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Review Article

MICROSPHERE AS A NOVEL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT:

The modified release product encompass the dosage form design includes enteric coated tablets (including immediate-release), and extended-release products where drug release is controlled by the dosage form to occur over a period of hours. Concept of targeted delivery is designed for attempting to concentrate the drug in the tissue and reducing the concentration in the remaining tissue of the body. By using the polymer by coupling the drug in the carrier such as microspheres, nanoparticles, liposomes, niosomes, pharmacosomes, aquasomes etc. which modulate the release and absorption characteristics of the drug. Microspheres are characteristically free flowing powders consist of drug and polymers having a particle size ranging from 1-1000 µm. In future by using various technology and strategies in microsphere that find the central place in novel drug delivery.

Keywords: *Targeted delivery, Microspheres, Novel drug delivery*

INTRODUCTION:

A controlled drug delivery system is used to overcome some problems associated with conventional therapy and enhance the therapeutic efficacy of a given drug. 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.[1]

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To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, micro particles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest.

One such approach is using micro spheres as carriers for drugs. Microspheres can be described as small particles (in 1-1000

micrometer size range) for use as carriers of drugs and other therapeutic agents consisting of proteins or synthetic polymers which are biodegradable in nature. The term microspheres describes a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles.[2]

Materials used

Microspheres used usually are polymers. They are classified into two types:

(A) Synthetic Polymers

(B) Natural polymers

(A) Synthetic polymers are divided into two types

Non-biodegradable polymers	**Biodegradable polymers**
• Poly methyl methacrylate Acrolein • Glycidyl methacrylate • Epoxy polymers	• Lactides, Glycolides & their co polymers • Poly alkyl cyano acrylates • Poly anhydrides

(B) Natural polymers obtained from different sources

Carbohydrates	**Chemically modified carbohydrates**	**Proteins**
• Agarose, • Carrageenan, • Chitosan • Starch	• Poly dextran, • Poly starch	• Albumin • Gelatin • Collagen

Advantages of Microspheress over Single Unit Dosage Forms

- Microspheres spread out more uniformly in the GIT, thus avoiding exposure of the mucosa locally to high concentration of drug.
- Microspheres ensure more reproducible drug absorption.
- The risk of dose dumping also seems to be considerably lower than with single unit dosage form.
- Microspheres allow the administration of much smaller dosage than normally required.
- This reduces local irritation when compared to single unit dosage form.
- Drug discharge in the stomach may be hindered and local unwanted effects may be reduced or eliminated.
- Microspheress posses many other advantages such as high bioavailability, rapid kinetic of
- absorption and improvent of patient compliance.
- Microsphere received much attention not only for prolonged release but also for targeting.[3]

Loading of drug in microspheres:

The active components are loaded or entrapped by using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. Drug loading in the microspheres is mainly depends on the method of preparations and formulation variable i.e. drug

or polymer. Maximum loading efficiency can be achieved by incorporating the drug during the time of preparation. But it may be affected by process variables such as processing variable, formulation variable and presence of additives. Processing variables are different for different method of preparation. Release of drug is important aspect from dosage form to achieve safe and effective therapy. Release of drug from microspheres are mainly depends on the polymer used in the preparation as well as nature of drug.[4]

Properties of an Ideal microsphere

Preparation of microspheres should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and
- Susceptibility to chemical modification.

Methods of Preparation

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TYPES OF MICROSPHERE

I. Bioadhesive microspheres

Adhesion means sticking of drug to the membrane by using the sticking property polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal, colon etc can be termed as bio adhesion. The term "bio adhesion" describes materials that bind to biological substrates, such as mucosal membranes. Adhesion of bio adhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Bio adhesive microspheres can be adhere to any mucosal tissue including those found in eye, nasal cavity, urinary, colon and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[6]

II. Muco adhesive microspheres

Muco adhesive microspheres are two approaches one is microspheres consisting entirely of a muccoadhesive polymer and second is coating of microsphere by muccoadhesive polymer. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of muco adhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, *etc.* on the surface of the microspheres.

Vivekananda SRV et al prepared metronidazole muccoadhesive microspheres by ionic gelation method. Formulation F9 was optimised, containing sodium alginate and methyl cellulose show the consistant drug release upto 10 hr.

Gavini E et al prepared metoclopromide muccoadhesive microspheres for nasal administration by spray drying method. Spray dried micro particle had a mean diameter in a 3-10 micron; they show good *in vitro* muccoadhesive property.

Chandrakant VP et al prepared valsartan microsphere using HPMC polymer by spray drying technique. Optimised formulation indicate good mucoadhesion with no severe sign of damage on nasal mucosa.

III. Floating microspheres

In floating types microsphere the delivery system have low density compared to gastric fluid and so they are float on the stomach fluid without affecting gastric emptying rate. The drug is released slowly at the desired rate this show reduce the dosing frequency and reduces chances of striking and dose dumping.
M. Najmuddin et al prepared ketoprofen floating microspheres by solvent evaporation method using ethyl cellulose and HPMC. The result shows that larger particle size longer the floating time. It was concluded that among all formulation F5 shows good release profile in sustained manner over constant period of time. [7]

Rohit BM et al prepared carvedilol floating microsphere by spray drying technique using PEG 6000 and ethyl cellulose. It is conclude that ethyl cellulose and PEG s a release retarding polymer and show the release up to 12 hr.

IV. 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. The different types are Therapeutic magnetic microspheres and diagnostic microsphere for particular diseases. The aim of the specific targeting is to enhance the efficiency of drug delivery & at the same time to reduce the toxicity & side effects.[8]

In the selection of a drug for formulation of magnetic microspheres, following points are taken into consideration:

- The drug is so dangerous or labile that we cannot allow it to circulate freely in the blood stream.
- The agent is so expensive, that we cannot afford to waste 99.9% of it.
- Requires a selective, regional effect to meet localized therapeutic objective.
- Requires an alternative formulation essential to continue treatment in patient whose systemic therapy must be temporarily discontinued due to life threatening toxicity directed at selective organs.

Magnetite is known as the magnetic oxide of iron and is a combination of the two oxides FeO and Fe_2O_3**.** It is also referred to as ferrous ferrite. It shows magnetic property just like pure iron. It is the form of fine particles and has been used for various applications, in transmission radiography, as contrast gastrointestinal agents, in inducing clotting in arteriovenous malformation, as a tracer of blood flow and in radionuclide angiography.[9]

V. Radioactive microspheres

Radio immobilization therapy by microspheres are size 10-30nm that have larger than the capillaries. They are injected to the arteries that lead to tumor of interest. Radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radioactivity 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. It offers new solutions for patients who need drugs delivered directly to tumours, diabetic ulcers and other disease sites.[10]

METHOD OF PREPRATION

- Single Emulsification Technique
- Double Emulsification Technique
- Phase Separation Coacervation Technique
- Spray Drying and Spray Congealing Technique
- Solvent Evaporation
- Ionic gelation
- Hot Melt Microencapsulation

- Ultra sonication technique

1. Single emulsion technique

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, di acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.

2. Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsion or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction a number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction.[11]

3. Co-acervation method

Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80C 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 twicely with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.

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 non solvent. After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50^0C for 4 hr.[3]

4. Spray drying

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high- speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheress in a size range 1-100 µm. Microspheress are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by
vacuum drying. [12]

The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid

using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles.[13, 14]

5. Solvent evaporation

It is the most extensively used method of microencapsulation, first described by Ogawa *et al.* A buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsions (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The microspheres can then be washed, centrifuged and lyophilize to obtain the free flowing and dried microspheres.[15]

7. Hot Melt Microencapsulation

In this technique, the drug is dissolved/ dispersed in the molten lipid/wax like beeswax, spermaceti wax, castor wax, carnauba wax under continuous stirring to form a homogeneous blend. During the emulsion step of microsphere preparation, the temperature is maintained at about 10^0C above the melting point of lipid/wax. A dispersant solution, previously heated to 5^0C above the lipid/wax melting point, is added to the melt with constant stirring to form an o/w emulsion. Hardening of the oily internal phase (containing lipoid/wax and drug) and formation of microspheres is accomplished by pouring twice the emulsion volume of ice-cold water into the emulsion.[16]

8. Ionic gelation technique:

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 drop wise to a solution containing Ca^{+2} /Al^{+3} 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.[17]

9. Hydroxyl appetite (HAP) microspheres in sphere morphology

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% 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.[18]

10. Polymerization techniques:

The polymerization techniques conventionally used for the preparation of the microspheres are mainly
classified as:
I. Normal polymerization
II. Interfacial polymerization. Both are carried out in liquid phase.

I. Normal polymerization:

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes.In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer

or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. B u lk polymerization has an advantage of formation of pure polymers.

II. Interfacial polymerization:

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

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 drop wise to sodium lauryl sulphate (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 dessicator at room temperature. The following microparticles were sieved and collected.[19]

Chaudhary PK et al prepared Metronidazole loaded ethyl cellulose (EC) microspheres were prepared by Novel Quasiemulsification solvent-diffusion method. A solution of EC in acetone containing drug was added to liquid paraffin.[20]

Charecterization/ Evaluation of Microspheres

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.[21]

Optical microscopy

This method was used to determine particle size by using optical microscope. The measurement was done under 10x (40x eye piece and 100x objective) and100 particles were calculated.[22]

Scanning electron microscopy (SEM)

Surface morphology was determined by the method SEM. In this microcapsule were mounted

directly on the SEM sample slub with the help of double sided sticking tape and coated with gold film under reduced pressure.[23]

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^{o}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.[23]

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 analytical method. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.[24]

% Entrapment = Actual content/Theoretical content x 100

X-ray diffraction

Change in crystalinity of drug can be determined by this technique. Microperticles and its individual components were analysed by the help of D & discover. Scanning range angle between $8^0 – 70^0$.

Scan speed - 40/min

Scintillation detector

Primary silt=1mm

Secondary silt=0.6 mm.[25]

In Vitro Methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physicochemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.[26]

Beaker method

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.[27-28]

Interface diffusion system

This method is developed by Dearden & Tomlinson. It consists of four compartments. The compartment A represents the oral cavity, and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing body fluids, contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and
returned to compartment A with a syringe.

Modified Keshary Chien Cell

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 370 C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.[29]

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using rotating elements, paddle and basket Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.[30]

Stability studies

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

- Ambient humid condition
- Room temperature (27+/-2^{0}C)
- Oven temperature (40+/-2^{0}C)
- Refrigerator (5^{0}C -8^{0}C).

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

Applications of Microspheres

- 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, pertusis, ricin toxoid, diphtheria, birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intraarterial/ 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.
- Can be used for radioembolisation of liver and spleen tumours.
- Used for radiosynvectomy of arthiritis joint, local radiotherapy, interactivity treatement.

CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is 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.

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