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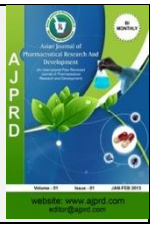

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Review Article

# Microsphere Overview

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## A B S T R A C T

The aim of developing continuous or managed delivery mechanisms has always been to minimise dosage duration, resulting in improved patient compliance and less side effects. Microspheres have been shown to minimise dosage, side effects, administration frequency, and the risk of dose dumping. As a result, patient compliance has improved.Targeted drug delivery mechanisms aim for a specific location in the body to maximise drug concentration in a specific tissue or organ, thus improving the drug's therapeutic effectiveness. Microspheres have promised targeted or managed drug distribution in the body for decades, and have shown to be superior to traditional drug delivery. The goal of this review different aspects of the microparticulate drug delivery system along with types of microspheres and methods of preparation and different applications as targeted or controlled drug delivery system.

**Keywords:** Types of Microsphere, Controlled Drug Release, Therapeutic Efficacy**,** Method of Preparation, Evaluation

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## INTRODUCTION

Microspheres are microscopic spherical objects with diameters ranging from ten millimetres to a thousand millimetres. Microsphere play an important role to improve bioavailability of conventional drugs and minimising side effects. The regulated release of the medication material is the key benefit of using microspheres as a drug delivery mechanism.There are two types of microspheres.

**Microcapsules**:

Microcapsules are those in which entrapped substance is directly surrounded by distinict capsule wall.

**Micrometrics:**

Entrapped material is scattered in the matrix of micromatrices. The controlled release of a drug can be achieved using solid biodegradable microspheres with a drug distributed or dissolved through the particle matrix. The function of a significant role in improving bioavailability and minimising side effects of traditional medicines. The characteristics of microspheres are perfect. Having the ability to integrate.

- After synthesis, the preparation must be stable and have a clinically acceptable shelf life.
- Controlled particle size and dispersion in aqueous injection vehicles.
- Release of active reagent across a large time scale with good control.
- Biocompatibility with a controllable biodegrade ability.
- Chemical modification susceptibility.

**Advantages**

- Microspheres have a healing impact that lasts for a long time.
- Improving the solubility of a poorly soluble drug by reducing particle size.
- Microspheres minimise dosing frequency, resulting in higher patient compliance.
- Protects the drug from enzymatic and photolytic cleavage, making it ideal for protein drug delivery.

- Compared to big polymer implants, biodegradable microspheres have the benefit of not requiring surgical procedures for insertion and removal.

**Disadvantages**

The cost of ingredients and processing for controlled release preparations is significantly greater than for normal formulations.

The controlled release rate of microspheres may vary owing to internal or external factors such as diet, rate of transit through the gut, and mucin turnover rat.

**Criteria for Microsphere Preparation**

- It is possible to incorporate liquid, solid, or gas into one or more polymeric coatings using the micro encapsulation 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.

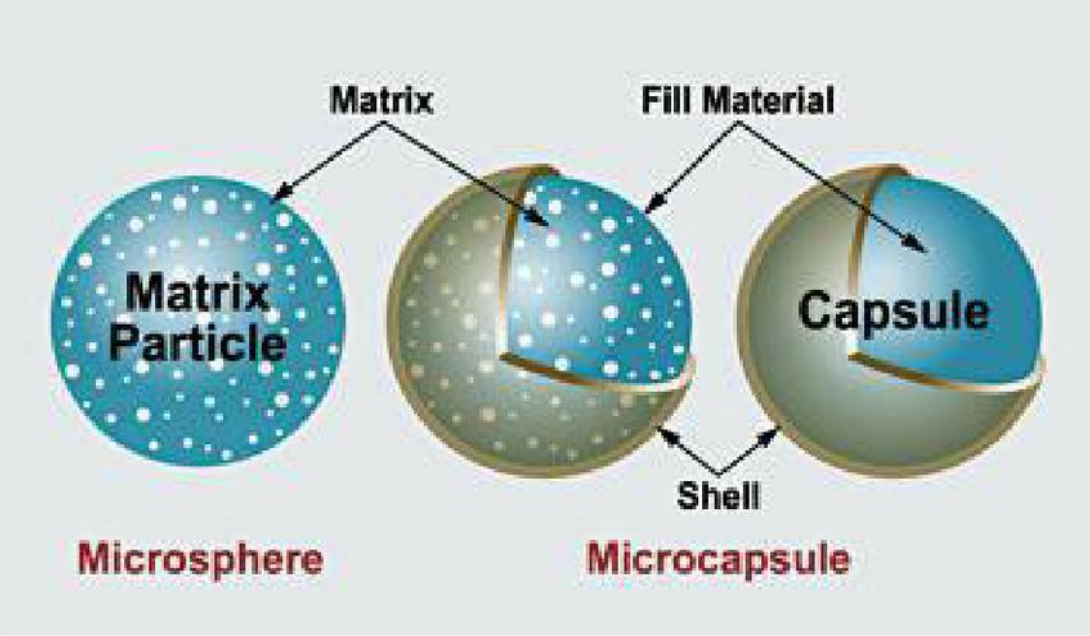



**Figure 1:** Microsphere and Microcapsule

**TYPES OF MICROSPHERES**[4]

**Bioadhesive microspheres:**

Adhesion is defined as the ability of a medication to adhere to a membrane using the adhesive properties of water soluble polymers. Bioadhesion refers to the adherence of a medication delivery device to a mucosal membrane such as the buccal, ocular, rectal, or nasal mucosa. Materials that bind to biological substrates, such as mucosal members, are referred to as "bioadhesion."The ability to create an intimate and sustained contact at the site of administration by adhering Bioadhesive drug delivery devices to mucosal tissue. This longer residence time can lead to better absorption, and when combined with a regulated release of the medication, it can also increase patient compliance by lowering administration frequency.Carrier technology is a smart method to drug delivery that involves attaching the drug to a carrier particle, such as microspheres, nanospheres, liposomes, or nanoparticles, which regulates the drug's release and absorption. Because of their tiny size and high carrier capacity, microspheres are a key component of these particulate drug delivery systems.

**Magnetic microspheres:**

This type of delivery mechanism is critical because it allows the medicine to be delivered to the illness location. A higher amount of freely circulating medication can be substituted with a smaller amount of magnetically focused drug in this situation. Magnetic carriers receive magnetic responses from integrated materials in response to a magnetic field. Chitosan, dextran, and other materials are used to make magnetic microspheres. Therapeutic magnetic microspheres of various kinds are utilised to deliver chemotherapy agents to liver tumours. This method can also target drugs such as proteins and peptides.

**Diagnostic microspheres**:

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate.If the system is floating on stomach content, the medication is released slowly at the optimal pace, which increases gastric residency and plasma concentration fluctuations. It also decreases the risk of striking and dosage dumping, as well as providing a longer-lasting therapeutic impact. This is how the drug (ketoprofen) is administered.

**Radioactive microspheres**:

When radio emobilisation treatment microspheres of 10-30 nm come across, they are bigger than capillaries and are tapped in the first capillary bed. They are injected into the arteries leading to the tumour. As a result, these radioactive microspheres provide a high dosage of radiation to the targeted regions while causing minimal harm to the surrounding tissues.It varies from a medication delivery system in that radioactivity is not discharged from microspheres, but instead acts from inside a radioisotope typical distance, and the various types of radioactive microspheres are emitters, emitters, emitters.

**Mucoadhesive microspheres:**

Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages. E.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio and a much more intimate contact with the mucus layer. A specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. On the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract. Thus, offering the possibilities of localized as well as systemic controlled release of drugs.

**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, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.

**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 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.

**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.

**List of Marketed Microspheres Drug Products**

**Table No 1:**Marketed Microspheres Drug Products

| Drug | Commercial name | Technology |
|---|---|---|
| Risperidone | RisperdalR , Consta | Double emulsion (o/w) |
| Naltrexon | VivitrolR | Double emulsion (o/w) |
| Leuprolide | Leupron DepotR | Double emulsion (o/w/o) |
| Octreotide | SandostatinR LAR | Phase separation |
| Somatropin | NutropinR | Spray drying |
| Triptorelin | Trelstar Depot, DecapeptylR SR | Phase separation |
| Lanreotide | SomatulineR LA | Phase separation |
| Bromocriptine | Parlodel LARTM | Spray drying |
| Minocycline | ArestinR | N/A |

**Methods of Preparation:**[2, 3]

Different techniques have been tried for the formulation of microspheres using different polymers. Some of these are discussed below:

- Emulsion solvent evaporation technique
  - Emulsion cross linking method
  - Coacervation phase separation method
  - Polymerization Techanique
  - Spray drying technique
  - Emulsion-solvent diffusion technique
  - Double emulsion technique
  - Ionic gelation
  - Hydroxyl appetite (HAP) microspheres in sphere morphology

**Emulsion solvent evaporation technique:** [4]

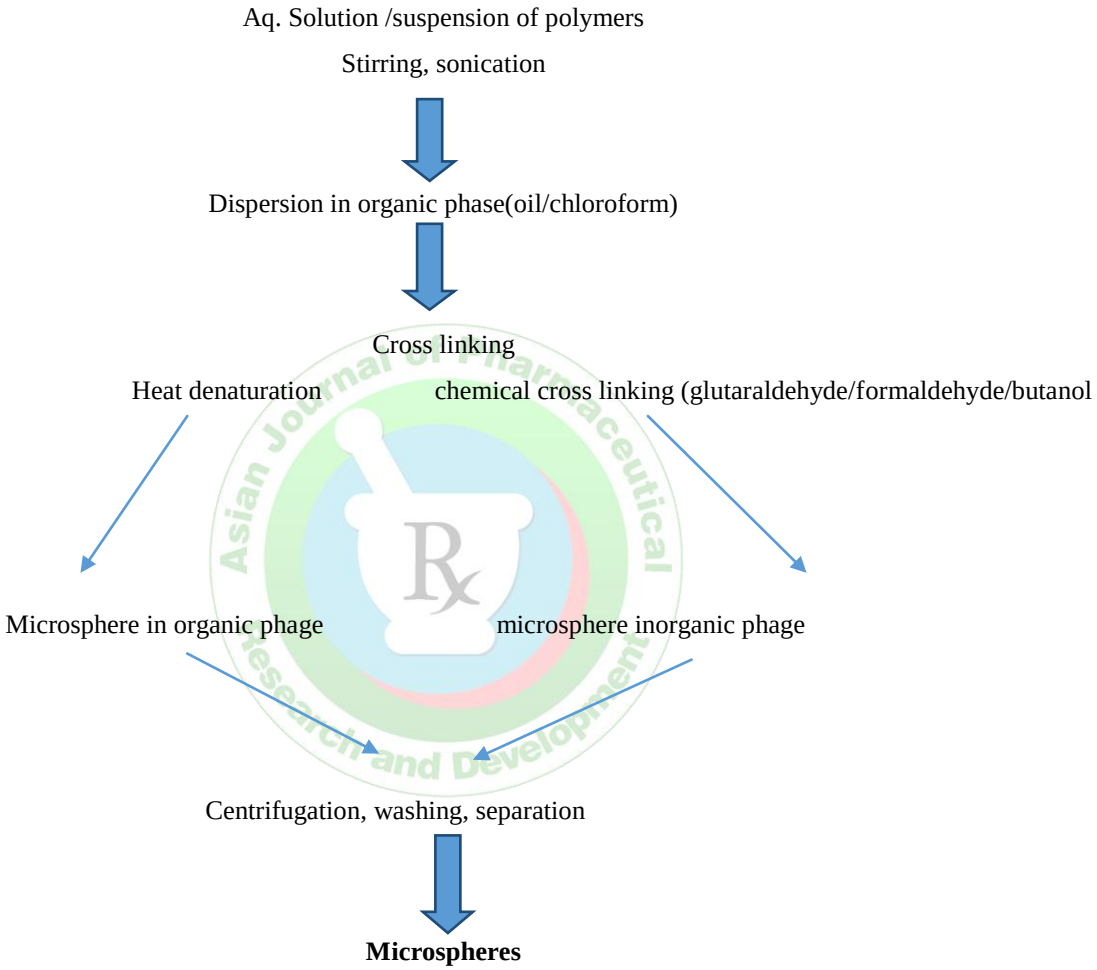



**Figure 1:** Emulsion solvent evaporation technique

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 percent 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 demineralised water and desiccated at room temperature for 24 hrs.

**Emulsion cross linking method:**[4]

In this technique, the drug was dissolved in an aqueous gelation solution that had been preheated at 40°C for 1 hour. The solution was added drop by drop to liquid paraffin while stirring at 1500 rpm for 10 minutes at 35°C, resulting in a w/o emulsion, which was then stirred for another 10 minutes at 15°C.Thus, the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking. Then, it was treated with 100mL of 10mm glyciene solution containing 0.1 percent w/v of tween 80 at 37 °C for 10 min to block un reacted glutaraldehyde.

**Double emulsion technique:**[4,8]

This method involves the formation of multiple emulsions or double emulsion of the type w/o/w & is best suited to the

water soluble drugs, proteins, vaccines, peptides. This method can be used with the both synthetic & natural polymers. In the lipophilic organic continuous phase the aqueous protein solution is dispersed. This protein solution may contain the active constituents.

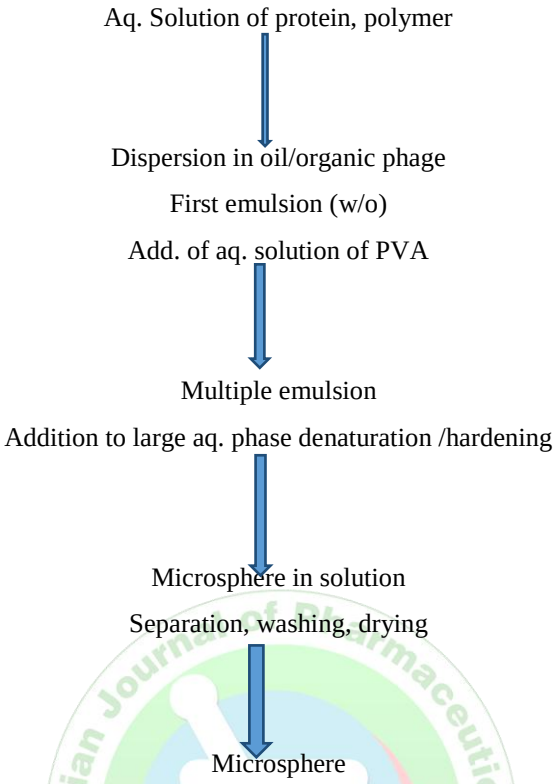



**Figure 2:** Double emulsion technique

**Coacervation method:**[4]

A weighed quantity of ethyl cellulose was dissolved in cyclohexane by heating at 80°C with vigorous stirring. The medication was then coarsely pulverised and added to the aforementioned solution with vigorous stirring, and phase separation was achieved by lowering the temperature and utilising an ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve no.40) to obtain individual microcapsule. Coacervation non solvent addition.The medication is distributed in it and stirring is maintained for 15 minutes after a weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in a closed beaker with magnetic stirring for 6 hours at 500 rpm.Then, with constant stirring, petroleum benzoin is used to separate the phases 14 times. The microcapsules were then rinsed with n-hexane and air dried for 2 hours before being baked at 50°C for 4 hours.

**Solvent Evaporation:**[5]

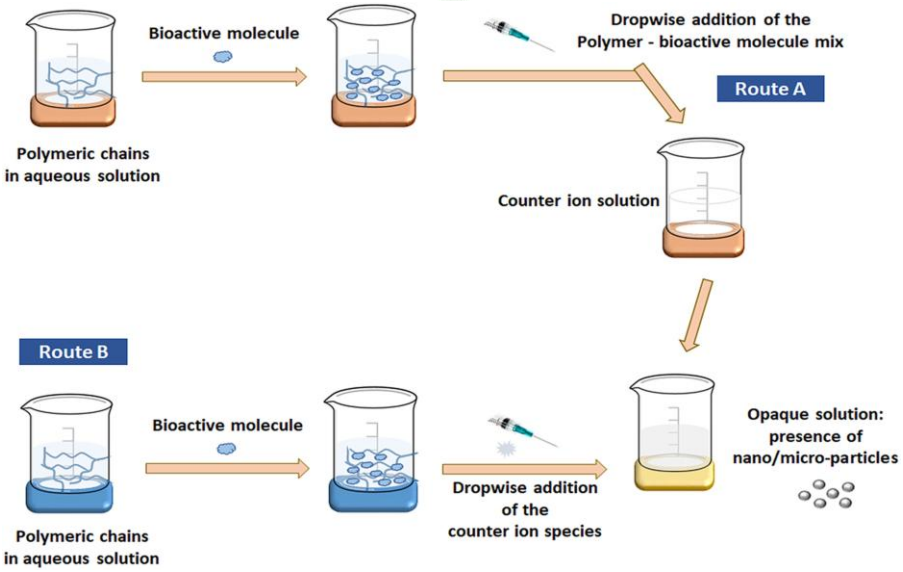
Solvent evaporation method is again similar to spray drying involving the use of volatile organic solvent. This process is the most extensively used for microencapsulation and carried out in a liquid manufacturing vehicle. Here the process consists of two phases. first is the buffered or plain aqueous solution phase of the drug with or without a viscosity building or stabilising agent and second is the organic phase consisting of polymer solution in volatile solvents likes dichloromethane (or ethyl acetate or chloroform). This polymer solution dispersed in a volatile solvent is immiscible with the liquid manufacturing vehicle phaseThe core material that needs to be microencapsulated is first dispersed in the liquid manufacturing vehicle phase with vigorous stirring to form the primary water in oil emulsion. The emulsion mixture is then either added to a large volume of water containing an emulsifier like PVA (polyvinyl alcohol) or PVP (poly vinyl pyrrolidone) to form the multiple emulsions (w/o/w). The double emulsion mixture is heated if necessary to evaporate the volatile solvent under continuous stirring. The polymer shrinks around the core material that may be either water soluble or water insoluble materials. After a particular time when whole of the solvent evaporates the core materials get encapsulated by the polymer solution leaving solid microspheres. These microspheres can then be washed, centrifuged and lyophilized to obtain the free flowing and dried microspheres of appropriate size.

**Spray drying method:**[8]


In this technique, in the volatile organic solvent such as acetone, dichloromethane etc, the polymer is dissolved first. A drug in the solid form is then dispersed in to the polymeric solution with a highspeed homogenization. In the hot air stream this dispersion is then atom. The atomization leads to the form the small droplets from which the solvent evaporates instantly which leads the formation of microspheres in the size range 1 to 100µm. From hot air by the cyclone separator the micro particles are separated while by vacuum drying the trace of solvent is removed. The major advantages of this process is under aseptic conditions there is feasibility of operation.

**Ionic gelation:**[8]

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25 percent (w/v) of diclofenac sodium was added to 1.2 percent (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise 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 filteration 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:**[8]

This was used to prepare microspheres with peculiar spheres in sphere morphology microspheres 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 percent 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-solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

**Solvent extraction:**[8]

For the manufacturing of microparticles the solvent evaporation method is used and it involves the removal of the organic phase by extraction of the non-aqueous solvent. This method involves the water miscible organic solvent which is the isopropanol.

**Polymerization:**

The polymerisation techniques conventionally used for the preparation of the microspheres, are mainly classified as:

1. Normal polymerisation

2. Interfacial polymerisation

**Normal polymerization:**[8]

Normal polymerisation proceeds and is carried out using different techniques as bulk, suspension precipitation, emulsion and micellar polymerisation processes. In bulk polymerisation, a monomer a mixture of monomers alongside with the initiator or catalyst is generally heated to initiate polymerization. Polymer so obtained may be moulded as microspheres.

**Interfacial polymerization:**[8]

It involves the reaction of various monomers at the crossing point between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed, one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase**.**

## EVALUATION OF MICROSPHERES[10, 12, 13]

**Particle size and shape:**

To visualise the microspheres the most widely used procedures are the conventional SEM (scanning electron microscopy) and LM (light microscopy). To determine the shape and outer structure of microspheres both procedures can be used. The light microscopy provides the control over the coating parameters in case of the double walled microspheres. The scanning electron microscopy provides the higher resolution in contrast to the light microscopy. The scanning electron microscopy allows the investigations of the microspheres surfaces and after the particles are cross-sectioned, for the investigation of double walled systems it can be used. For the structure characterization of multiple walled microspheres the conflocal fluorescence microscopy is used. The laser light scattering & multi size coulter counter other than the instrumental methods which can be used for the characterization of the shape, morphology and size of the microspheres.

**Drug Entrapment efficacy:**

Weighed amount of microspheres were dissolved in methanol and sonicated for 15 min the solution was filtered and diluted suitably and the filtrate was analysed for drug concentration by spectrophotometerically by the following equation.

**% Entrapment= (Actual content /theoretical content) × 100**

**Angle of contact:**

To determine the wetting property of the micro particulate carrier the angle of contact is measured. In terms of hydrophobicity or hydrophilicity it determines the nature of the microspheres. This thermodynamic property is specific to the solid and is affected by the presence of the adsorbed component. At the solid/air/water interface the angle of contact is measured. By placing the droplet in the circular cell mounted above objective of inverted microscope the advancing and receding angle of contact are measured. Within a minute of the deposition of the microspheres the contact angle is measured at 20°C.

**% Entrapment Efficiency:**

The encapsulation efficiency was calculated according to the following relationship.

% Entrapment efficiency = AQ/TQ × 100

Where,

AQ= actual amount of drug found in the microspheres,

TQ- Theoretical amount of drug found in the microspheres.

**Swelling studies:**

The accurately weighed dried microspheres were placed in USP dissolution apparatus II containing 900ml, phosphate buffer (pH 6.8) maintained at 37 ± 2 ºC and allowed to swell upto constant weight. The microspheres were removed, blotted with filter paper and changes in weight were measured. The experiments were carried out in triplicate. The degree of swelling (Swelling index) was then calculated from the formula.

Swelling index = (Wg –Wo) × 100 / Wo

Where,

W o = the initial weight of microspheres

Wg = the weight of microspheres at equilibrium swelling in the medium.

**Density determination:**

The density of the microspheres can be measured by using a multi volume pycnometer.

**Electron spectroscopy for chemical analysis:**

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA).

***In vivo* methods:**

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrate at the surface. The most widely used methods include in-vivo studies using animal models, buccal absorption tests and perfusion chambers for studying drug permeability.

***In vitro* methods:**

In vitrodrug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physic-chemically and hydrodynamically defined conditions are necessary, however no standard in vitromethod has yet been developed. Different workers have used apparatus of varying designs and under varying conditions. It depending on the shape and application of the dosage form developed.

**Applications** [3,6,8,12,13]

**Applications of Microparticles in Drug Delivery Systems:**

Microparticulate delivery system advances various applications for drugs that have poor bioavailability. Many pharmaceutical encapsulated products are capturing the market, like aspirin, theophylline and its derivatives, Vitamins, antihypertensive, potassium chloride, progesterone and contraceptive hormone combinations.

**In Vaccine Delivery:**

For an ideal vaccine, it must have capability, convenience and safety in application and its cost must be reasonable. Traditional vaccine's weakness can be overcome by biodegradable delivery systems for vaccines supplied by parenteral route. The prerequisite of vaccine is protection against microorganism or its toxic product.

**Colonic drug delivery:**

Polymer has been used for the specific delivery of insulin to the colon. Eg. Chitosan.

**Vaginal drug delivery:**

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract. Eg. Chitosan, Gelatin, PLGA. Targeting by using microparticulate carriers: Pellets are prepared with polymer by using the extrusion/spheronization technology. Eg. Chitosan, Microcrystalline cellulose.

**In Oral Drug Delivery:**

To administer any drug in the body, oral drug delivery system is the utmost preferable and the most suitable route. Therefore, there are large numbers of controlled or sustained release methods for oral administration of drug. Orally administered drugs generally depend on its solubility and absorption. These drugs which exhibits poor aqueous solubility and low bioavailability microsizing of such drugs leads to increase the oral absorption and bioavailability. Microparticles are having in achieving quick onset of action for drugs that are completely but slowly absorbs and this system is used by many researchers for sustained the release of drug in the stomach or upper GIT.

**Ocular Drug Delivery System:**

For opthalmic application, microspheres are very good drug carriers. The ocular bioavailability of many drugs is increased considerably as compared to traditional aqueous eye drop formulations. Conventionally, drugs having small particle size are more desirable in acceptance by the patients than large particle size drugs. Due to this, microspheres are commonly used for long lasting ocular drug delivery systems, while microparticles having large particle size exhibit slower elimination kinetics from the prepared ophthalmic drug delivery systems of acetazolamide using Eudragit RS 100 and RL 100 by compressed anti-solvent technology. The prepared microparticles exhibited slower release than single drug.

**Intranasal Delivery:**

The intranasal route is exploited for delivery of peptides and proteins. The conventional dosage forms are rapidly cleared from nasal mucosa. The bioadhesive microspheres providing greater control over surface character and release pattern is better alternative to gel dosage formulations. Yadav et al. (2008) prepared domperidone microspheres for intranasal administration by emulsification cross-linking technique using starch and epichlorhydrine as cross-linking agent and showed good mucoadhesive property and swelling behaviour.

**Gastrointestinal Drug Delivery:**

When applied to acidic and neutral media, polymer granules with internal cavities prepared by de acidification are buoyant and provide a regulated release of the drug, e.g. Gelatin, Eudragit, Ethyl cellulose + Carbopol BSA

**Transdermal Drug Delivery:**

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. e.g. Chitosan, Alginate, PLGA

**Topical Porous Microspheres:**

Microsponges are porous microspheres with a plethora of interconnected voids ranging in size from 5 to 300 micrometres. These sponges have the ability to absorb a variety of active ingredients, such as emollients, fragrances, and essential oils, and are used for topical application 40.

**Radioactive Application:**

It may be used to embolize various liver and spleen tumours for radio synvectomy of local radiotherapy, arthritis, imaging of the liver, bone marrow, local radiotherapy, and also imaging of thrombus in deep vein thrombosis**.**

**The microspheres in chemotherapy:**

Microspheres could be used as carriers for anti-tumor agents, which is one of the most promising applications. Microspheres were administered due to increased endocytic activity and a leaky vasculature. By Stealth microspheres are made by coating them with soluble polyoxy ethylene. The aggregation of non-stealth microspheres in the RES Reticulo Endothelial System] may also be used for cancer chemotherapy

**The adjuvant effect for vaccines:**

The adjuvant effect of nanoparticles/microspheres with either matrix entrapped or surface adsorbed vaccines has been demonstrated in several studies on substances or oral administration. The poly methyl methacrylate microspheres containing the influenza antigen induced a strong antibody response, according to Kreuter and colleagues. The use of microspheres to deliver antigens to the mouth may be a clever way to boost IgA (Immunoglobin A) antibody response.

**The microspheres for DNA Delivery:**

Microspheres have recently been used as a delivery vehicle for plasmid DNA transfer, which has resulted in improved plasmid DNA transfer and stability in the bio-environment38. Truong-Le and colleagues developed a novel gene delivery system based on the use of DNA-gelatin nanoparticles/microspheres generated by salt-induced complex coacervation of gelatin and plasmid DNA in 1998.

**Lung Cancer:**

Microspheres are also effective in the treatment of lung carcinoma cells. According to Chao et al. (2013), camptothecin loaded polyethylene glycolated (PEGylated) microparticles extended Camptothecin release, and in-vitro and in-vivo studies revealed a substantial increase in anti-cancer activity.

## CONCLUSION:

Because of their advantages of controlled and sustained release action, reduced dose frequency, and improved stability, bioavailability, and dissolution rate, microspheres drug delivery system is the most common drug delivery system among researchers and scientists. Microspheres may also have some drawbacks, such as dose dumping, poor entrapment and loading performance, polymer toxicity, higher cost, and a limited number of marketed formulations due to difficulties scaling up from lab to industrial scale. Microspheres will play a central and significant role in novel drug delivery in the future by combining various other strategies, especially in diseased cell sorting, diagnostics, gene & genetic materials, secure, targeted, precise, and efficient in vivo delivery, and supplements as miniature versions of diseased organs and tissues in the body.

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