the evaporation of the solvent resulting in the forming of solid microspheres. This technique is commonly applied to hydrophobic drugs and polymers that give a controlled drug release profile to the drug loaded within the microspheres (21, 22).

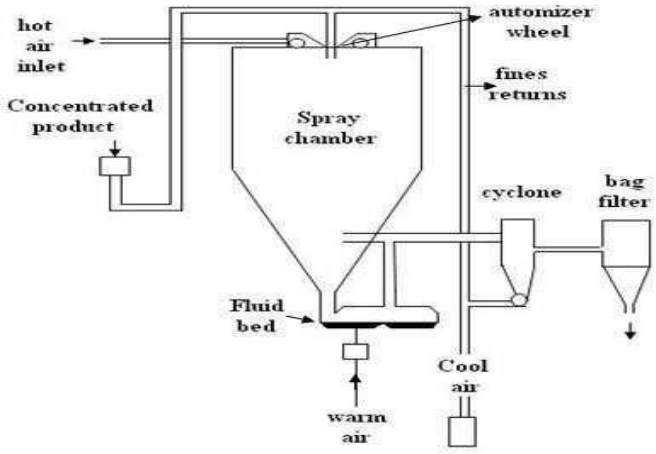

Fig 7: Spray drying and spray congealing

5.2 Double Emulsion: This method is well-suited for hydrophilic drugs such as proteins, vaccines & peptides. Here, an aqueous drug solution is emulsified in an organic phase, which is called the W/O emulsion. It is then

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further emulsified in another aqueous phase, and that is called the W/O/W emulsion. In the double emulsion process, solvent evaporation or extraction leads to the formation of microspheres. This encapsulates the hydrophilic drugs in the polymer matrix, so there will be a controlled release over time (23, 24).

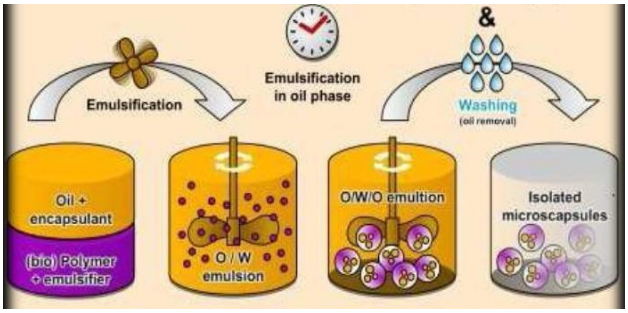

Fig 7: Double Emulsion

5.3 **Coacervation Method**: Coacervation separation of a polymer solution into a polymer-rich coacervate phase & a polymer-poor phase. A temperature change or addition of a non-solvent can be used to introduce phase separation. Coacervation is particularly suited to produce microspheres of different morphologies and incorporation of drugs in a polymer-rich environment, like ethyl cellulose based microspheres.

5.4 **Ionic Gelation method:** Ionic gelation is extensively applied to obtain crospheres from natural polymers such as alginate and chitosan. Here, a drug-polymer solution is dropped into a solution of crosslinking ions for example, calcium or aluminum ions causing the material to solidify thereby forming gel-like microspheres. This technique is ideal for delivering microspheres in controlled fashion in conditions with a neutral pH as the microspheres do not degrade until the same pH value as reached.

5.5 **Solvent extraction:** Solvent extraction consists of a dispersion of the substance in an aqueous phase and extraction of the organic solvent in an aqueous phase. This method lowers the hardening time and enables microsphere formation often used with PLGA polymers for controlled release formulations (25).

5.6 **Freeze-Drying:** Freeze-drying is a process of freezing, and solvents removal that is best used for drugs such as proteins. Primarily, the stages are cryo, primary, and secondary drying in which cryoprotective agents are used to protect drug molecules. Even though freeze-drying tends to be expensive it promotes the formation of microspheres while not affecting the integrity of the drug (26).

5.7 **Quasi-Emulsion Solvent Diffusion**: The formation of microsponges involved the dispersion of the drug-ernal phase in aqueous solution containing stabilizer such as PVA. Microsphere formation occurs as solvent diffuses into the external phase gradually leading to solvent diffusion. It is quite suitable for the controlled-release formulation which needs to sustain the release rate and be stable in aqueous media .

5.8 **Precipitation:** A modification of solvent evaporation, where co-solvents are used to demix from dispersed polymer droplets, raising the polymer concentration and thus causing precipitation of microspheres. This method is useful for the preparation of stable microsphere suspensions for polar drugs in non-polar liquids (27,28).

6. EVALUATION TEST:

6.1. Particle Size Analysis:

Microscopic Method: Particle size is one of the key factors that affect both drug release and absorption. The size of dried microspheres has been measured by calibrated optical microscopy to define their size. Since Standard light microscopy (LM) is widely used to ascertain particle size distribution, researchers easily and effectively quantify it (29).

6.2. Scanning Electron Microscopy (SEM):

Surface Morphology: SEM can provide high-resolution images of the microsphere surface. For sample preparation, mount it on a sample holder, then apply a conductive material such as gold or platinum to prevent charging upon

exposure to the electron beam. The focused electron beam then scans the sample allowing the observation of very detailed surface structures. Elemental composition identification can also be carried out using EDXA (30).

6.3 Flow Properties:

Carr's Compressibility Index and Hausner Ratio: Both of these parameters are quite vital in determining the flowability of microspheres that affects the process of production. The Carr index is calculated from bulk density and tapped density measurements, reflecting how compressible the powder is. The Hausner ratio, as calculated using these densities, represents the flowability. In this case, the Hausner ratio of less than 1.25 often shows excellent flow characteristics (31).

6.4 Thermal Analysis:

Thermal stability and phase transitions are studied by Differential Scanning Calorimetry andThermogravimetricAnalysis. DSC is the measurement of heat flow in a sample when it is heated at a controlled rate, transitions might include melting or crystallization. TGA is the measure of weight change with respect to temperature variation, thus an estimate of thermal stability and composition(32).

6.5 Percentage Yield:

Percentage yield of microspheres is the determination of actual amounts obtained relative to theoretical amounts as set up based on input polymers. The higher the percentage yield, the better it will indicate the effectiveness of the encapsulation process applied to the formulation and methods used for production(33).

6.6 Drug Content:

Drug content in microspheres is determined by allowing the mixture to settle and a certain volume of the supernatant to be diluted with 0.1N NaOH. The concentration of the drug is then determined using UV-Vis spectroscopy. This assay gives information on how much of the drug is actually encapsulated in the microspheres (34).

6.7 Entrapment Efficiency:

Entrapment efficiency is measured by determining the ratio of the actual amount of drug content (recovered after dissolving microspheres) to the theoretically calculated amount of drug. It is important because it has a direct implication on the therapeutic value of microspheres: the drug that has been encapsulated well(35).

6.8 Swelling Index:

For sodium alginate microspheres, swelling index estimation is done by suspending them in various buffer solutions at the physiological temperature of 37°C. At predetermined time intervals, the weights of microspheres are measured; this determines the amount of swelling, which consequently would affect the release profile and drug bioavailability(36).

6.9 X-ray Diffraction (XRD):

Uses XRD in testing the microsphere's crystalline properties compared to that of the drug. Excellent diffraction pattern with that of parts of it, which gives rise to great implications into aspects of state-solid of drug when in and on a polymatrix end(37).

6.10 Stability Studies:

Stability tests are required to determine the shelf life of microspheres. Samples are stored in different conditions, namely, ambient humidity, room temperature, oven, and refrigerator, for a predetermined time, for example, 60 days. The drug content is analyzed periodically to evaluate the stability and integrity of the microspheres over time(38).

6.11 Zeta Potential:

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Zeta potential measurements describe the surface charge of microspheres, affecting stability and biological system interactions. The case is specifically with the polyelectrolyte chitosan: variation in molecular weights might impact the zeta potential, affecting the formulation stability(39).

7 APPLICATION OF MICROSPHERES

7.1 Vaccine Delivery: Microspheres ensure the controlled release of antigens and provide safety and stability to vaccines, especially parenterally administered vaccines. Biodegradable microspheres also aid in intravenous delivery of vaccines, thus increasing the efficacy and reducing the side effects (40).

7.2 Gene Delivery: Non-viral microspheres are being used for gene therapy. They target cells specifically and reduce the immune response. Polymers can carry DNA, and they are used as an alternative to viral vectors, as they can be easily prepared and scaled up (41).

7.3 **Oral Drug Delivery:** Polymer-based microspheres, such as diazepam, ensure stability and effectiveness in drug delivery pH sensitivity ensures controlled release for oral administration(42).

7.4 **Transdermal Drug Delivery:** Chitosan-alginate films with microspheres offer a slow release, which enhances effectiveness for drugs such as prednisolone and lidocaine in the treatment of inflammation and pain through controlled transdermal application (43).

7.5 **Targeting by Micro Particulate Carriers**: Microspheres target specific sites in the body. Formulation materials such as MCC and chitosan are improved through extrusion and spheronization to increase bioavailability (44).

7.6 **Monoclonal Antibodies**: Microspheres containing monoclonal antibodies deliver drugs to the targeted drug-delivery sites. Immunoactive spheres are significantly specific and bind exactly at the target tissues, making targeted therapy highly accurate (45)

7.7 **Intratumoral and Local Drug Delivery:** Microspheres made from polymers like PLGA, chitosan, and PCL enable local drug delivery to the tumor sites, thereby increasing the intensity of therapy and minimizing systemic exposure (46)

7.8 **Other Applications**: In addition to pharmaceuticals, microspheres are applied in industries such as biotechnology, where they help in diagnostics, for example, temperature-sensitive cancer tests and manufacturing, for example, carbonless paper, scratch-n-sniff products (47).

7.9 **Wastewater Treatment:** The magnetical and porous nature of the microspheres utilized within the adsorption mechanism serves to adsorb toxins along with heavy metals in the water. Its major surface area helps to acquire contaminant capture, including ease of separation through magnets (48).

7.10 **Oil Spill Cleanup:** These are used in oil spill cleanups because they are buoyant and can potentially hold a large amount of oil; the hollow and porous microspheres, especially those made of polymers like polystyrene(49).

7.11 **Cosmetic and Personal Care Products:** They have been used in cosmetic formulation to give smooth textures and a mattifying effect to the product with controlled release of active ingredients. The use of silica microspheres in face powders provides oil absorption and the soft-focus effect (50).

7.12 **Pesticide Delivery:** Incorporating the microspheres in the delivery of pesticides, pesticide encapsulation brings slow, targeted release, minimizing environmental effects but doubling efficacy by ensuring minimal leaching and volatilization.

7.13 **Fertilizer Encapsulation:** Fertilizers are encapsulated in microspheres, just like pesticides, to provide nutrients in a controlled release. Loss of nutrients is reduced and growth is maintained in plants (51).

CONCLUSION:

Thus, microspheres constitute a promising and efficient drug delivery system due to its size, ability for a slow release and compatibility with various materials. Bioadhesive, floating, magnetic and radioactive microspheres fabricated from these spherical carriers whether solid or hollow can be created via different classifications to suit the type of therapy or diagnosis needed. Techniques such as spray drying, solvent evaporation, coacervation and ionic gelation enable encapsulation of several drugs and durations of release enhancing drug stability, increasing bio availability and decreasing dosing frequency. It is not limited to conventional medication but can be incorporated into gene delivery systems, vaccines, cancer treatment, and probes for diagnosis; microspheres testify

to the fact that it will revolutionize treatment and specifics medicine for the better. In spite of some limitations including variability of release rate and sensitivity to other factors, there are constant improvements in both polymer sciences and fabrication technology that offer microsphere mechanisms promising fundamental ingredients into novel systems of drug delivery.

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