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# Microsphere

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**ABSTRACT:**
Microspheres are small spherical particles with diameters from 1 to 1000µm (or 50nm to 2mm). In some cases, microspheres are also known as micro particles. Microspheres can be produced from several natural and synthetic polymeric materials or even from inorganic. Depending on the method, solid or porous microspheres can be obtained for specific intended applications. They are made from polymeric waxy or other protective materials such as natural, semi synthetic and synthetic polymers. Microsphere received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. In the present study the microspheres were prepared by solvent evaporation method by embedding Liquorice extract. Microspheres were evaluated for particle size and particle size was found to be 7.5µm. Study also includes various novel formulations available in market. Novel herbal drug delivery system targeting various types of diseases/ disorders includes diabetes, Hepatotoxicity antioxidant, cardiovascular disordered, cancer etc.

**Keyword**: Microsphere, Liquorice, Cancer, Evaluation .

## I. INTRODUCTION:

Microspheres are the solid spherical particles ranging from 1 to1000µm in size. Microspheres consist of proteins or synthetic polymers & they are spherical free flowing particles. They are biodegradable in nature.These used usually are polymers. (1)They are classified into three types,

1. Synthetic polymers
2. Semi-synthetic polymers
3. Natural polymers

**1. Synthetic polymer:**

**a) Nonbiodegradable polymers:**Example-Polymethyl methacrylate (PMMA),
Acrolein, Glycidyl methacrylate, Epoxy polymers (2).

b) **Biodegradable Polymers**:ExampleLactides, their glycolides and their Copolymers, Polyalkyl Cyano. Acrylate, Polyanhydrides (3).

**2.Semi Synthetic:**metal anginate derivatives, cellulose derivatives,
Acrylic acid derivatives. Modified Carbohydrates: Poly (acryl)
Dextran, Poly (acryl) starch (4).

**3. Natural polymers:**Natural polymers are obtained from different sources.Example-proteins, carbohydrates and chemically modifiedcarbohydrates. These are given below,

A) **Proteins:**Example-Albumin, Gelatin, andCollagen.

B) **Carbohydrates:**Example- Agarose, Carrageenan, Chitosan10, Starch**.**

C) **Chemically modified carbohydrates:**ExamplePoly dextran11 Polystarch.(5)

Microspheres have two types: microcapsules and micromatrices. Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes called to as micro-particles. These are plays an important role to improve bioavailability of conventional drugs and minimizing side effects (6).

The variety of methods for the manufacturating of microspheres offers ainfinite of opportunities to control the aspects of administration of the pharmaceutical compound. This focus facilitates the precise release of the desired amount of a component at the site of action and its abatement at non-target sites. As well as,this factor guarantees the protection of the compounds before and after administration. Additionally, the initialization of pharmaceutical compounds can be handled by coupling aidentification molecule to the microsphere. The utilization of these changes in pharmacokinetic behavior can lead to an improved therapeutic effect. The focus of any pharmaceutical compound administration system is to provide a therapeutic amount of the compound at the correct site in the body to quickly achieve an effective concentration and then maintain it for a given time. A well-designed modified release system for the

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compound can overcome some of the complications of conventional therapy and better the therapeutic regulation, thus improving the patient's quality of life (7)

**Advantages of Microspheres:**

1. Microspheres particle size reduction, enhance the solubility of the poorly soluble drug.
2. These are providesconstant and prolonged therapeutic effect.
3. Provide constant drug concentration in blood thereby enhance patent compliance.
4. Decrease the dose and toxicity.
5. It is use to protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery.
6. Reduce the dosing frequency and thereby improve the patient compliance.
7. Better drug utilization will better the bioavailability and decrease the incidence or intensity of adverse effects.
8. Microspheres use to protect the GIT from irritant effects of the drug.
9. In biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
10. Controlled release delivery biodegradable Microspheres are used to control drug release rates therebyreducing toxic side effects and also decrease theproblems of repeated injections
11. The microspheres are taste and odor masking.
12. These are conversion of oils and other liquids to solids for easy ofhandling.
13. These are protection of drugs against themoisture, light etc.
14. These are improvement of flow of powders.
15. These are helps in the dispersion of water-insoluble Substances in aqueous media.(8)

**Disadvantages of Microspheres:**

1. The changed releases from the formulations.
2. The release rate of the regulated dose process of release which varies from a number of factors like diet and transfer levels through gut.
3. Variations in rate of discharge from one dosage to the next.
4. Controlled release formulations typically have a higher dose load and so any lack of quality of the release properties of the drug substance can contribute to
5. These are potentially dangerous.
6. These dosing types must not be broken or chewed.(9)
7. The fate of polymer matrix and its effect on the environment.
8. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
9. These reproducibility is less.(10)

**Characteristics of microspheres**

**Microspheres property: (11)**

| Sr.No | Property | Consideration |
|---|---|---|
| 1 | Size Diameter | Uniformity/distribution |
| 2 | Composition | Density, Refractive index, Hydrophobicity/ Hydrophilicity |
| 3 | Surface Chemistry | Reactive group level of functionalization charge |
| 4 | Special Properties | Visible dye/ flouorophoresuper paramagnetic |

**Ideal properties of microspheres:**

1. The ability to establish reasonably high concentrations of the drug.
2. They have stability of the preparation after synthesis with a clinically acceptable shelf life.
3. They have property to controlled particle size and dispersability in aqueousvehicles for injection.
4. The release of active reagent with a good control over a wide time scale. They are biocompatibility with a controllable biodegradability.
5. Susceptibility to chemical modification (12)

**Type of microspheres:**

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

a) Biodegradable polymeric microspheres
b) Synthetic polymeric microsphere

**1. BioadhesiveMicrospheres:**

Adhesiondefined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal,

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ocular, rectal, nasal etc. can be termed as bioadhesion. These kinds of microspheres show a prolonged residence time at the site of application and causes close contact with the absorption site and produces better therapeutic activity (13).

2. **Magnetic Microspheres:**These microspheresare very much important which limits the drug to the infection site. The maximum amount of freely circulating drug can be replaced by minimum amount of magnetically targeted drug. Magnetic carriers collect magnetic responses to a magnetic field from included materials that are used for magnetic microspheres are chitosan, dextran etc. The various types are therapeutic magnetic microspheres and diagnosticmicrospheres (14).

**Therapeutic MagneticMicrospheres:** These areused to provide chemotherapeutic agent to liver cancer.Proteins and peptides drugs can also be targeted through this system.

**Diagnostic Microspheres:** It used for imaging liver metastases, also can be used to different bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides (14).

3. **Floating microspheres:**The floating types the bulk density is less than the gastric fluid and so remains floating in stomach withoutaffecting gastric emptying rate. The drug is released steady at the desired rate. The system is found to be floating on gastric content and enhances gastric residence and increases change in plasma concentration.This also reduces chances of dose dumping. They produce prolonged therapeutic effect and soreduce dosing frequencies. Eg.Ketoprofen (15).
4. **Radioactive microspheres:** The microspheres of sized 10 to 30 nm are of larger than the capillaries & it gets blocked in the first capillary bed when they come across in radio emobilisation treatment. They are injected tothe arteries that lead to the cancer of interest. These radioactive microspheres deliver the high radiation dose to the targeted areas, without damaging the normal surrounding tissues.From the drug delivery system it differs, as the radio activity is not released from the microspheres but acts from within the radioisotope typical distance & the different kinds of the radioactive microspheres are γ emitters, α emitters & β emitters (16).
5. **Polymeric Microspheres:** These classified as follows biodegradable polymeric microspheres and Synthetic polymeric microspheres.

**a) Biodegradable Polymeric Microspheres:** Thenatural polymers such as starch are used with the concept.The starch is biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers extend the residence time. When they contact with mucous membrane due to its high degree of swelling property with aqueous medium as results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained way. The main disadvantage is, the clinical use drug loading regulation of biodegradable micro-spheres is complex and is difficult to control the drug release. But they provide wide range of application in microsphere based therapy (17).

**b) Synthetic Polymeric Microspheres:** Theseare widely used in clinical application, added that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and show to be safe and biocompatible. The main disadvantage of these microspheres, are tend to move away from injection site and show to potential risk, embolism and further organ injured (18).

**METHOD OF PREPARATION:**

1. Spray Drying.
2. Solvent Extraction.
3. Single emulsion technique.
4. Double emulsion technique.
5. Phase separation coacervation technique.
6. Spray drying and spray congealing.
7. Solvent extraction.

1. **Spray drying:**In this method the polymer dissolved in a suitable volatile organic solvent such as acetone, dichloromethane etc. Drugin the solid form is then dissolved in the polymeric solution under high speed homogenization. This dispersion is then atomized in a stream of hot and dry air in opposite flow that leads to the formation of tiny droplets from which the solvent evaporates immediately leading the development of microspheres before settle down into the below of spray dryer (19).
2. **Solvent Evaporation**: It is one of the most important methods for the preparation of microsphere. This process is mostly used in the liquid manufacturing vehicle. The organic solvent (polymer) and the aqueous protein solution is added.For mixing the material use

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thesonication. For making the solution uniform use process homogenization. Then second aqueous phase emulsifier is added. After that hardening is occur and then harvest it. After harvesting freeze drying technique is used. This is called as lyophilization.It preserves the material by freezing it very quickly and then subjecting it to a vacuum which removes ice. And then microsphere is produce.(20)

3. **Single emulsion method:**Natural polymers aredissolvedin aqueous medium followed by spread in the non-aqueous medium e.g. oil with at the same timecontinuous stirring. The cross linking is achieved by twomethodsby heat or by means of chemical cross linkingagents including glutaraldehyde, formaldehyde, diacid chlorideetc.(21).
4. **Double emulsion Method:** In this method the formation of multiple emulsions or double emulsion of the type w/o/w. It is best suited to the water soluble drugs, proteins, vaccines, peptides. This technic can be utilized with both synthetic & natural polymers. The lipophilic organic continuous phase the aqueous protein solution is spreaded. This protein solution may contain the active components (22).
5. **Phase Separation and Coacervation:** This method planned for produce the reservoir type of the system (to encapsulate water soluble drugs). Some of the preparations are of matrix type, when the drug is hydrophobic in nature.The principle of process is based on the reducing the solubility of the polymer(23).
6. **Spray drying and spray congealing:** In this method polymer dissolved in suitable volatile organic solvent (acetone, chloroform), dissolved in polymer solution under high speed homogenization atomized in stream of hot air and this show to formation of small droplets and then solidifying and form of very smallparticles (24).
7. **Solvent extraction:** The polymer and drug soluble in organic solvent which forms a solution that called aqueous phase and extract this solution with water miscible organic solvent to produce microsphere in aqueous media (24).

**Evaluation parameters of microspheres**

1. **Micrometrics Properties (ParticleSize and Shape):** The mostly used process to see micro-particles are conventional light microscopy (LM), particle size analyzers and scanning electronmicroscopy (SEM) (26).
2. **Density determination:** The density of the microspheres can be measured by using a multi volume pycnometer (27).
3. **Electron spectroscopy for chemical analysis:**By using the electron spectroscopy for chemical analysis (ESCA)determinedthe surface chemistry of the microspheres (28).
4. **Flowproperties:**The flow properties can examined by determining the Carr's compressibility index, Hausner ratio and resting angle of repose. A volumetric cylinder was used to evaluate bulk density and tapped density (29).
5. **Isoelectric Point:** The micro electrophoresis is an apparatus used to measure the microspheres from which the isoelectric point can be evaluated (27).
6. **Fourier Transfom-Infrared Spectroscopy:** FourierTransfom-Infrared Spectroscopy is usedto determine the degradation of the polymeric matrix of the carrier system(30).
7. **Drug entrapment efficiency:** Drug entrapment efficiency can be calculated by,

% Entrapment = Actual content/帽heoretical content x 100. (31)

8. **Swelling Index:** The swelling index of the microsphere was calculated by,

Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) 100. (32)

9. **Angle of contact:** The angle of contact is measured to determine the wetting property of a micro particulate carrier.(33)
10. **Thermal analysis:**These techniques analyse these changes routinely by applying scheduled variants in temperature for heating and cooling, also applying defined atmospheres and pressures (34).
11. **CoulterCounter**:It is gives an absolute particle number per volume unit for various size ranges and is very important in the particle analysis of microparticles for intravenous use.(35)
12. **Drugrelease**:The known amount of drug loaded microspheres is weighed given quantity and suspended in the dialysis tube. The release behaviour of drug from system is tested at 37°C in pH 7.4 phosphate buffer for 12 hours at the rotation speed of 100 RPM. The amount of drug released is estimated by using UV spectrometry or HPLC. (36)
13. **Porosity**: In this parameter the Hg-He and $N_2$ krypton adsorption/desorption method apparatus are used.(37)

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**Application of microspheres**

1. **Ocular delivery:** Ophthalmic delivery systems are used for the glaucoma therapy specially pilocarpine. short time (1 to 3 min) the short elimation half-life of the aqueous eye drops can be extended to prolonged time (15-20 min)using the microspheres. which have the biodegradable properties. For Eg- Poly alkyl cyanoacrylate(38).
2. **Oral drug delivery:** The polymer matrix usually contains diazepam like an oral drug delivery has been evaluated through rabbits. Its showed that even a film consisting of a 1:0.5 drug-polymer combination may have been an effectual dosage form which is similar to commercial tablet formulations. The capacity of polymer to establish films could allow apply in the formulation of film dosage forms, as an option with drug tablets. The pH sensitivity, combined with both the reactions of the main amine groups, start making polymer a particular polymer for oral drug delivery administrations.(39)
3. **Vaccine deliver:** The essential of a vaccine is protection against the microorganism. An ideal vaccine must fulfill the requirement of effective, safety, convenience in application and cost. The aspect of safety and less of adverse reaction is a complex issue. The aspect of safety and the degree of the production of antibody responses are closely related to mode of use. Biodegradable delivery systems for vaccines that are given by Parenteral route may overcome the shortcoming of the conventional vaccines.(40)
4. **Chemotherapy:** One of the applications of the microspheres is possible to application as the carriers for the anti- tumor agents. The increased endocytic activity & the leaky vasculature administrated microspheres. Coating with the soluble polyoxy ethylene the stealth microspheres are manufacture. For cancer chemotherapy the buildup of the non-stealth microspheres in RES [Reticulo Endothelial System] may also be utilized.( 41)
5. **Nasal Drug Delivery:** Polymer based drug delivery systems, such as micro-spheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and expand easily when in contact with the nasal mucosa enhancing the solubility and residence time of the drugs to the nasal route. Eg. Starch, Dextran, Albumin, Chitosan + Gelatin 40(42).
6. **Buccal Drug Delivery:** Polymer is used for buccal delivery because it has muco / bioadhesive properties as well as act as an absorption enhancer. Chitosan, Sodium alginate.(42)
7. **Transdermal drug delivery:** In the transdermal drug delivery polymer has good film-forming characteristics. The release profile from of the devices is impacted by the membrane thickness as well as crosslinking of a film. Chitosan-alginate polyelectrolyte structure has also been prepared in-situ in beads and microspheres for potential uses in packaging, controlled release systems and surgical instruments.(43)

**Material and method:**

Extraction of Liquorice –In this process the Liquorice drug is boiled in a specific volume of water (1:4) for a defined time. Volume is reduced to 1/4 th the original. It is then cooled and filtered.

Procedure-Microsphere prepared by Solvent evaporation method. Weighed amounts of 1.5 ml of extract of Liquorice dissolved in water and chloroform(80:20) .Added 0.5 g HPMC as a polymer in above solution .under stirring at 700 RPM ,add emulsifier tween 20 for 15 min after that increase the stirring up to 1000 rpm .about 1.5h until the formation of microsphere. The resultant microsphere was filtered and then oven dried at 60ºC. Dry powders of microsphere are prepared. (25)

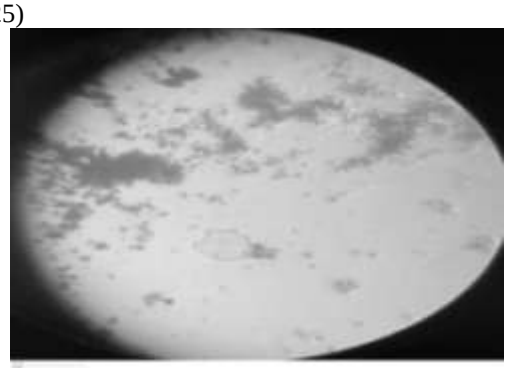

Fig. image of microsphere.

**Observation:**

| Sr. No | Reading |
|---|---|
| 1 | 6.25 |
| 2 | 6.25 |
| 3 | 12.5 |
| 4 | 6.25 |
| 5 | 12.5 |
| 6 | 12.5 |
| 7 | 12.5 |
| 8 | 6.25 |
| 9 | 6.25 |

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| | |
|---|---|
| 10 | 12.5 |

**CALCULATION-**

Eye piece=8, Stage micrometer= 5
Total microspheres size found to be= 75
Total reading taken by=10
Average microspheres size is = Total microspheres size found to be/ Total reading taken by
= 75/10
=7.5µm

## II. CONCLUSION:

Microspheres are having wide application in novel drug delivery system. The microsphere has the drug located centrally within the particle where it is encased within the unique polymeric membrane. By combining various other strategies, in future the microspheres will find the significant & central place in the novel drug delivery particularly in the diagnostics, diseased cell sorting, gene & genetic materials, targeted, safe, effective & specific in vitro delivery & supplements as the miniature versions of the diseased tissues & organ in the body. Preparation of microsphere by using solvent evaporation method is done successfully.

**Result**:

Average size of microspheres found to be 7.5 µm.

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