Formulation and Evaluation of Microspheres: A Review

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***Abstract*: The use of microspheres circumvents all of the disadvantages that are encountered while using powders and granulates. Pharmaceuticals embedded in the Microsphere matrix are released continuously and at a constant rate. Microspheres are free-flowing and roll with practically no friction that means there is no abrasion, guaranteeing a dust-free environment. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm. The range of techniques for the preparation of microspheres offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. The term nano-spheres are often applied to the smaller spheres (sized 10 to 500 nm) to distinguish them from larger microspheres.**

***Keywords*: Microspheres, Applications, Types of microspheres, Method of preparation, Evaluations.**

INTRODUCTION:

Microspheres are small spherical particles, with diameters in the micrometre range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as micro particles Microspheres are defined as "monolithic spheres or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" or can be defined as structure made up of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size less than 200 µm. Materials used Microspheres used usually are polymers. They are classified into two types: [1- 3]

1. Synthetic Polymers
2. Natural polymers

Advantages:

1. Controlled release for longer period of time (like 1-3 months).
2. Frequency is reduced and hence patient compliance is increased.
3. Constant release and hence no peaks and troughs in concentration of drug.
4. Low dose and hence toxic effect is less.

Disadvantages:

1. Intended mainly for parenteral route which causes pain.
2. Forms a depot in tissue or muscle for long period and hence may produce pain when muscle activities are done.
3. Once administered, it is difficult to take back the dose.

APPLICATION IN DRUG DELIVERY SYSTEM:

Pharmaceutical applications in drug delivery system

1. Ophthalmic Drug Delivery
2. Oral drug delivery
3. Gene delivery
4. Nasal drug delivery
5. Intratumoral and local drug delivery
6. Buccal drug delivery

TYPES OF MICROSPHERES:

1. Bio adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

1. Bio adhesive microspheres: [4, 18]

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers.

2. Magnetic microspheres: [5-7]
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.

3. Floating microspheres: [8- 10]
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, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration.

4. Radioactive microspheres: [2, 7]
Radio immobilization therapy micro spheres sized 10-30 nm is 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.

5. Polymeric microspheres:
The different types of polymeric microspheres can be classified as follows:

Biodegradable polymeric microspheres: [13, 14]
Biodegradable microspheres can be prepared from certain synthetic as well as natural polymers. An important requirement of such polymers is that the degradation products should be non-toxic because such products eventually enter circulation or result in tissue deposition. Long term toxicological evolution of the degradation products therefore is important in determining the clinical suitability of such carriers.

Synthetic polymeric microspheres: [15, 17]
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.

METHOD OF PREPARATION:
1. Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction

Spray Drying:
Concept of spray drying technique (Fig. 1) depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray is congealing.

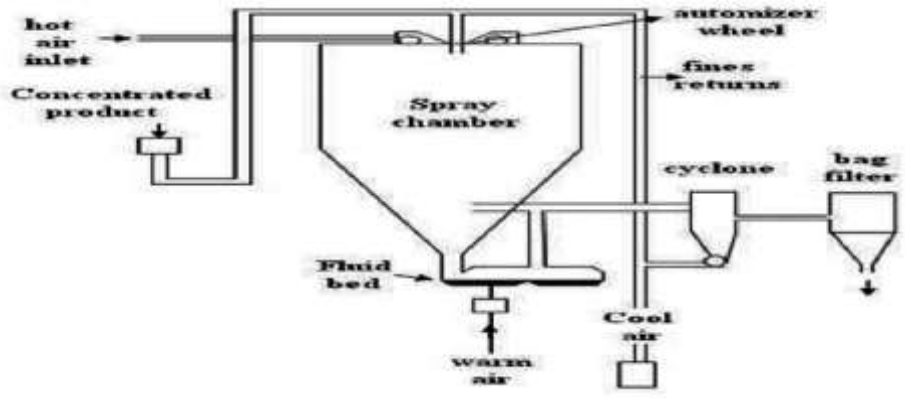

Fig. 1: Spray drying method for preparation of microspheres

Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process where the end product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.

Principle:
Three steps involved in spray drying:
a) Atomization: of a liquid feed change into fine droplets.
b) Mixing: it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

c) Dry: Dried powder is separated from the gas stream and collected.
In this technique 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 spray congealing. Very rapid solvent evaporation, however leads to the formation of porous micro particles [13- 15].

Solvent evaporation method:
For the formation of the emulsion between polymer solution and an immiscible continuous phase in aqueous (o/w) as well as non-aqueous phase (w/o). The suspension of microspheres was filtered, washed and dried. Magnesium stearate was also added for preventing agglomeration as a preventing agent. The results showed that average particle size decreased with increasing amount of magnesium stearate used for microsphere preparation [16]. chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelatine prepared by complex coacervation [17-19].

Single emulsion technique:
There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods [19- 22].
(1) Cross linking by heat: by adding the dispersion into heated oil, but it is unsuitable for the thermo labile drugs.
(2) Chemical cross linking agents: by using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation.

Double emulsion technique:
It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put at constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method [16, 21].

Phase separation coacervation technique:
It is the simple separation of a micro molecular solution into two immiscible liquid phases. In this process, the polymer is solubilised to for a solution. This process is designed for preparing the reservoir type system e.g. encapsulate water soluble drugs i.e. peptides, proteins etc. The principle of coacervation is decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates [18, 19].

Spray drying and spray congealing:
Spray drying technique is also useful for preparing chitosan microsphere [21], In 1999 He et.al. Used formaldehyde as a cross linking and also reported a novel method in which cimetidine and famotidine were entrapped in microspheres prepared by spray drying of multiple emulsions (o/w/o or w/o/w). They found that the release of the drugs from microspheres by this novel method was significantly sustained as compared to those prepared by conventional spray drying or o/w emulsion method. In 1994 Giunchedi et al. was used spray drying used for the preparation of PCL microspheres [13- 22].

Solvent extraction:
In this method preparation of micro particles, involves removal of the organic phase by extraction of the organic solvent. Isopropanol can be used as water miscible organic solvents. By extraction with water, Organic phase is removed. Hardening time of microsphere can be decrease by this method. One variation of the process involves direct addition of the drug or protein to polymer organic solution [16, 18, 24].

EVALUATION OF MICROSPHERES: [20- 24]

Particle size:
The mean particle size of freshly prepared microsphere samples of each batch was determined by laser light scattering (model Mastersizer 2000, Malvern Instruments, Malvern, UK).

Table 1 Sizes obtained from various bead-forming techniques:

Sr. No.	Method of preparation	Size range
1.	Emulsion Polymerization	0.01-1 µm
2.	Dispersion Polymerization	0.5-10 µm
3.	Suspension polymerization	50-500 µm
4.	Sedimentation Polymerization	mm sizes

Surface morphology:
Surface Morphology of E3 batch was studied by using scanning electron microscope (SEM) (Model: JEOL JSM-6360) with an accelerating voltage of 10 kV.

Percent yield:
Microspheres recovered at the end of preparation were weighed and the % yield was calculated by using the following equation.
% Yield= (Practical yield/Theoretical yield) ×100.

Isoelectric Point:
The micro-electrophoresis is an apparatus used to measure the electrophoresis mobility of microspheres from which Isoelectric point can be determined.

Capture Efficiency:
% Drug Loading = (Weight of drug in microspheres/ Weight of microspheres) × 100.
% Entrapment Efficiency = (% Drug loading/ %Theoretical loading) × 100.

Release Studies:
• Rotating paddle apparatus
• Dialysis method

Angle of Contact:
Determine wetting property of micro particulate carrier.

Drug entrapment efficiency:
Drug entrapment efficiency can be calculated using following equation,
% Entrapment = (Actual content/Theoretical content)x 100.

Swelling index:
The swelling index of the microsphere was calculated by using the formula,
Swelling index = (Mass of swollen microspheres: mass of dry microspheres/ Mass of dried microspheres) x 100.

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.

CONCLUSION:

This review mainly emphasis on the microspheres. It is observed that as compared to other novel drug delivery system. The concept of microsphere drug delivery systems offers certain advantages over the conventional drug delivery systems such as controlled and sustained delivery. Apart from that microspheres also allow drug targeting to various systems such as ocular, intranasal, oral and IV route. Microspheres have better choice for drug delivery, particularly in disease d cell sorting, diagnostic of gene, targeted and effective in vivo delivery. Therefore in future microspheres will have an important role to play in the advancement of medicinal field.

CONFLICT OF INTEREST:
The authors declare no conflict of interest.

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