A Novel Microscopic vesicle: Microsphere: A Recent Review

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Abstract
A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of drug. There are various approaches in delivering a drug to the target site in a controlled release fashion. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. Microspheric drug delivery system has gained enormous attention due to its wide range of application as it covers targeting the drug to particular site to imaging and helping the diagnostic features. Microspheres also has advantage over other dosage forms like aerosol dosage form are used for local delivery of drugs for lungs disease but it has disadvantage of shorter duration of action. So microspheres can be used for sustained release and reducing side effects and hence to achieve better patient compliance. It also has advantage over liposomes, as it is physicochemically more stable. Microspheres are of micron size so they can easily fit into various capillary beds which are also having micron size. It is the reliable means to deliver the drug to the target site with specificity and to maintain the desired concentration at the site of interest without untoward effects. Microsphere is not only for prolonged release, but also for targeting of anticancer drugs to the tumour.

Key words: Microspheres, Novel drug delivery, Therapeutic efficacy, Target site

Introduction
To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Advantages

1. Self-life enhancement by preventing degradative reactions.
2. Safe and convenient handling of toxic materials.
3. Protection of unstable, sensitive materials from their environments prior to use.
4. Better processability (improving solubility, dispersibility, flowability).
5. Enzyme and microorganism immobilization.
6. Controlled and targeted drug delivery.
7. To improve bioavailability
8. Improving patient compliance.
9. To improve the stability.
10. Decreasing dosing frequency.

Limitation
1. The modified release from the formulations.
2. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.

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3. Dosage forms of this kind should not be crushed or chewed.
4. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.
5. Differences in the release rate from one dose to another.

Types of Microspheres

1. **Magnetic microspheres**
   - This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are:
   - **Therapeutic magnetic microspheres**: Are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.
   - **Diagnostic magnetic microspheres**: 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 supramagnetic iron oxides.

2. **Radioactive microspheres**
   - Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So in all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.
   - It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

3. **Bioadhesive microspheres**
   - Adhesion can be defined 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, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

4. **Floating microspheres**
   - In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gasteric contentand increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) given through this form.

5. **Polymeric microspheres**
   - The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

6. **Synthetic polymeric microspheres**
   - The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

7. **Biodegradable polymeric microspheres**
   - Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

Characterization / Evaluation of Microspheres

1. **Particle size analyser**
   - Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of tween 80, to prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer.

2. **X-ray diffraction**
   - Change in crystalinity of drug can be determined by this technique. Microparticles and its individual components were analysed by the help of D & discover (Bruker, Gernony).

3. **Thermal analysis**
   - Thermal analysis of microcapsule and its component can be done by using:
     a. Differential scanning calorimetry (DSC)
b. Thermo gravimetric analysis (TGA)
c. Differential thermometric analysis (DTA)

Accurately the sample was weighed and heated on alumina pan at constant rate of 10°C/min under nitrogen flow of 40 ml/min.

4. **Optical microscopy**
This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and 100 particles were calculated.

5. **Scanning electron microscopy (SEM)**
Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure.

6. **In vitro release:**
The in vitro dissolution studies were carried out in 900 ml of phosphate buffer, pH 7.4, maintained at 37±0.5°C and 100 rpm by using USP type II dissolution test under sink conditions. Accurately weighted samples of the microspheres were added to the dissolution medium and at preset time intervals; 5 ml aliquots were withdrawn and replaced with an equal volume of fresh dissolution medium. After suitable dissolution, the amount of drug released was calculated using standard calibration curve.

7. **Swelling index**
This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique Different solution (100mL) were taken such as (distilled water, buffer solution of pH (1.2, 4.5, 7.4) were taken and alginate microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37°C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.

8. **Entrapment efficiency**
Microspheres containing of drug (5mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

9. **Stability studies:**
Stability studies were carried out as per ICH Guidelines. The microspheres were stored at 40°C ± 2°C/75% RH ± 5% RH for 6 months. The formulations were analyzed for appearance, entrapment efficiency and drug content.

**Applications of Microspheres**
1. Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intraarterial/intravenous application.
2. Gene therapy with DNA plasmids and also delivery of insulin.
3. Release of proteins, hormones and peptides over extended period of time.
4. Tumour targeting with doxorubicin and also treatments of leishmaniasis.
5. Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
6. Radioactive microsphere can be used for radioembolisation of liver and spleen tumours.
7. Radioactive microsphere used for radiosynvectomy of arthritis joint, local radiotherapy, interactivity treatment.
8. Fluorescent microspheres can be used for membrane based technologies for flow cytometry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbert Assay.
10. Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.

**Conclusion**
It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

**References**