

Available online on 15.11.2021 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

A Novel Drug Delivery of Microspheres

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Article Info:



Article History:

Received 21 September 2021
Reviewed 28 October 2021
Accepted 03 November 2021
Published 15 November 2021

Cite this article as:

Walia S, Dua JS, Prasad DN, A Novel Drug Delivery of Microspheres, Journal of Drug Delivery and Therapeutics. 2021; 11(6):257-264

DOI: <http://dx.doi.org/10.22270/jddt.v11i6.5059>

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Abstract

Microspheres are multiparticulate drug delivery systems that distribute medications at a predetermined rate to a specific region. Microspheres are free-flowing powders manufactured from biodegradable proteins or synthetic polymers, with particle sizes ranging from 1 to 1000 micrometers. Benefits of using microspheres in medication delivery, bone tissue manufacture, and pollutant absorption and desorption by regeneration. The study demonstrates how microsphere parameters are planned and measured. Bioadhesive microspheres, polymeric microspheres, magnetic microspheres, floating microspheres, and radioactive microspheres are only a few examples of complicated microspheres. Cosmetics, oral medication administration, target drug delivery, ocular drug delivery, gene delivery, and other industries covered in the paper could all benefit from microspheres. To ensure best therapeutic effectiveness, the agent must be delivered to target tissue at an optimal amount during the appropriate timeframe, with low toxicity and adverse effects. There are several methods for delivering the therapeutic substance to the target site in a controlled manner. The use of microspheres as medication carriers is one such technique. The value of microspheres as a novel drug delivery carrier to accomplish site-specific drug delivery was discussed in this article.

Keywords: Microspheres, method of preparations, polymer bioadhesion, types of microspheres.

INTRODUCTION:

The purpose of the novel drug delivery system is to distribute medications at a rate that is appropriate for the body's needs throughout therapy, while also getting the active component to the site of action as rapidly as feasible. The capacity of drug delivery systems (DDS) to precisely monitor drug release rates or target medications to specific body regions has had a significant impact on the health-care system. The finest drug delivery system provides pharmaceuticals at a defined pace determined by the body's demands and delivers active components to the site of action over the duration of treatment. Drug carrier technology offers an intelligent approach by binding the drug to carrier particles such as microspheres, nanoparticles, or lipids to drug delivery.¹

MICROSPHERES:

Entrapped substances are scattered within the microsphere's matrix in micromatrices, while entrapped substances are clearly confined by the characteristic capsule wall in microcapsules. Micromatrices have the trapped material spread throughout the microspheres matrix, while microcapsules have the trapped substance clearly confined by a defined capsule wall. The medication was disseminated or dissolved via the particle matrix, and the solid biodegradable microspheres have the potential to allow for regulated drug release. Microspheres are solid spherical particles that range in diameter from 1 to 100µm. They're

biodegradable, spherical, free-flowing proteins or synthetic polymer particles. 2 Microspheres are divided into two categories;

- Microcapsule
- Micro matrices

Microcapsules have a distinct capsule wall around the entrapped substance, whereas micromatrices have the entrapped substance spread throughout the matrix of the microsphere. Solid biodegradable microspheres with a drug disseminated or dissolved via a particle matrix can be used to provide controlled drug release. Biodegradable synthetic polymers and modified natural goods, as well as polymeric waxy or other protective compounds, are used to make them.³ Polymers and waxes of natural and manmade sources are used to make them. Microsphere stability, solubility, and drug release are all affected by the type of polymer employed to form them. Polyethylene, polystyrene, and expandable microspheres are the most common types of polymeric microspheres. Solid and hollow microspheres are available. Hollow microspheres are used as an addition to lower the density of a material. Topical formulations based on microspheres have gained popularity for their therapeutic efficacy over longer periods of time. In recent years, the usage of micro particle medication delivery devices has grown in popularity.^{4,5,6,7,8}

HISTORY

- **Bunge berg de Jong** and coworkers' work on the trapping of substance using coacervates in the 1930s gave birth to the concept of packaging minuscule quantities of stuff in microspheres.
- Microspheres were first used in industry in the 1960s.⁹

ADVANTAGES OF MICROSPHERES¹⁰

1. Microspheres have a predictable and long-term therapeutic effect.
2. Lower the frequency of dosing to increase patient compliance.
3. They can be introduced into the body due to their spherical shape and lower size.
4. Better drug use will increase bioavailability while reducing the likelihood of negative effects.
5. Microsphere shape enables for regulated medication release and degradation variations.
6. Oils and other liquids are solidified to make them more manageable.
7. Compared to big polymer implants, biodegradable microspheres have the benefit of not requiring surgical procedures for installation and removal.

DISADVANTAGES OF MICROSPHERES:

1. The ingredients and processing costs of controlled release formulations are significantly greater than regular formulations.
2. The fate of polymer matrix and its environmental impact.
3. Plasticizers, stabilizers, antioxidants, and fillers are examples of polymer additives.
4. Reproducibility is less.
5. Process variables such as temperature, pH, solvent addition, and evaporation/agitation might affect the stability of encapsulated core particles.
6. The influence on the environment of polymer matrix breakdown products produced in reaction to heat, hydrolysis, oxidation, solar radiation, or biological agents.

IDEAL CHARACTERISTICS OF MICROSPHERES:¹¹

1. The ability to assimilate medication concentrations that are relatively high.
2. After synthesis, the preparation's stability and shelf life must be clinically acceptable.
3. Injections in aqueous vehicles with controlled particle size and dispersibility.
4. Controlled release of active substances over a long period.
5. Controllable biodegradability and biocompatibility
6. Susceptibility to chemical modification.

CRITERIA FOR MICROSPHERES

PREPARATION:¹¹

- It is possible to incorporate liquid, solid, or gas into one or more polymeric coatings using the microencapsulation technique.
- The different methods for preparing various microspheres are dependent on the route of administration, particle size, drug release length and the rpm, cross linking process, drug of cross linking, co precipitation, evaporation time, and other factors.
- The preparation of microspheres should satisfy certain criteria:
 - The release of active reagent under strict supervision on a long time scale.
 - It should be capable of incorporating very high drug concentrations.
 - It should be able to withstand chemical alteration.
 - After synthesis, the consistency of the preparation for a clinically suitable shelf life.
 - Biodegradability and controllable biocompatibility.
- The controlled particle size and dispersability in the aqueous vehicles for injection.

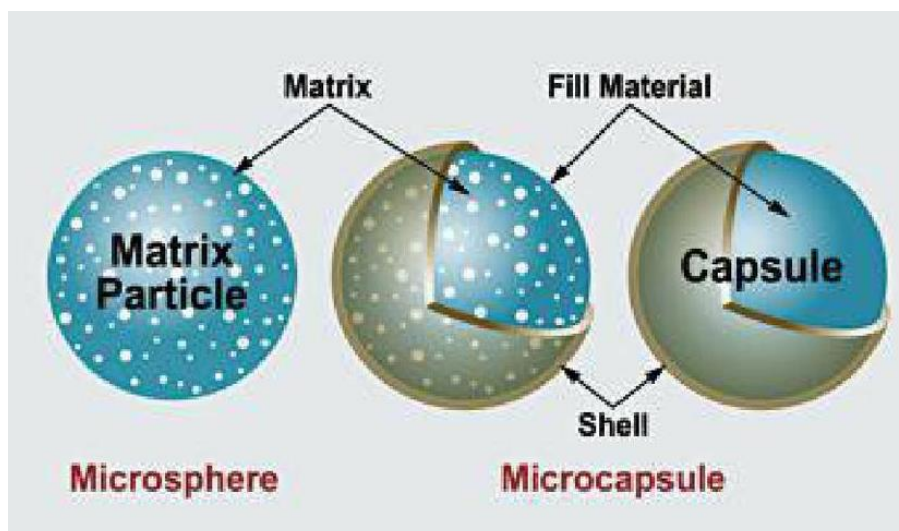


Figure 1: Microspheres and Microcapsules

CLASSIFICATION OF POLYMERS:

Synthetic Polymers: Divided into two types:

- Non – biodegradable: Acrolein, glycidyl methacrylate, Epoxy polymers etc.¹²
- Biodegradable: Polyanhydrides, polyalkylcyanoacrylates lactides glycosides and their copolymers.^{13,14}

Natural Materials: They are obtained from different sources like:^{15,16}

- Proteins (albumin, gelatin, collagen)
- Carbohydrates (starch, agarose, carrageenan)
- Chemically modified carbohydrates (poly acryl dextran, poly acryl starch)

TYPES OF MICROSPHERES:

• Bioadhesive Microspheres

The technique of adhering a medication to a membrane using the adhesive characteristics of water-soluble polymers is known as adhesion. A drug delivery system's adhesion to a mucosal membrane, such as the buccal, ocular, rectal, nasal, and other mucosal membranes, is referred to as bio adhesion. These microspheres have a longer residence time at the application site, resulting in better absorption and therapeutic activity.¹⁷

• Magnetic Microspheres

This type of delivery mechanism is crucial because it allows the drug to be administered precisely where it is required. In this situation, a smaller quantity of magnetically focused medicine will replace a larger quantity of freely circulating drug. Magnetic responses to a magnetic field can be found in chitosan, dextran, and other integrated materials utilized in magnetic microspheres.¹⁸ The different types are:

Therapeutic Magnetic Microspheres

These are used to deliver a chemotherapeutic drug to malignancies in the liver. This technique can potentially be used to target drugs like proteins and peptides.¹⁷

Diagnostic Microspheres

By producing nano-size particles of paramagnetic iron oxides, they can be used to image liver metastases as well as distinguish bowel loops from other abdominal structures.¹⁹

• Floating Microspheres

Floating forms have a lower bulk density than gastric fluid; therefore they float in the stomach and have no effect on the rate of gastric emptying. The medicine is released slowly and at the desired rate if the system is floating on gastric contents, which enhances stomach residency and plasma concentration variability. Strikes are also less common, as is dose dumping. It also offers a longer therapeutic effect, reducing the need for frequent dosage.²⁰

• Radioactive Microspheres

Radioembolization is a type of treatment that involves injecting a substance into the body. Microspheres with a diameter of 10-30nm are larger than capillary microspheres and are trapped in the first capillary bed as they pass through before being introduced into the arteries that create a tumor of interest. As a result, radioactive microspheres deliver a high dosage of radiation to the target locations while causing no harm to the surrounding tissues in all of these scenarios. 21 It differs from a drug delivery system in that radioactivity is not released from microspheres but instead acts from

within a radioisotope typical distance, and the various types of radioactive microspheres are α, γ, β emitters.²²

• Polymeric Microspheres

The different types of polymeric microspheres can be classified as:

Biodegradable Polymeric Microspheres

Biodegradable, biocompatible, and bioadhesive natural polymers such as starch are employed. Biodegradable polymer extends the residency period when in touch with mucous membranes due to its excellent degree of swelling in an aqueous media, resulting in the development of gels. The rate and degree of medication release are controlled by the polymer concentration and the release pattern throughout time. The key problem is that biodegradable microspheres' drug loading performance in clinical application is tricky, making drug release difficult to control. Microspheres, on the other hand, offer a wide range of uses in microsphere-based therapy.²³

Synthetic Polymeric Microspheres

Synthetic polymeric microspheres have been proved to be safe and biocompatible in clinical applications as bulking agents, fillers, embolic particles, drug delivery vehicles, and other applications.²⁴ The main disadvantage of these microspheres is that they have a proclivity for moving away from the injection site, providing a danger of embolism and subsequent organ injury.

MECHANISM OF MICROSPHERES

The majority of drug delivery using micro particles avoids the establishment of a matrix-like internal solid dispersion morphological structure. It's possible that the medication is insoluble in the polymeric matrix and is released during erosion. Water diffuses into the matrix first, causing it to dissolve towards the device's surface. The osmotic pressure is relieved by establishing a conduit to the surface and releasing a predefined amount of medicine in the initial drug burst.²⁵

METHOD OF PREPARATION

Methods used for the preparation of microspheres are:

- Single emulsion techniques
- Double emulsion techniques
- Polymerization
- Normal polymerization
- Interfacial polymerization
- Phase separation coacervation technique
- Spray drying
- Emulsion cross linking method
- Solvent evaporation
- Solution –enhancement dispersion method
- Ionic gelation method²⁶

• Single Emulsion Technique

A wide range of proteins and carbs can be prepared using this technology. The natural polymers are dispersed in an oil phase, which is a non-aqueous media, after being dissolved in an aqueous medium. That is the first stage of the procedure.²⁷ The two methods are used to cross link the next step as:

Cross Linking by Heat

It can be done by dispersing the dispersion in hot oil. However it is not suited for thermo sensitive medications.

Chemical Cross Linking Agents

Formaldehyde, diacid chloride, glutaraldehyde, and other substances are used in this process. When active ingredients are administered at the time of preparation and subsequently centrifuged, washed, and separated, it is detrimental to the unnecessary exposure of active substances to chemicals. By introducing a chitosan solution (in acetic acid) to liquid paraffin containing a surfactant without using an emulsion as a cross-linking agent, a 25% glutaraldehyde solution is used to make microspheres.²⁸

- **Double Emulsion Technique**

The primary w/o emulsion is poured into an aqueous polyvinyl alcohol solution, resulting in W/O/W. For 30 minutes, the w/o/w emulsion must be stirred continuously. For 30 minutes, gradually add water to the emulsion. Filtration and drying of microcapsules under vacuum Water-soluble medications, peptides, proteins, and vaccines are all well-suited to it. This procedure can be done with both natural and synthetic polymers. In a continuous organic lipophilic phase, the aqueous protein solution is dispersed.³⁰

- **Polymerization Techniques**

Two techniques are mainly used for the formulation of microspheres are as follow;

Normal Polymerization

A monomer or a combination of monomers, along with the initiator or catalyst, is commonly heated to commence polymerization in bulk polymerization. The resulting polymer can be molded into microspheres. Drugs can be added during the polymerization process. Although this is a pure polymer production technique, it is difficult to dissipate the heat of the reaction, which can harm thermo labile active components. Suspension polymerization, also known as pearl polymerization, involves heating the monomer combination with the active medication as droplets dispersion in a continuous aqueous phase at a lower temperature.³¹

Interfacial Polymerization

At the interface between the two immiscible liquid phases, different monomers react to generate a polymer film that basically envelops the dispersed phase. This effectively encloses the dispersed phase. Two reactive monomers are used in this process; one is dissolved in the continuous phase, while the other is disseminated in the continuous phase (naturally aqueous) throughout which the second monomer is emulsified.³²

- **Phase Separation Coacervation Technique**

This method is based on the idea of lowering the polymer's solubility in the organic phase in order to affect the production of coacervates, a polymer-rich phase. The drug particles are disseminated in a polymer solution, and the device is then filled with an incompatible polymer that separates the first polymer phase and engulfs the drug particles. The addition of the non-solvent causes the polymer to solidify. Using butadiene as an incompatible polymer, this method was utilized to make polylactic acid (PLA) microspheres. The pace of accomplishment of the coacervates determines the distribution of the polymer film,

hence process variables are important. The particle size and aggregation of the produced particles are both important factors. Because as the process of microsphere formation begins, the produced polymerized globules begin to stick and form agglomerates, agglomeration must be avoided by stirring the suspension with an appropriate speed stirrer. Process variables are crucial because they govern the kinetics of the produced particles, as there is no predetermined state of equilibrium.³²

- **Spray Drying**

Before being spray dried, the polymer is first dissolved in a suitably volatile organic solvent, such as dichloromethane or acetone. After that, high-speed homogenization is used to disseminate the chemical in a polymer solution. After that, the dispersion is atomized, resulting in a heated air current. The atomization process produces tiny droplets or fine mists from which the solvent evaporates almost instantly, forming microspheres in the 1-100 nm range. By a cyclone separator, micro particles are separated from hot air, and the solvent residue is removed using vacuum drying. The procedure's survivability under aseptic circumstances is one of its key advantages. This is a fast process that results in the production of porous micro particles.³³

- **Emulsion Crosslinking Method**

The reactive functional group of polymers is used to crosslink with the aldehyde group of cross linking agents in this procedure. Emulsifying the polymer aqueous solution in the oily phase yield water-in-oil emulsion in this approach. A appropriate sulphosuccinate was used to stabilize aqueous droplets. To harden the droplets, a cross linker such as glutaraldehyde was added to the stable emulsion. To eliminate residues of oils, the microspheres were filtered and washed repeatedly with hexane or petroleum ether. They were eventually washed with water to remove the cross linker, and then dried for 24 hours at room temperature.³⁴

- **Solvent Evaporation**

A liquid production vehicle is used to carry out the processes. A volatile solvent is used to disperse the microcapsules, which is not mixed with the liquid stage of the manufacturing process. The microencapsulated core material is dissolved or dispersed in a polymer coating solution with agitation. The core material mixture is spread during the vehicle's liquid production process to achieve the appropriate microcapsule size. The combination is then heated, if possible, to evaporate the solvent for the primary material's polymer dispersion in the polymer solution, and the polymer shrinks around the core. A matrix - a type of microcapsule - is formed when the core material is dissolved in a polymer coating solution. Water-soluble or water-insoluble core materials are available. Aqueous (o/w) or non-aqueous formations result from solvent evaporation.³⁵

- **Ionic Gelation Method**

The alginate/chitosan particulate system was created using this approach for the release of diclofenac sodium. The medication is mixed with an aqueous sodium alginate solution in this stage. To obtain a full solution, the stirring is continued and the Ca^{2+}/Al^{3+} solution is added drop by drop. Internal jellification was achieved by leaving the microspheres in the original solution for 24 hours before filtration and separation. PH 6.4-7.2 allows for full release, but the drug will not release at an acidic pH.³⁶

LIST OF MARKETED MICROSPHERES DRUG PRODUCT³⁷

Table 1: Marketed Microspheres Drug Products

DRUG	COMMERCIAL NAME	TECHNOLOGY
Risperidone	Risperdal IR, Consta	Double emulsion(o/w)
Naltrexon	Vivitro IR	Double emulsion(o/w)
Leuprolide	Leupron DepotR	Double emulsion(o/w/o)
Octreotide	SandostatinR LAR	Phase separation
Somatropin	NutropinR	Spray drying
Triptorelin	Trelstar Depot, DecapeptylIR SR	Phase separation
Lanreotide	SomatulineR LA	Phase separation

EVALUATION PARAMETERS OF MICROSPHERES:

- **Characterization**

The characterization of micro particulate carriers is an important phenomenon that contributes in the development of a suitable carrier for the transport of proteins, medicines, or antigens. These microspheres have different microstructures. These microstructures control the carrier's release and stability.³⁸

- **Particle size and shape:**

Conventional light microscopy (LM) and scanning electron microscopy (SEM) are the most widely utilized technologies for seeing tiny particles. Both can be used to investigate the form and structure of micro particles. In the case of double-walled microspheres, LM allows you to modify the coating settings. Before and after coating, the microspheres' structures can be viewed, and the difference may be assessed microscopically. In comparison to LM, SEM has a better resolution. SEM can be used to investigate the surfaces of microspheres, and it can also be used to investigate double-walled structures when the particles are cross-sectioned.³⁸

- **Electron spectroscopy for chemical analysis**

Electron spectroscopy for chemical analysis (ESCA) can be used to determine the surface chemistry of microspheres.³⁸

- **Density Determination**

A multi-volume pycnometer can be used to calculate the density of the microspheres.³⁹

- **Iso electric point**

Micro-electrophoresis is used to determine the electrophoretic mobility of microspheres, which can then be used to determine the isoelectric point.⁴⁰

- **Angle of contact**

The wetting qualities of the micro particle carrier are determined by the contact angle.⁴¹

- **Percentage yield**

It is computed by multiplying the weight of microspheres obtained from each batch by the total weight of medication and polymer used to prepare that batch by 100.⁴³

- **Swelling Index**

The swelling index of the microspheres was determined by using the formula:

Swelling Index= (mass of swollen microspheres mass of dry microspheres /mass of dried microspheres)⁴³

- **Bulk Density:**

It's calculated by pouring a known-weight sample of microspheres into a measuring cylinder, measuring the length of the cylinder, and then dividing the weight by volume.

Bulk Density =wt. of the microspheres/bulk volume

- **Tapped Density**

It's calculated by pouring a known-weight sample of microspheres into a measuring cylinder, tapping it completely, and measuring the volume, then dividing the weight by the volume.

Tapped density = wt. of the microspheres/ volume after tapping

- **Hausner's Ratio**

The ratio of tapped density to bulk density of microspheres is known as Hausner's ratio, and it can be used to forecast how microspheres would flow. The presence of free-flowing microspheres is indicated by a low Hausner's ratio of 1.2.

Hausner's ratio= bulk density- tapped density

- **Angle of repose**

A heap of microspheres can achieve the highest angle to the horizontal. One of the approaches for estimating the angle of repose is to use a set height cone and a fixed base cone.

Angle of repose $\theta = \tan^{-1}h/r$

r= the radius of the base of the heap of a microspheres

h= height of the heap of microspheres

- **Zeta Potential**

The polyelectrolyte shell is formed by combining different atomic loads of chitosan in the W2 stage, and the succeeding particles are determined by Zeta potential estimate.⁴⁶

APPLICATIONS OF MICROSPHERES^{49, 50}

- **Microspheres in vaccine delivery**

The following requirements must be met by an ideal vaccine: effectiveness, safety, convenience of use, and affordability.

Biodegradable vaccine delivery systems for vaccines given via the parental route may be able to overcome the drawbacks of traditional vaccines.

- Improved antigenicity by adjuvant action
- Modulation of antigen release
- Stabilization of antigen.

• Targeting using micro particulate carriers

The concept of site-specific medication delivery, often known as targeting, is a well-established doctrine that is gaining traction. The ability of a medication to reach and interact with its target receptors determines its therapeutic effectiveness. At the heart of pharmacological action, which is mediated via a carrier system, is the ability to leave the pool in a repeatable, effective, and exact manner.

• Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies directed against microspheres are known as immune microspheres. This is a method of attaining site-specific targeting. Monoclonal antibodies are highly selective molecules. Mabs can be directly linked to the microspheres thanks to covalent binding. Mabs can be connected to microspheres using any of the ways described below.

- Non-specific adsorption and specific adsorption
- Direct coupling
- Coupling via reagents

• Chemoembolisation

Chemoembolisation is an endovascular treatment that involves targeted tumor artery embolization and local delivery of a chemotherapeutic medication at the same time or later.

• Imaging

The particle size range of microspheres is an important consideration when imaging specific regions with radio-labeled microspheres. The particle is caught in the lungs capillary bed after being introduced intravenously outside of the portal vein. This phenomenon is used to create scintigraphic imaging of tumor masses in the lungs using tagged human serum albumin microspheres.

• Topical porous microspheres

Micro sponges are porous microspheres with an interconnected network of voids ranging in size from 5 to 300µm. The topical carry system is made up of micro sponges that can entrap a wide range of active compounds like emollients, perfumes, and essential oils, among others.

• Medical Applications

Microspheres are utilized in vaccine administration for diseases such as hepatitis, influenza, pertussis, diphtheria, and many others, and have a wide range of medical applications, including long-term release of proteins, hormones, and peptides. For DNA plasmid and insulin delivery therapy, microspheres are the most effective. Through intra arterial/intravenous treatments, microspheres will be used to target leaky tumor arteries passively and tumor cells and antigens dynamically.

• Radioactive Microspheres Applications

It can be utilized for radio embolization of liver and spleen tumors, as well as radio synovectomy of rheumatic joints,

local radiotherapy, and interactivity care. In a deep vein thrombosis, the liver, spleen, bone marrow, lung, and even the thrombus can be imaged.

• Other Application

Fluorescent microspheres can be employed in membrane-based flow cytometry, cell biology, and fluorescent immunosorbent assays, among other things. Yttrium 90 can be used for both primary and pre-transplant management of HCC, according to promising data.

• Colonic Drug Delivery

Chitosan, for example, has been utilized to transport insulin to the colon in a targeted manner.

• Vaginal Drug Delivery

Chitosan, Gelatin, and PLGA are polymers with thioglycolic acid added to the main amino groups. They're commonly utilized to treat genitourinary tract mycotic infections.

• Targeting by using Micro Particulate Carriers

The concept of targeting is a well-established dogma that has recently gotten a lot of attention. The ability of a medication to reach and engage with receptors determines its reaction. Pellets, such as microcrystalline cellulose (MCC) and chitosan, are typically employed, which can be manufactured utilizing extrusion/spherization technique.

ACKNOWLEDGEMENT:

I am very thankful to Principal, Shivalik College of pharmacy, Nangal, Punjab and my guide Dr. J.S Dua sir for their valuable guidance. I am also thankful to my colleagues for their time to time support.

CONCLUSION

Because of its enhanced patient enforcement and targeting accuracy, microspheres are a safer drug administration system than other types of drug delivery systems. Because of its benefits of continuous and controlled-release action, increased stability, lower dose frequency, dissolving rate, and bioavailability, the microspheres drug delivery system is the most commonly used drug delivery system. Microspheres drug delivery is a safe and effective drug delivery technique that can be utilized for a range of applications including precision medication targeting, floating and vaccination distribution, and more. The methods for preparing and evaluating microspheres are widely available and effective. Microspheres are used to imaging malignancies, identify bimolecular interactions, and cure cancer, among other things. As a result, microspheres will become increasingly essential in medical research in the future.

REFERENCES:

1. Choudhary KPR, Yarraguntla SR, Mucoadhesive microsphere for controlled drug delivery. *Biological and Pharmaceutical Bulletin* 2004; 1717-24. <https://doi.org/10.1248/bpb.27.1717>
2. Inada A, Oue T, Yamashita, Yamasaki M, Oshima T and Matsuyama H. Development of highly water-dispersible complexes between coenzyme Q10 and protein hydrolysates. *European Journal of Pharmaceutical Sciences*. 2019; 136. <https://doi.org/10.1016/j.ejps.2019.05.014>
3. Chaudhary A, Jadhav KR, Kadam VJ. An overview: Microspheres as a nasal drug delivery system. *International Journal of Pharmaceutical Sciences Review and Research*. 2010Nov; 5[1].
4. Jain NK *Controlled and Novel drug delivery*; CBS Publishers New Delhi, India; 04 Edition. 2004; 236-237, 21.

5. Venkatesan P, Manavalan R, Valliappan K. Microencapsulation: a vital technique in novel drug delivery system. *Journal of Pharmaceutical Sciences and Research*. 2009 Dec 1; 1(4):26-35.
6. Ramteke KH, Jadhav VB, Dhole SN. Microspheres; as carriers used for novel drug delivery system. *IOSR Journal of Pharmacy* 2012 Jul; 2(4):44-8. <https://doi.org/10.9790/3013-24204448>
7. Chein YM. *Novel Drug Delivery System*, second edition, revised & expanded, Marcel Dekker, Inc, New York 1992.
8. Sachan AK, Gupta A, Arora M. Formulation & characterization of nanostructured lipid carrier (NLC) based gel for topical delivery of etoricoxib, *Journal of drug delivery and therapeutics* 2016; 6(2):2-13. <https://doi.org/10.22270/jddt.v6i2.1222>
9. Vyas SP & Khar RK Targeted and controlled drug delivery novel carrier system, 1st edition CBS Publications and distributors, New Delhi; 2002; 417-418.
10. Das M.K, Ahmed A.B, Saha D. Microsphere a drug delivery system: A review. *Int J Curr Pharma Res*. 2019; 11(4):34-41. <https://doi.org/10.22159/ijcpr.2019v11i4.34941>
11. Rajput S, Agarwal P, Pathak A, Shrivastava N, Baghel R.S A review on microspheres: Method of preparation and evaluation. *World J Pharm PharmaSci*. 2012; 1(1):422-38.
12. Verma NK, Alam G, Vishwakarma DK, Mishra JN, Khan WU, Singh AP, Roshan A. Recent Advances in Microspheres Technology for Drug Delivery. *International Journal of pharmaceutical sciences and nanotechnology*. 2015 May 31; 8(2):2799-813. <https://doi.org/10.37285/ijpsn.2015.8.2.2>
13. Saini S, Kumar S, Choudhary M, Nitesh, Budhwar V. Microspheres as controlled drug delivery system: An updated review. *Int J Pharma Sci Res*. 2018; 9(5):1760-68.
14. Kreuter J, Nefzger M, Liehl E, Czok R, Voges R. Microspheres-A Novel approach in Drug Delivery system. *Journal of Pharmaceutical sciences*. 1983; 72:1146. <https://doi.org/10.1002/jps.2600721009>
15. Singh C, Purohit S, Singh M, Pandey BL. Design and evaluation of microspheres :A Review *Journal of drug delivery research*. 2013; 2(2):18-27.
16. Midha K, Nagpal M, and Arora S. Microspheres: a recent update. *International journal of Recent Scientific Research*. 2015; Jul: 5859-67.
17. Sipai AB, Vandanayadav M, Mamatha Y, Prasanth VV. Mucoadhesive Microspheres An overview. *American Journal of Pharmaceutical Research*. 2012; 2(1):237-58.
18. Liu G, Yang H, Zhou J. Preparation of magnetic microsphere from water-in-oil emulsion stabilized by block copolymer dispersant, *Biomacromolecules*. 2005; 6:1280-1288. <https://doi.org/10.1021/bm049316f>
19. Shanthy N.C, Gupta R, Mahato K.A. Traditional and Emerging Applications of Microspheres: A Review, *International Journal of Pharm Tech Research*. 2010; 2(1):675-681.
20. Najmudin M, Ahmed A, Shelar S, Patel V, Khan T. Floating Microspheres of Ketoprofen: Formulation and Evaluation *International Journal of Pharmacy and pharmaceutical sciences*. 2010; 2(2):83-87.
21. Hafeli U. Physics and chemistry Basic of Biotechnology. Focus on biotechnology. Review. *Radioactive Microspheres for Medical Application*. 2002; 7:213-48. https://doi.org/10.1007/0-306-46891-3_9
22. Yadav AV, Mote HH. Development of biodegradable starch Microspheres for Intranasal Delivery, *Indian Journal of pharmaceutical sciences* 2008; 70(2):170-174. <https://doi.org/10.4103/0250-474X.41450>
23. Saralidze K, Leo H, Koole, Menno L, Knetsch W. Polymeric Microspheres for Medical Applications, *Materials*. 2010; 3:3357-3564. <https://doi.org/10.3390/ma3063537>
24. Trivedi P, Vermal, Garud N, Preparation and Characterization of Aclofenac Microspheres, *Asian Journal of pharmaceuticals* 2008; 2(2):110-115. <https://doi.org/10.4103/0973-8398.42498>
25. Nikam VK, Gudsoorkar VR, Hiremath SN, Dolas RT, Kashid VA. Microspheres-A Novel drug delivery system: An overview; *International Journal of pharmaceutical and chemical sciences*. 2012; 1:113-128.
26. Alagusundaram M, Madhu C, Umashankari K, Attuluri B, Lavanya C, Ramakant S. Microspheres: As novel drug delivery system *International Journal of chem. Tech Research*. 2009; 1(3):526-534.
27. Sinha VR, Singla AK, Wadhawan S, Kaushik R, Kumria R, Bansal K, Dhawan S. Chitosan microspheres as potential carrier for drugs. *International Journal of pharmaceuticals*. 200; 274:1-33. <https://doi.org/10.1016/j.ijpharm.2003.12.026>
28. Jayaprakash S, Halith S M, Mohamed Firthouse P U, Kulaturanpili K, Abhijith, Nagarajan M. Preparation and evaluation of biodegradable microspheres of methotrexate. *Asian journal of pharmaceutical science*. 2009; 3:26-9. <https://doi.org/10.4103/0973-8398.49171>
29. Sinha V R, Bansal K, Kaushik R, Kumria R, Trehan A. Poly-Caprolactone microspheres and nanospheres. *International journal of pharmaceuticals*. 2004; 278 1-23. <https://doi.org/10.1016/j.ijpharm.2004.01.044>
30. Kumar A, Jha S, Rawal R, Chauhan PS and Maurya SD. Mucoadhesive microspheres for novel drug delivery system: A review *American Journal of Pharm Tech Research*. 2013; 3(4):197-13.
31. Gurung B.D, Kakar S. An review on microspheres. *Int J Health Clin Res*. 2020; 3(1):11-24.
32. Meena KP, Dangi JS, Samal PK, Naredo KP. Recent advances in microspheres manufacturing technology. *International Journal of pharmacy and technology*. 2011; 3(1):854-855.
33. Kadam NR, Suvarna V. Microspheres: A Brief review. *Asian Journal of Biomedical and Pharmaceutical Sciences*. 2015 Aug 1; 5(47):13. <https://doi.org/10.15272/ajbps.v5i47.713>
34. Thanoo BC, Sunny M, Jayakrishnan A. Cross-linked chitosan microspheres. Preparation and evaluation as a matrix for the controlled release of pharmaceuticals. *Journal of pharmacy and pharmacology*. 1992; 44:283-286. <https://doi.org/10.1111/j.2042-7158.1992.tb03607.x>
35. Parmar H, Bakliwal S, Gujarathi N, Rane B, Pawar S. Different method of formulation and evaluation of mucoadhesive microspheres. *International Journal of Applied Biology and pharmaceutical technology*. 2010; 1(3):1157-1167.
36. Moy AC, Mathew ST, Mattapan R, Prasanth VV. Microspheres -An Overview. *International journal of Pharmaceutical and Biomedical Sciences*. 2011; 2(2):332-338.
37. Alagusundaram M, Chetty MSC, Umashankari K, Badarinath AV, Lavanya C, Ramakant S. Microspheres as a novel drug delivery system-A review. *International Journal of chem. Tech Research*. 2009; 1:526-34.
38. Singh K, Purohit S, Singh M, Pandey B.L. Design and evaluation of microspheres: A review, *Journal of drug development and research* 2013; 2(2):18-27.
39. Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B. Microsphere: A review. *International journal of research in pharmacy and chemistry* 2011; 1(11):84-98.
40. Pavan K. B, Chandiran I.S, Bhavya B, Sindhuri M. Microparticulate drug delivery system: A review. *Indian journal of pharmaceutical science & research*. 2011; 1(1):19-37.
41. Dhakar R.C, Maurya S.D, Sagar B.P.S, Bhagat S, Prajapati S.K, Jain C.P. Variables influencing the drug entrapment efficiency of microspheres: A Pharmaceutical review. *Der Pharmacia Lettre*. 2010; 2(5):102-116.
42. Gogu P.K Preparation & in vivo characterization of spray dried microspheres formulations encapsulating 4-chlorocurcumin.

- Indian Journal of pharmaceutical sciences.2010; 72:346-352. <https://doi.org/10.4103/0250-474X.70481>
43. Alagusundram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery system: A review .International Journal of Chem. Tech Research 2009; 1(3):526-534.
44. Patel NR, Patel DA, Bharadia PD, Pandya V, Modi V. Microspheres as a novel drug delivery .International Journal of pharmacy &life sciences. 2011; 2(8). <https://doi.org/10.4103/0975-8453.86290>
45. Thadanki M, Chadalawada PK, Lavanya P, Umashankar D:Formulation and evaluation of sustained release saxagliptin microspheres by ionotropic gelation method. International Journal of bioassays. International journal of bioassays . 2017; pgn0.5328-5333. <https://doi.org/10.21746/ijbio.2017.03.0010>
46. Dupinder K, Saini S:Variable Effecting Drug Entrapment Efficiency of microspheres :A review, International Research Journal of pharmaceutical and applied Science (IRJPAS); 2013; 3(3):24-28.
47. Sailaja A, Anusha K. Review on microspheres as a drug delivery carrier. International journal of Advances in pharmaceutics 2017; 06(05):96-102.
48. Tarun V, Gupta J. Pharmaceutical Applications of microspheres: An approach for the treatment of various diseases; International journal of pharmaceutical sciences and research, 2017; 8(1):3257-3259.
49. Sharma N, Purwar N, and Gupta PC. Microspheres as drug carriers for controlled drug delivery. A Review .International Journal of pharmaceutical sciences and research 6(11):4579-87