A REVIEW ON MICROSPHERE

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ABSTRACT
There are various departments of medicine like cardiology, radiology, gynaecology, and oncology etc, numerous drugs are used and they are delivered by various types of drug delivery system. Among them 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. It also has advantage over various other dosage forms like we know for lungs disease now a days aerolised drugs are used for local delivery of drugs but it has disadvantage of shorter duration of action so for sustained release and reducing side effects and hence to achieve better patient compliance microspheres can be used. It also has advantage over liposomes as it is physicochemically more stable. Moreover the microspheres are of micron size so they can easily fit into various capillary beds which are also having micron size. The purpose of the review is to compile various types of microspheres, different methods to preparation, its applications and also various parameters to evaluate their efficiency.

KEYWORDS: microspheres, characterization of microspheres, drug delivery.

INTRODUCTION
In contrast to drug delivery system, the word novel is searching something out of necessity. The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half life and all these leads to decrease in patient’s compliance.\(^1\) In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effect decreases by lowering peak plasma concentration.\(^2\) The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time. One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system.\(^2\) Microspheres are defined as “Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic...
level. It has a particle size of (1-1000nm).\cite{3} Further, currently available slow release oral dosage forms, such as enteric coated/ double-layer tablets which release the drug for 12-24 hours still result in inefficient systemic delivery of the drug and potential gastrointestinal irritation. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.\cite{4} Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.\cite{5}

**TYPES OF MICROSPHERES**

**Bio adhesive 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 bioadhesion. 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.\cite{6}

**Magnetic microspheres**

This kind of delivery system is very much important which localises 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.\cite{5} The different type 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.\cite{6} Diagnostic 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 particleless supermagnetic iron oxides.\cite{7}

**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 gastric content and 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.[8]

**Radioactive microspheres**

Radio embolisation therapy microspheres sized 10-30 nm are of larger than capillaries and get trapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.[9] 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 kind of radioactive microspheres are α emitters, β emitters, γ emitters.[10]

**Polymeric microspheres**

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

**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[10] 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.[11]

**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.[11] 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.[12]

**METHOD OF PREPERATION**

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by microencapsulation technique.[1] The different methods used for various microspheres preparation depend on particle size, route of administration, duration of drug release and these above
characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc.\[^5\] The various methods of preparations are

**Emulsion solvent evaporation technique**

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2% sodium of pvp as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with deionised water and desiccated at room temperature for 24 hrs.\[^12\] Aceclofenac microspheres were prepared by this technique.

**Emulsion cross linking method**

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40°C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C results in w/o emulsion then further stirring is done for 10 min at 15°C. Thus the produced microspheres were washed respectively three times with acetone and isopropanol which then air dried and dispersed in 5 mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100 mL of 10 mg glycine solution containing 0.1% w/v of tween 80 at 37°C for 10 min to block unreacted glutaraldehyde.\[^18\] Examples for this technique is Gelatin A microspheres.

**Co-acervation method**

Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80°C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.\[^1]\]

Co-acervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propyl isobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin 5 times with continuous stirring.\[^1]\] After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50°C for 4 hr.\[^1]\]

**Spray drying technique**
This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organicsolution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may lose crystalinity due to fast drying process.

**Emulsion-solvent diffusion technique**

In order to improve the residence time in colon floating microparticles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added dropwise to sodium laurylsulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a desiccator at room temperature. The following microparticles were sieved and collected.

**Multiple emulsion method**

Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was then reemulsified in aqueous medium. Under optimized condition discrete microspheres were formed during this phase.

**Ionic gelation**

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

**Hydroxyl appetite (HAP) microspheres in sphere morphology**

This was used to prepare microspheres with peculiar spheres in sphere morphologymicrospheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and...
appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules. This prevented the droplets from co-solvency and helped them to stay individual droplets. While stirring the DCM was slowly evaporated and the droplets solidify individually to become microspheres.\[19\]

CHARACTERIZATION/ EVALUATION OF MICROSPHERES

**Particle size analyser**

Microsphere (50 mg) was suspended in distilled water (5 mL) 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.\[20\]

**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.\[21\]

**Scanning electron microscopy (SEM)**

Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample stub with the help of double sided sticking tape and coated with gold film under reduced pressure.\[22\]

**Swelling index**

This technique was used for characterization of sodium alginate microspheres. Different solutions (100 mL) were taken such as (distilled water, buffer solution of pH 1.2, 4.5, 7.4) were taken and alginate microspheres (100 mg) 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.\[2\]

**Entrapment efficiency**

Microspheres containing of drug (5 mg) 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.\[23\]

**X-ray diffraction**

Change in crystallinity of drug can be determined by this technique. Microparticles and its individual components were analysed by the help of D & discover (Bruker, Germany). Scanning range angle between 60°C - 70°C. Scan speed - 4°/min Scintillation detector Primary silt = 1 mm
Secondary silt = 0.6 mm. [1]

**Thermal analysis**

Thermal analysis of microcapsule and its component can be done by using - Differential scanning calorimetry (DSC) Thermo gravimetric analysis (TGA) 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. [1]

**UV-FTTR (Fourier transform infra red)**

The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR. [24]

**Stability studies**

By placing the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition
2. Room temperature (27+/-2°C)
3. Oven temperature (40+/-2°C)
4. Refrigerator (5°C -8°C).

It was carried out of a 60 days and the drug content of the microsphere was analysed. [15]

**Zeta potential**

The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles were determined by zeta potential measurement. [25]

**APPLICATION OF MICROSPHERES**

**Medical application:** [9]

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, ricin toxoid, diphtheria, birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/intravenous application.
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.
Radioactive microsphere’s application: [7]

- Can be used for radioembolisation of liver and spleen tumours.
- Used for radiosynvectomy of arthritis joint, local radiotherapy, interactivity treatment.
- Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.

Other applications

- Fluorescent microspheres can be used for membrane-based technologies for flow cytometry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.
- Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pretransplant management of HCC with promising results. [25]

Table II: Various types of polymers and their application: [9, 14, 24, 25]

<table>
<thead>
<tr>
<th>POLYMER</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified starch, HPMC, Carbopol 974P</td>
<td>Slower release of drug.</td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
<td>Controlled release for longer period of time.</td>
</tr>
<tr>
<td>PLGA, Chitosan</td>
<td>Vaccine delivery.</td>
</tr>
<tr>
<td>PLA, PLGA, Starchycanoacrylate etc (PEG-) liposomes</td>
<td>Drug delivery without toxic side effects.</td>
</tr>
<tr>
<td>Magnetic polystyrene microspheres</td>
<td>Specific cell labelling.</td>
</tr>
<tr>
<td>Polymer resins such as Agarosepolyacrolne, sephadex</td>
<td>Affinity chromatography.</td>
</tr>
<tr>
<td>Chitosan coated PlGA microspheres</td>
<td>Targeted drug delivery</td>
</tr>
<tr>
<td>Polyvinyl alcohol, polyacrylamide</td>
<td>Adsorption of harmful substances in blood.</td>
</tr>
</tbody>
</table>

FUTURE CHALLENGES

Future challenges of microspheres look bright particularly in the area of medicinal field because of its wide spectrum of application in molecular biology, eg: microsphere based
genotyping platform is used to detect six single nucleotide polymorphism, yttrium-90 microspheres is used to prevent tumour after liver transplantation and it’s advanced way in delivery of vaccines and proteins.

CONCLUSION

It has been observed that microspheres are a better choice of drug delivery system than many other types of drug delivery system because it having the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumours, detecting biomolecular interaction etc. So in future microspheres will have an important role to play in the advancement of medicinal field.

REFERENCES


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