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A Comprehensive Review on Microsphere Drug Delivery Systems: - Novelapproach for Drug Targeting

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ABSTRACT: In the pharmaceutical industry, the recent creation of innovative drug delivery technologies is critical. Microspheres are small, spherical shaped particles with a diameter range 1 µm to 1000 µm. They are free flowing particles with size below 200 µm and composed of biodegradable proteins or synthetic polymers. There are different varieties of microspheres such as bio adhesive microsphere, magnetic microsphere, floating microspheres, radioactive microspheres and polymeric microspheres. They can be delivered through various routes like oral, nasal, colonal, parentally, ophthalmic and transdermal etc. Various recent advancements such as cosmetic industry, dental medicine, wound healing, cancer therapy, vaccine delivery, etc. Thanks to a variety of strategies, microspheres play a significant role in novel drug delivery in the future, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted, and effective in-vivo delivery, and supplements as miniature versions of diseased organs and tissues in the body.

Keywords: Microspheres, Novel Drug Delivery, Application, Advancement, Marketing Formulations.

I. INTRODUCTION

Microspheres are small, spherical shape particles with diameter range 1 µm to 1000 µm. [1] They are free flowing particles with size below 200 µm and comprised of biodegradable proteins or synthetic polymers in nature.[2] An 18 or 20 number needle can be used to inject it.[3] Microspheres are also known as microparticles. Microspheres are often made up of different natural and synthetic materials like polymers, glass, and ceramic microspheres. [4] Microspheres play a vital role to improve the bioavailability of conventional drugs, minimizing its side effects and also boost a drug's therapeutic effectiveness.[5] Each particle of the microsphere is a mixture of drugs, diffused in a polymer form with release occurring by first order process. Due to the size and form of the matrix, drug release is controlled by dissolution or degradation; microspheres have a ball-bearing action. Novel drug carriers such as bio adhesive microspheres have been developed as a result of new advancements in polymer science and drug carrier technology.[4]

II. CLASSIFICATION OF MICROSPHERE

Microspheres are of two types;
1. Micrometrics
2. Microcapsules

The entrapped component is dispersed throughout the matrix in micrometrics, whereas the entrapped substance is distinctly surrounded by the capsule wall in microcapsules. [7,8]

III. TYPES OF POLYMERS USED

Microspheres used usually are polymers. There are two types of polymers;
1. Natural Polymers
2. Synthetic Polymers

Natural polymers derived from various sources like carbohydrates, proteins and chemically modified carbohydrates. [9]

a. Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.
b. Proteins: Albumin, Collagen and Gelatine.
c. Chemically modified carbohydrates: Poly-starch, Poly-dextran.

Synthetic polymers are classified into two types;

a. Biodegradable Polymers: E.g., Lactides, Glycosides& their co-polymers,Poly anhydrides, Poly alkyl cyanoacrylates. [10]
b. Non-biodegradable Polymers: E.g., Poly methyl methacrylate (PMMA), Glycidylmethacrylate, Acrolein, Epoxy polymers. [11]

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IV. IDEAL PROPERTIES OF MICROSPHERE

The materials used to make microspheres should have the following characteristics:

1. Longer duration of action.
2. Provide protection of drugs.
3. Sterilizability.
4. Water solubility or dispersibility.
5. Non-toxic.
6. Relative stability.
7. Increase of therapeutic efficiency.
8. Control of content release. [12]

V. ADVANTAGES OF MICROSPHERE

1. They protect unstable drugs before and after administration.
2. They reduce concentration of drugs at sites aside from the tissue or the target organ.
3. Decrease dose and toxicity.
4. Microspheres provide a consistent and long-lasting therapeutic impact.
5. Improved drug usage will boost bioavailability and reduce adverse effects.
6. Taste and odour masking.
7. Conversion of oils and other liquids to solids for easy handling.
8. Improvement of flow of powders. [13,14]

VI. DISADVANTAGES OF MICROSPHERE

1. Controlled release formulations have relatively larger material and manufacturing costs
than standard formulations.
2. Stabilizers, plasticizers, antioxidants, and fillers are examples of polymer additives.
3. Reproducibility is less.
4. The environmental impact of polymer matrix breakdown products produced by heat,
oxidation, hydrolysis, solar radiation, or biological activity.[15]

VII. TYPES OF MICROSPHERES

7.1. Bio adhesive microspheres:

A bio adhesive microsphere is a composite of microparticles and microcapsules (with a core of a drug) ranging from 1 to 1000 m in diameter and composed entirely of a bio adhesive polymer or having an outer coating of it. [16,17] Bio adhesive microspheres adhere to the location of application for extended periods of time and produce desirable therapeutic drug concentration in the sustained manner. [18,19]

7.2. Magnetic microspheres:

It is necessary to localize the drug to the diseased site. Larger quantities of freely circulating medication is frequently replaced by smaller quantities of magnetically focused pharmaceuticals in this method.[20]

There are two different types of magnetic microspheres: therapeutic and diagnostic.

7.2.1. Therapeutic magnetic microspheres:

It is used to distribute chemotherapeutic agents to liver tumours. Through this system, proteins and peptides can also be targeted.[21]

7.2.2. Diagnostic microspheres:

It 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 super magnetic iron oxides.[22]

7.3. Floating microspheres:

They are retained in the gastric fluid for prolonged periods of time due to their low-density which provide buoyancy to float over gastric fluids and deliver the drug slowly to sustain the action.[23]

7.4. . Radioactive microspheres:

The radioactive microspheres target the diseased areas without harming the surrounding healthy tissues. Different radioactive microspheres such as α, β and γ-emitters are injected through the arteries that cause target tumours where these deliver the high radiation dose. [24]

7.5. Polymeric microspheres:

Polymeric microspheres are widely used for controlled delivery of small as well large therapeutics via different routes of administration (mainly subcutaneous and intramuscular).[25]

7.5.1. Biodegradable polymeric microspheres:

Starch, a natural polymer, is biocompatible, biodegradable, and bio adhesive. They delay the residence time when come in contact with mucous membrane. This is due to its higher level of swelling in aqueous media, which results in the production of gel. [4,15]

7.5.2. Synthetic polymeric microspheres:

Synthetic polymeric microspheres have been shown to be effective and excellent biocompatibility in clinical applications as bulking agents, fillers, and drug delivery vehicles. However, such microspheres have the problem of migrating away from the injection site, causing embolization and further organ failure. [26,27,28]

VIII. APPLICATIONS OF MICROSPHERE

8.1. Microspheres in Vaccine delivery:

Vaccination provides protection against the microbe or its harmful product. The following requirements should be met by an ideal

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vaccination: efficacy, safety, convenience of use, and cost. The aspect of safety and minimization of adverse reactions may be a complex matter. The safety and the efficacy of antibody responses are closely linked with mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the lack of the conventional vaccines. There are several advantages to using microspheres with parenteral carriers (intramuscular, subcutaneous, intradermal), including:

1. Adjuvants improve antigenicity
2. by modulating antigen release
3. and stabilizing the antigen.[29]

8.2. Chemoembolization:

This is an endovascular treatment that involves selective tumour artery embolization and simultaneously or subsequently local delivery of a chemotherapeutic drug. Ideally, such embolization's will not only cause vascular blockage, but will also result in sustained therapeutic amounts of chemotherapeutics in tumour regions. Chemoembolization is an extension of traditional percutaneous embolization techniques. [30]

8.3. Monoclonal antibodies mediated microspheres targeting:

Microspheres are unaffected by monoclonal antibodies that target them. This targeting is a process used to achieve selective targeting to the specific sites. Monoclonal antibodies are exceptionally specific molecules. monoclonal antibodies can be immediately joined to the microspheres by covalent coupling using following methods: -

1. Adsorption which is not specific and Specific adsorption
2. Direct coupling
3. Coupling via reagents

8.4. Imaging:

Diameter of microspheres plays a significant role in determining the imaging of targeted sites using already labelled microspheres having radioactivity. Microspheres injected using an IV route other than the portal vein is typically stuck in the lungs. Utilizing human serum albumin microspheres, this phenomenon is employed for scintigraphy imaging of tumour masses in the lungs.[31]

8.5. Nasal drug delivery:

Polymer-based drug delivery systems, such as microspheres, liposomes, and gels, have been shown to have high bio adhesive properties and to swell readily when they come in contact with the nasal mucosa, increasing drug bioavailability and nasal cavity residence time. E.g., Starch, Dextran, Albumin. [32,48]

Table no 8.5. Microspheres for nasal drug delivery:

Drug	Route Of Administration	Polymer Use	Result
Gentamicin [33]	Nasal	Degradable Starch Microspheres And Lys phosphatidylcholine	Increased Nasal Absorption
Insulin [33]	Nasal	Degradable Starch Microspheres And Lys phosphatidylcholine	Efficient Delivery of Insulin into The Systemic Circulation Through Nasal Route
Human Growth Hormone (Hgh) [34]	Nasal	Degradable Starch Microspheres And Lys phosphatidylcholine	Rapid And Increased Absorption
Desmopressin [35]	Nasal	Starch	Addition Of LPC Causes A 5 Folds Increase inCmax And 2 Folds Increase In Bioavailability

8.6. GI drug delivery:

Once added to neutral or acidic environments, polymer granules with interior voids generated by deacidification were found to be robust and offered a regulated release of the medicine. e.g. Eudragit, Ethyl cellulose+Carbopol BSA, Gelatine. [31]

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Table no 8.6. Microspheres for GI drug delivery:

Drug	Route Of Administration	Polymer	Result
Amoxicillin [36]	GI	Ethyl Cellulose-Carbopol-934P	Greater Anti H. Pylori Activity
Glipizide [37]	GI	Chitosan	Long-Term Blood Glucose Control
Vancomycin [38]	Colonic	PGEF (Polyglycerol esters Of Fatty Acids Coated) With Eudragit S 100	Well Absorbed Even Without Absorption Enhancers.
Furosemide [39]	GI	Polyglycerol Esters Of Fatty Acids (Pgefs)	Increased Bioavailability

8.7. Ophthalmic Drug Delivery:
Polymer-based microspheres exhibit a variety of appealing biological characteristics like bio adhesion and permeability enhancement. These properties make polymer an excellent material for the development of ocular medication delivery systems vehicles. Examples are Chitosan, Alginate, Gelatine.
8.8. Gene delivery:
Microspheres could be useful as oral gene carriers due to their adhesive and transport properties. Example: chitosan, gelatine, polycation complexes, viral vectors, cationic liposomes.
8.9. Transdermal Drug Delivery:
Polymer has good film-forming properties. The thickness of the membrane and the cross-linking of the film affect medication release from the devices. e.g., Chitosan, Alginate, PLGA.
8.10. Oral Drug Delivery:
Since microspheres containing polymer may form films, they can be utilised instead of pharmaceutical tablets in the development of film dosage forms. The microspheres are more helpful for oral drug administration applications because of their pH sensitivity and the reactivity of the main amine groups. e.g., Chitosan, Gelatine.

8.11. Colonic Drug Delivery:
Insulin has been transferred specifically to the colon using polymer. e.g., Chitosan.

8.12. Vaginal Drug Delivery:
Polymer modified by adding thioglycolic acid to the major amino groups of the polymer is widely utilized in the treatment of genitourinary tract mycotic infections. e.g., Chitosan, Gelatine, PLGA.

8.13. Buccal Drug Delivery:
Chitosan, Sodium alginate polymer is an excellent polymer to be used for buccal delivery because it has muco / bio adhesive properties and can act as an absorption enhancer. [31]

8.14. Intratumoral and Local Drug Delivery:
Polymer films are used to carry paclitaxel to the tumour location in therapeutically appropriate concentrations. Mixtures of drug has auspicious possibility of regulated administration in the oral cavity in the oral cavity e.g.,Gelatine, PLGA, Chitosan. [40]
8.15. Pharmaceutical application
1. For Taste and odour masking
2. Delay the volatilisation
3. Separation of incompatible substances
4. Improvement of flow properties of powders
5. Safe handling of toxic substances
6. Improve the solubility of water-insoluble substances by incorporating dispersion of such material in aqueous media [41]

IX. RECENT ADVANCEMENTS

9.1. Important Utilizations of Chitosan Polymer Cholesterol-lowering Effects Chitosan and cellulose were used as samples of fibres with high, average and low bile acid-binding capacities, respectively. In a control group of mice fed a high cholesterol/high fat diet for three weeks, serum cholesterol levels increased by almost twofold to 4·3mM, but involvement of either of these fibres at 75% of the diet stopped this increase. Additionally, Treatment with these fibres reduced the amount of cholesterol acquired in hepatic reserves as a result of the HFHC diet. The 3 sorts of fibres showed identical hypocholesterolaemia activity; but

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cholesterol deficiency of liver tissue was maximum with cholestyramine.

1) Lower cholesterol (food) intake,
2) Lower cholesterol absorption efficiency, and
3) Increased faecal bile acid and cholesterol excretion are the mechanisms causing cholestyramine's cholesterol-lowering impact. The other effects can be attributed to cholestyramine's strong bile acid binding ability.

The latter effects can be applied to the high bile acid binding capacity of cholestyramine. Incorporation of chitosan or cellulose in the diet reduced cholesterol absorption, but did not affect either intestinal cholesterol absorption or faecal sterol amount. The present study provides solid evidence that above all satiation and satiety effects underlie the cholesterol lowering.[42]

9.2. Increase Stability of Drug

Chitosan polymer is used to increase the stability of drugs that are coupled with chitosan and are ground for 45 minutes until a dough mass is formed. The dough mass is passed through sieve no.16, which produces granules that are completely stable under any condition.

9.3. Orthopaedic Patients

Chitosan is a biopolymer with osteoconductive, wound-healing, and antibacterial properties, making it a good choice for application as a bioactive coating to aid Osseointegration of orthopaedic and craniofacial implant devices. It has been accepted to be useful in promoting tissue growth in tissue repair and increasing wound-healing and bone regeneration.

9.4. Cosmetics Industry

The content of pure quaternary chitin and chitosan of the formulation is investigated in cosmetic compositions for hair or skin care. The chitosan derivatives are excellent for hair keratin and confirm to have hair strengthening and hair conditioning characteristics. e.g.; Hair setting lotion, Oxidation Hair-colouring Composition, Hair toning Composition, Skin Cream, Hair-treatment Composition, Gel-form.

9.5. Dental Medicine

In dental medicine, chitosan is used as a dressing for an oral mucous wound and a tampon radical treatment of maxillary sinusitis. In addition, it is being inspected as an absorbing membrane for periodontal surgery.

9.6. Chitosan as Permeation Enhancer

Chitosan is said to be able to open tight connections in cell membranes because of its cationic nature. As a result, a number of studies have been conducted to investigate the use of chitosan as a penetration enhancer for hydrophilic medicines with limited oral bioavailability, such as peptides. Because the absorption enhancement is due to interactions between the cell membrane and positive charges on the polymer, this phenomenon is pH and concentration dependent. Furthermore, increasing the charge density on the polymer would lead to high permeability.

9.7. Chitosan as Mucoadhesive Excipient

Bio adhesive is generally used as an approach to enhance the residence time of a drug in the GI tract, thereby increasing the oral bioavailability. The correlation between chitosan and different other commonly used polymeric excipients display that the cationic polymer has higher bio adhesive in contrast to other natural polymers, like cellulose, Xanthan gum, and starch.

9.8. Development of Chitosan: Citric acid ratio on Drug Release

It has been approved that polymer with suitable viscosity and expanding properties can be used as osmotic agents for the release of water-insoluble drugs. Because of its large molecular weight and unbranched linear shape, chitosan is completely biodegradable, toxicologically nontoxic and low cost, and exhibits a wonderful gelation characteristic. Hence the potential for chitosan to be used as a polymeric osmotic agent in osmotic pumps is understandable. Upon dissolution, amine groups of the polymer turn protonated, forming a resultant viscous and dissolved polysaccharide.

In addition, the developed formulations use citric acid as a pH-regulating excipient to decrease the microenvironmental pH of the core to the level at which chitosan could become a gelling solution, and therefore increase osmotic pressure.

9.9. Chitosan as Permeation Enhancer

It has been approved that chitosan, because of its cationic nature, is capable of opening cell membrane tight junctions. This property has prompted a number of research into the use of chitosan as a penetration enhancer for hydrophilic medicines, such as peptides, that otherwise might have poor oral bioavailability. Due to the absorption enhancement being caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration reliant. Moreover, increasing the charge density on the polymer would lead to higher permeability.

9.10. Direct Compressible Excipients and as Binder

Chitosan has excellent properties as excipients for direct compression of tablets were the additions of 50% chitosan result in rapid disintegration. The limit of moisture absorption is determined by the degree of deacetylation. Chitosan, higher than 5%,

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was better than corn starch and microcrystalline cellulose as disintegrant. Efficacy was affected by crystallinity, degree of deacetylation, molecular weight, and particle size of chitosan. Chitosan has been found to be a superior tablet binder when compared to other excipients for binder efficiency.

9.11. Wound Healing Properties

Efficacy of chitosan in the advancement of the healing of wounds first reported in 1978. Chitosan acetate films, which were tough and protective, had the advantage of good oxygen permeability, high water absorptivity and slow enzymatic degradation.[43]

9.12. Microspheres in Cancer Therapy

9.12.1. Lung tumour:

Paclitaxel-loaded PLGA microspheres have been significantly effective in inhibiting lung tumours without any clinical toxicity in the patients.[44]

9.12.2. Prostate cancer:

Microspheres have also been useful in Androgen Replacement Therapy for prostatic adenocarcinoma where Leuprolide acetate follows a controlled release mechanism when administered during a microsphere formulation, an FDA approved differentiated formulation that aids in the treatment of advanced prostate cancer.

9.12.3. Brain cancer:

Microspheres have also been useful in treating brain tumours. Sustained release of 5-fluorouracil was accomplished with the help of polymeric microspheres for local delivery of anti-neoplastic agents in the brain. The regulated polymer degradation causes a long-term delivery of the drug to
the tumour site.

9.12.4. Endocrine tumour:

Formulations based on microspheres containing octreotide acetate are responsible for the long acting release of the drug in the treatment of neuroendocrine tumours.

9.12.5. Ovarian cancer:

Studies suggest that cisplatin containing microspheres have been found advantageous in treating ovarian cancer.[45]

9.12.6. Bladder cancer:

Polymeric microspheres also are getting used in treating cancers of the bladder and pancreas. Microspheres are also administered in combination with technologies like magnetism, radiation and ultrasound in oncology. [46]

X. MARKETED FORMULATIONS: [47]

Sr.No	Product	Api	Route Of Administration	Indication
1	Leupron Depot ®	Leuprolide	Intramuscular	Prostate Cancer
2	Sandostatin Depot ®	Octreotide	Intramuscular	Acromegaly
3	Trelstar Depot ®	Triptorelin	Intramuscular	Prostate Cancer
4	Somatuline LA ®	Lanreotide	Subcutaneous	Acromegaly
5	Neutropin Depot ®	Somatropin	Subcutaneous	GH Deficiency
6	Risperdal Consta ®	Risperidone	Intramuscular	Bipolar Mania And Schizophrenia
7	Arestin ®	Minocycline	Sub Gingival	Periodontitis
8	Retin-A Micro ®	Tretinoin	Topical	Acne
9	Zmax ®	Azithromycin	Oral	Sinusitis
10	SIR-Spheres ®	Yttrium-90	Through Hepatic Artery	Liver Tumor

XI. CONCLUSION

From this review, we could conclude that various types of pharmaceutical application are being used for microspheres as a drug delivery system. It may include oral, targeted, sustained, topical, naso-pulmonary and various biotechnology applications like gene therapy etc. By enhancing safety and reducing toxicity, innovative delivery systems can provide substantially more therapeutic and commercial benefits.

Microspheres will play a key role in novel drug delivery in the future, particularly in damaged cell sorting, diagnostic testing, gene and genetic materials, safe, targeted, and effective in-vivo delivery, and supplements as miniature replicas of infected organs and tissue in the body, due to a combination of different strategies.

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