Review Article

Review on Microspheres: A Novel Approach in Drug Delivery System

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Abstract:

A well-designed controlled drug delivery system has the potential to address the limitations of conventional drug therapy and enhance the therapeutic effectiveness of a drug. Microspheres, which are characterized by their particle size being 1-1000 µm, are considered a novel and controlled drug delivery system. The spherical shape of microspheres contributes to their advantageous properties. This review focuses on the utilization of microspheres as a novel drug delivery system. These characteristics can be modified by altering the materials, methods, polymers, or techniques used in the production of microspheres. Microspheres are composed of natural or synthetic polymers. They are utilized in drug delivery systems to achieve prolonged or controlled drug release, enhancing bioavailability, stability, and action at specific sites at predetermined rates. Microspheres can be manufactured using various natural or synthetic materials. Different types of microspheres include bio adhesive, magnetic, floating, radioactive, polymeric, biodegradable polymeric, and synthetic polymeric microspheres. These microspheres are prepared using methods such as spray drying, solvent evaporation, single emulsion technique, double emulsion technique, phase separation coacervation technique, spray drying and spray congealing, solvent extraction, and quasi-emulsion solvent diffusion. Microspheres have a wide range of applications and evaluation parameters.

Keywords: Microsphere, Novel Drug Delivery, Types of Microspheres, Methods of preparation Microspheres, Biodegradable.

Introduction:

A well-designed controlled drug delivery system has the potential to address some of the challenges associated with conventional therapy and improve the effectiveness of a specific drug. In order to achieve maximum therapeutic efficacy, it is necessary to deliver the drug to the target tissue in the optimal dosage and within the appropriate time frame, while minimizing toxicity and side effects. There are various approaches to delivering therapeutic substances in a sustained and controlled manner to the desired site. One such approach involves using microspheres as carriers for drugs.

Microspheres:

Microspheres are solid spherical particles with sizes ranging from 1-1000µm. They are composed of proteins or synthetic polymers and have a spherical shape, allowing them to flow freely. These microspheres are biodegradable in nature and can be used as powders consisting of proteins or synthetic polymers.

There are two types of microspheres:

- Microcapsules
- Micromatrices

Microcapsules have a distinct capsule wall that surrounds the entrapped substance, while micromatrices disperse the entrapped substance throughout the matrix of the microspheres. Solid biodegradable microspheres that incorporate a drug dispersed or dissolved within the particle matrix have the potential for controlled drug release. These microspheres are composed of biodegradable synthetic polymers, waxy materials, or other protective substances [1]. There exist various techniques for delivering a medicinal chemical to the desired location in a controlled and prolonged manner. One such technique involves the utilization of microspheres as carriers for drugs. Within the field of pharmaceutical sciences, the development of innovative delivery systems for the controlled release of medications is an area of great interest. A well-designed controlled drug delivery system has the potential to address the limitations associated with traditional therapy, while simultaneously enhancing the therapeutic effectiveness of a medication. In order to achieve the utmost level of therapeutic efficacy, it becomes imperative to transport the active agent to the target tissue in the optimal dosage and at the appropriate timing, thereby minimizing toxicity and adverse effects. Numerous methods are available for delivering a medicinal chemical to the desired location in a regulated and sustained manner. By attaching bioactive molecules to liposomes, bio-erodible polymers, implants, monoclonal antibodies, and other particulates, precise targeting and site-specific delivery can be achieved. The utilization of microspheres as carriers for

drugs represents one such method. Microspheres can be employed to deliver medications, vaccines, antibiotics, and hormones in a controlled manner [2]. Controlled release systems have proven to be effective in achieving the desired outcome of delivering drugs at a predetermined rate and to a specific target. The limitations of traditional drug delivery methods can be addressed through the use of innovative drug carriers such as microspheres [3].

There exist two distinct categories of microspheres

- reservoir type
- matrix type

Reservoir types involve the entrapment of the drug within a water-insoluble polymer core, which effectively regulates the rate at which the drug is released. Ethylcellulose or polyvinyl acetate are commonly employed polymers in such devices. This particular type is also referred to as microcapsules.

On the other hand, matrix types entail the uniform dispersion of the drug within a polymeric matrix, which serves to control the rate of drug release. Sodium alginate or hydroxypropyl methylcellulose (HPMC) are frequently utilized polymers in matrix types. This type is also known as micromatrices [4].

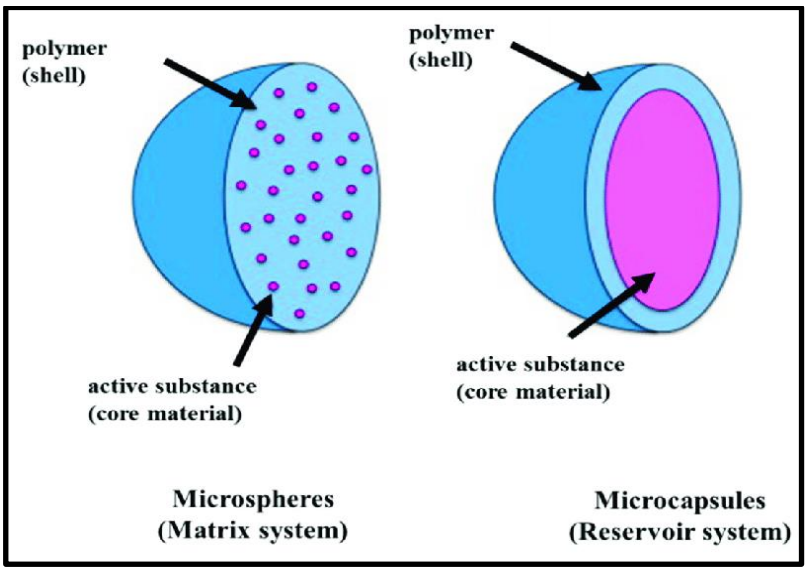


Fig no. 1 structure of microspheres

History:

During the period spanning from the 1940s to the 1960s, the notion of chemical microencapsulation technology emerged as a viable alternative for drug delivery. As the pursuit for more sophisticated systems persisted.The polymer/membrane technology gained prominence in the 1980s and became recognized as a leading approach [5].

Ideal micro particulate carriers:

The selection of appropriate material for preparation of micro particulate carriers containing following key properties

- Extended duration of action
- Drug protection
- Sterilizability
- Water solubility
- Toxicity
- Water dispersibility
- Relative stability
- Bioresorbability [6]

Mechanism of action of microspheres:

The mechanism of microspheres in drug delivery predominantly inhibits the development of a solid dispersion structure resembling a matrix. In this process, the drug may exhibit insolubility within the polymeric matrix and is subsequently released through erosion. Initially, water permeates into the matrix, leading to the elimination of the resulting substance near the device's surface. By establishing a pathway to the surface and dispensing a precise quantity of medication during the initial drug burst, the subsequent osmotic pressure is diminished [7].

Materials used in preparation of microspheres:

The materials utilized in the preparation of microspheres primarily consist of polymers. These polymers can be categorized into two main types:

1. Natural polymers

2. Synthetic polymers

1. Natural polymers are derived from various sources, including carbohydrates, proteins, and chemically modified carbohydrates.

a) Carbohydrates: agarose, carrageenan, chitosan, and starch are commonly used.

b) Proteins:

Albumin, collagen, and gelatin are also utilized.

c) Chemically modified carbohydrates, such as polydextran and polystarch, are additional options.

2.Synthetic polymers, on the other hand, can be further divided into two subcategories:

a) Biodegradable polymers

b) Non-biodegradable polymers

a) Biodegradable polymers include lactides, glycolides, their copolymers, poly anhydrides, and poly alkyl cyanoacrylates.

b) Non-biodegradable polymers encompass poly methyl methacrylate (PMMA), glycidyl methacrylate, acrolein, and epoxy polymers [8].

Various types of polymers and their application:

Table no.1: Types of polymers and their application [9].

Polymer	Mechanism
Modified starch, HPMC, Carbopol 974P	Slower release of drugs.
Ethyl Cellulose	Controlled release for longer period of time
PLGA, Chitosan	Vaccine delivery
Chitosan coated PLGA microspheres	Targeted drug delivery
PolyvinylAlcohol, Polyacrylamide	Adsorption of harmful substances in blood

Properties of Microspheres:

Table 2: property of microspheres [10]

Serial.no.	Properties	Consideration
A	Surface Chemistry	Reactive groups Level of functionalization Charge.
B	Diameter Size	Distribution/Uniformity
C	Composition	Hydrophilicity Nonspecific binding Autofluorescence/Density, Refractive Index, Hydrophobicity
D	Special Properties	Visible dye/fluorophore Superpara-magnetic.

Advantages of microspheres:

A. The reduction in size contributes to an increase in surface area, which can enhance the potency of poorly soluble materials.

B. The provision of a consistent quantity of medication in the body can improve patient compliance.

C. The dosage and associated risks can be reduced.

D. Drug packaging utilizing polymers can prevent enzymatic cleavage of the drug while also facilitating its delivery.

E. A shorter duration of dosing can lead to improved patient compliance.

F. The effective utilization of medications can enhance their bioavailability while reducing the occurrence and severity of harmful side effects.

G. It can help protect the gastrointestinal tract from opioid irritants.

H. The transformation of liquid medication into a solid form can eliminate unpleasant tastes.

I. A reliable means of precisely delivering medication to the target location and sustaining targeted concentrations without undue impact is essential.

J. It can reduce central reactivity related to external stimuli.

K. Degradable microspheres offer advantages over large polymer implants as they do not require invasive medical procedures for implantation and removal.

L. Controlled release delivery utilizing degradable microspheres can regulate drug release, reduce toxicity, and minimize the discomfort associated with repeated injections [11].

Disadvantage of microspheres:

1. The costs associated with the materials and processing of the controlled release preparation are significantly higher compared to standard formulations.
2. The destiny of the polymer matrix and its impact on the environment.
3. The destiny of polymer additives, such as plasticizers, stabilizers, antioxidants, and fillers.
4. Reproducibility is diminished.
5. Process conditions, such as temperature variations, pH changes, solvent addition, and evaporation/agitation, may affect the stability of the core particles to be encapsulated.
6. The environmental consequences of the degradation products of the polymer matrix generated in response to heat, hydrolysis, oxidation, solar radiation, or biological agents [12].

Table no. 3: Marketed formulation of Microspheres: [13]

MARKETED NAME	COMPANY NAME	DISEASE	DRUG
Mesacol tablet	Sunpharma	Ulcerative colitis	Mesalamine
Asacol	Win Medicare pharma	Ulcerative colitis, Crohn's disease	Mesalamine
SAZO	Wallac India	Ulcerative colitis, Crohn's disease	Sulphasalazine
Intazide	Intas, India	Ulcerative colitis,	Balsalazide
COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
CYCLOMINOL	Neol India	Irritable colon syndrome	Dicyclomine
Decapeptyl	Ferring pharmaceuticals	Advanced prostate cancer	Triptorelin
Arestin	OraPharma	Periodontitis	Minocycline
Risperdal	Apollo	Schizophrenia	Risperidone
Nutropin	Genentech	Growth hormone deficiency	Somatropin

Types of microspheres:

1) Bioadhesive microspheres
2) Magnetic microspheres
    A. Therapeutic magnetic microspheres
    B. Diagnostic microspheres
3) Floating microspheres
4) Polymeric Microspheres
    A. Biodegradable polymeric microspheres
    B. Synthetic polymeric microspheres
5) Radioactive microspheres
6) Mucoadhesive microspheres

1) Bio adhesive Microspheres:

Adhesion can be defined as the process by which a drug adheres to a membrane through the utilization of the adhesive properties of water-soluble polymers. The adhesion of a drug delivery device to mucosal membranes, such as buccal, ocular, rectal, nasal, etc., is commonly referred to as bioadhesion. These types of microspheres demonstrate an extended duration of stay at the application site, facilitating close contact with the absorption site and resulting in improved therapeutic efficacy [14]. Carrier technology provides an intelligent approach to drug delivery by attaching the drug to carrier particles such as microspheres, nanospheres, liposomes, nanoparticles, etc., which regulate the release and absorption of the drug. Microspheres play a crucial role in these particulate drug delivery systems due to their small size and efficient carrier capacity [15].

2) Magnetic Microspheres:

This particular delivery system holds significant importance as it enables the localization of drugs to the specific disease site. By utilizing magnetically targeted drugs, a smaller quantity of the drug can replace a larger amount of freely circulating drug. The magnetic carriers used in this system respond to a magnetic field due to the incorporation of materials such as chitosan and dextran into magnetic microspheres. These magnetic microspheres can be classified into therapeutic and diagnostic types.

A) Therapeutic magnetic microspheres:

Therapeutic magnetic microspheres are utilized for the purpose of delivering chemotherapeutic agents specifically to liver tumours. Additionally, this system can effectively target drugs such as proteins and peptides.

B) Diagnostic Microspheres:

Diagnostic microspheres have the capability to facilitate the imaging of liver metastases. Additionally, they possess the ability to differentiate bowel loops from other abdominal structures through the formation of superparamagnetic iron oxide particles at the nanoscale.

3) Floating Microspheres:

Floating microspheres are a type of drug delivery system that possess a lower bulk density than gastric fluid, allowing them to remain buoyant in the stomach without interfering with the rate of gastric emptying. This unique characteristic enables the slow release of the drug at the desired rate when the system is floating on the gastric content. Additionally, it prolongs the residence time in the stomach, leading to increased fluctuation in plasma concentration. Furthermore, it reduces the likelihood of drug striking and dose dumping. Ultimately, this mechanism results in a prolonged therapeutic effect, thereby reducing the frequency of dosing.

4) Radioactive Microspheres:

Radio immobilization therapy microspheres, which measure between 10-30 nm, are larger than capillaries and become trapped in the first capillary bed they encounter. These microspheres are administered via injection into the arteries that lead to the targeted tumor. As a result, the radioactive microspheres deliver a high radiation dose to the intended area without causing damage to the surrounding healthy tissues. This method differs from drug delivery systems, as the radioactivity is not released from the microspheres but instead acts directly on the tumor. From a distance typical of radioisotopes, various types of radioactive microspheres can be observed, including emitters of gamma radiation, beta particles, and alpha particles [14].

5) Polymeric Microspheres:

The various categories of polymeric microspheres can be delineated as biodegradable polymeric microspheres and synthetic polymeric microspheres [15].

A) Biodegradable polymeric microspheres:

Natural polymers, such as starch, are utilized with the intention of their biodegradability, biocompatibility, and bioadhesive properties. The biodegradable nature of these polymers allows for an extended residence time upon contact with mucous membranes, as they possess a high degree of swelling in aqueous mediums, resulting in gel formation. The concentration of the polymer controls the rate and extent of drug release in a sustained manner. However, a major drawback in the clinical use of biodegradable microspheres is the complexity and difficulty in controlling the drug loading efficiency and release pattern.

B) Synthetic polymeric microspheres:

Synthetic polymeric microspheres have gained significant interest in clinical applications, serving as bulking agents, fillers, embolic particles, and drug delivery vehicles. They have been proven to be safe and biocompatible. However, a notable disadvantage of these microspheres is their tendency to migrate away from the injection site, posing potential risks such as embolism and organ damage [14].

6) Mucoadhesive Microspheres:

Mucoadhesive microspheres, ranging in diameter from 1 to 1000 mm, possess the ability to adhere to mucosal tissues. These microspheres can be composed entirely of a mucoadhesive polymer or have an outer coating of it. The coupling of mucoadhesive properties to the microspheres provides additional advantages, such as efficient absorption and enhanced bioavailability of drugs. This is due to the high surface to volume ratio, allowing for a more intimate contact with the mucus layer. Furthermore, specific targeting of drugs to the absorption site can be achieved by anchoring plant lectins, bacterial adhesions, antibodies, and other substances onto the surface of the microspheres. Mucoadhesive microspheres can be customized to adhere to various mucosal tissues, including those in the eye, nasal cavity, urinary tract, and gastrointestinal tract. As a result, they offer the potential for localized as well as systemic controlled release of drugs [15].

Theories of Mucoadhesion:

The phenomenon of bio adhesion occurs through a complex mechanism. Numerous scientists have dedicated their research to bioadhesion, resulting in the proposal of six theories that enhance our comprehension of this phenomenon and can also be applied to explain the mechanism of bioadhesion. These theories are as follows:

(a) Electronic Theory:The electronic theory suggests that the transfer of electrons among the surfaces leads to the formation of an electrical double layer, which generates attractive forces.

(b) Wetting Theory:The wetting theory postulates that when the contact angle of liquids on the substrate surface is lower, there is a greater affinity for the liquid to adhere to the substrate surface.

(c) Adsorption Theory:The adsorption theory proposes that adhesive interaction among the substrate surfaces is facilitated by intermolecular forces, such as hydrogen bonding and Vanderwaal's forces.

(d) Diffusion Theory:The diffusion theory assumes that the polymer chains present on the substrate surfaces diffuse across the adhesive interface, forming a networked structure.

(e) Mechanical theory: The mechanical theory explains that liquid adhesives diffuse into micro cracks and irregularities on the substrate surface, creating an interlocked structure that results in adhesion.

(f) Cohesive Theory: The cohesive theory suggests that the phenomena of bioadhesion primarily occur due to intermolecular interactions among like molecules [16].

Methods of preparation of Microspheres:

The preparation of microspheres must adhere to specific criteria to ensure their efficacy and safety. These criteria include

1.The ability to incorporate high concentrations of the drug.

2.Stability of the preparation after synthesis with a clinically acceptable shelf life.

3.Controlled particle size and dispersibility in aqueous vehicles for injection.

4.Release of active reagent with precise control over a wide time scale.

5.Biocompatibility with controllable biodegradability, and susceptibility to chemical modification [17].

1.Solvent Evaporation method

a) Double emulsion technique

b) Single emulsion technique

2.Coacervation phase separation

3.Spray drying and spray congealing

4.Polymerization

a) Normal polymerization

b) Interfacial polymerization

5. Solvent extraction [18]

6.Quassi Emulsion Solvent Diffusion

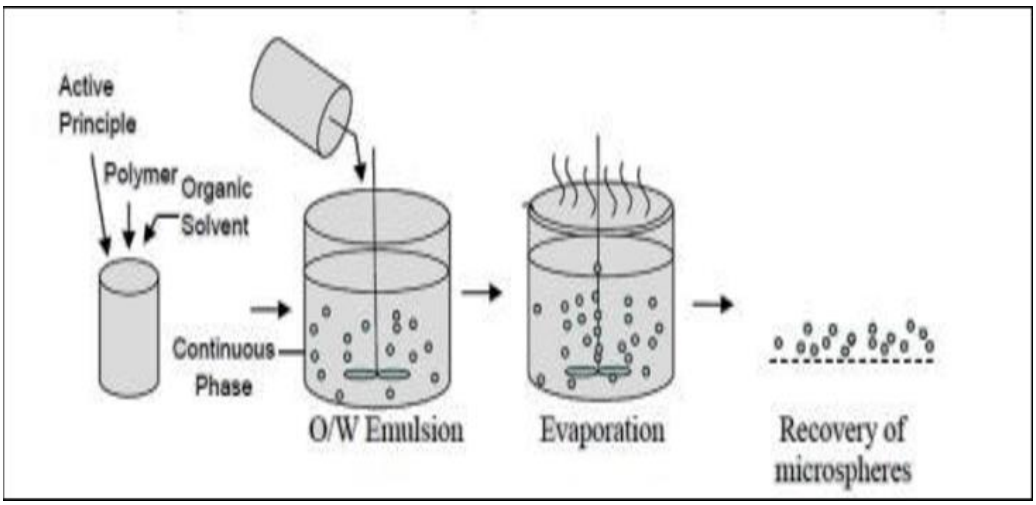
7.Ionic gelation

8.Hydroxyl appetite (HAP) microspheres in sphere morphology [19]

1) Solvent evaporation method:

The aforementioned process is conducted within a liquid manufacturing vehicle phase. The microcapsule coating is dispersed in a volatile solvent that is immiscible with the liquid manufacturing vehicle phase. The core material, which is to be microencapsulated, is either dissolved or dispersed in the coating polymer solution. Through agitation, the core material mixture is dispersed in the liquid manufacturing vehicle phase to achieve the appropriate size of microcapsule. If necessary, the mixture is heated to evaporate the solvent, allowing the polymer to disperse around the core. If the core material is dissolved in the coating polymer solution, matrix-type microcapsules are formed. The core materials may be either water-soluble or water-insoluble. Solvent evaporation involves the formation of an emulsion between the polymer solution and an immiscible continuous phase [19].

Fig. no.2- Solvent evaporation method



a) Double emulsion technique:

The double emulsion technique involves the creation of multiple emulsions, specifically the W/O/W emulsion. This is achieved by pouring the primary W/O emulsion into an aqueous solution of polyvinyl alcohol. The resulting W/O/W emulsion is then stirred continuously for 30 minutes while slowly adding water for another 30 minutes. The microcapsules are then collected through filtration and dried under vacuum. This technique is particularly suitable for water-soluble medicines, peptides, proteins, and vaccines, and can use both natural and synthetic polymers. The aqueous protein solution containing active ingredients is distributed in a continuous organic lipophilic phase. The first emulsion is

formulated through oil/organic phase homogenization/vigorous dispersion, followed by the addition of the aqueous PVA solution to produce the multiple emulsion. After separation, denaturation/hardening, washing, drying, and collection of the microspheres are carried out using the O/W/O multiple emulsion process.

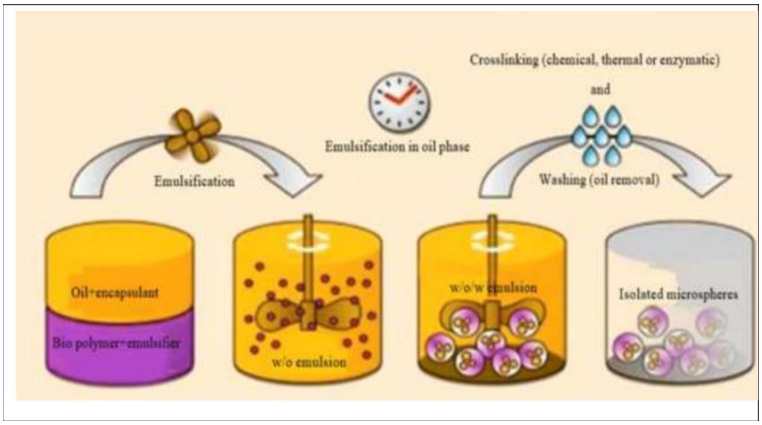


Fig.no.3- Double emulsion technique

b) Single emulsion technique:

This method can be utilized for the preparation of a variety of proteins and carbohydrates. The natural polymers are initially dissolved in an aqueous medium and then dispersed in a non-aqueous medium, which is an oil phase. This marks the beginning of these process. Two methods are employed for the next step of cross-linking, namely:

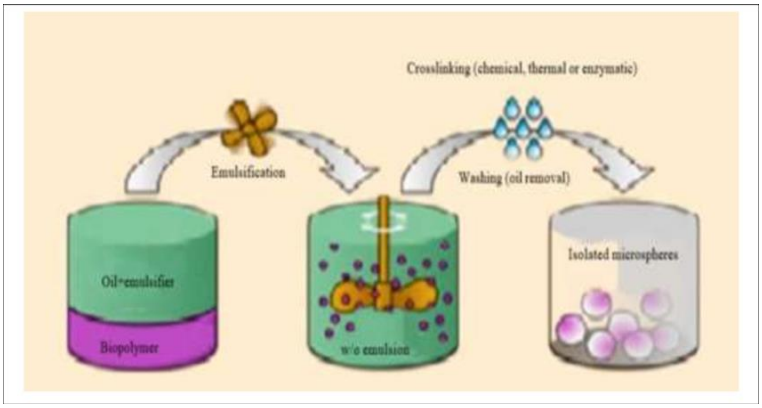


Fig. no. 4- Single emulsion technique

1. Cross-linking by heat:

The dispersion is added to heated oil. However, this method is unsuitable for thermolabile drug

2. Chemical cross-linking agents:

Agents such as Formaldehyde, diacid chloride, glutaraldehyde, etc. are used. However, this method is detrimental to the active ingredients due to undue exposure to chemicals during preparation and subsequent centrifugation, washing, and separation.

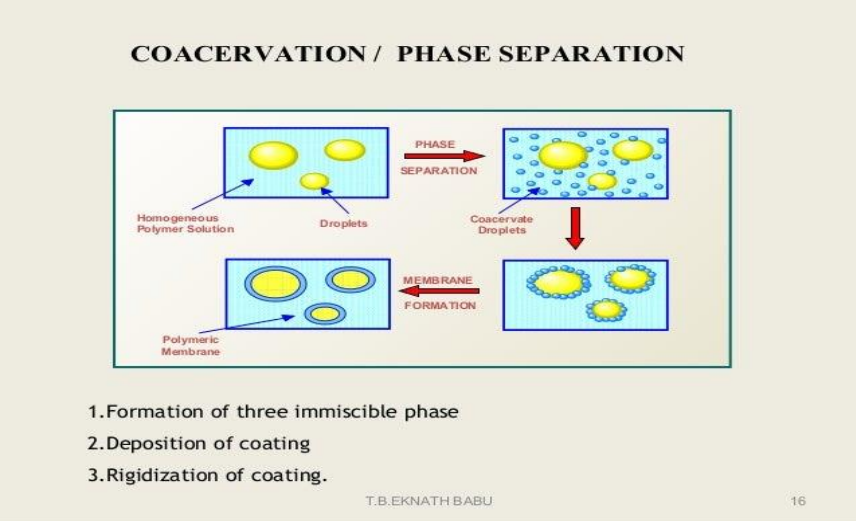
Chitosan solution (in acetic acid) is prepared by applying w/o emulsion to liquid paraffin containing a surfactant. Microspheres are prepared using a 25 percent solution of glutaraldehyde as a cross-linking agent [20].

3) Coacervation phase separation:

This process is based on the principle of decreasing the solubility of the polymer in the organic phase in order to influence the formation of a polymer-rich phase known as coacervates. In this method, the drug particles are dispersed in a solution of the polymer, and an incompatible polymer is introduced to the system. This causes the first polymer to separate into phases and encapsulate the drug particles. The addition of a non-solvent leads to the solidification of the polymer. Poly lactic acid (PLA) microspheres have been prepared using this method, with butadiene serving as the incompatible polymer. The process variables play a crucial role, as the rate at which coacervates are achieved determines the distribution of the polymer film, particle size, and agglomeration of the formed particles. To prevent agglomeration, the suspension must be stirred using an appropriate speed stirrer. As the formation of microspheres begins, the polymer globules formed tend to stick together and form agglomerates. Therefore, the process variables are of utmost importance as they govern

the kinetics of the formed particles, given that there is no defined state of equilibrium attainment [21].

Fig. no. 5- Coacervation phase separation



4) Spray drying and spray congealing:

The above-mentioned techniques have facilitated the desiccation of the aerosol of polymers and pharmaceuticals in the atmosphere. These two procedures, namely spray drying and spray congealing, are contingent upon the elimination of the solvent or the cooling of the solution [22]. In this process, the polymer is dissolved using volatile organic solvents, such as Dichloromethane, acetone, and other solvents are utilized in conjunction with high-speed homogenization to distribute the product in solid form within a polymer solution. Subsequently, the dispersion is atomized within a hot air stream, facilitating the formation of small droplets from which the solvent rapidly evaporates. The resulting micro particles are then separated by hot air using a cyclone separator, and any remaining traces of solvent are eliminated through vacuum drying.

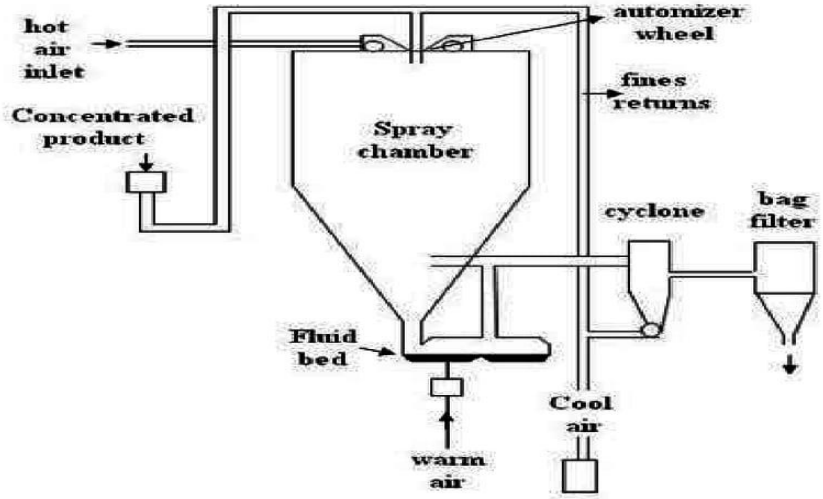


Fig.no.6- Spray drying and spray congealing

Principle:

1. Atomization: The process of converting liquid feed into small droplets.

2. Mixing: This step entails the passage of the liquid droplets through a hot gas stream, resulting in the evaporation of the liquid and the formation of dry particulates.

3. Drying: The dry powder is then separated from the gas stream and collected [23].

4. Polymerization:

The polymerization techniques traditionally utilized for the preparation of microspheres are primarily categorized as follows:

a) Normal polymerization

b) Interfacial polymerization.

Both methods are conducted in a liquid phase.

a) Normal polymerization:

Is performed using various techniques such as bulk, suspension, precipitation, emulsion, and micellar polymerization processes. In **bulk polymerization**, a monomer or a mixture of monomers, along with an initiator or catalyst, is typically heated to initiate polymerization. The resulting polymer can be molded into microspheres, and drug loading can be performed during the polymerization process. **Suspension polymerization**, also known as bead or pearl polymerization, involves heating the monomer or mixture of monomers as droplets dispersed in a continuous aqueous phase. The droplets may also contain an initiator and other additives. **Emulsion polymerization** differs from suspension polymerization in that an initiator is present in the aqueous phase, which later diffuses to the surface of micelles. Bulk polymerization offers the advantage of producing pure polymers, but it is challenging to dissipate the heat generated during the reaction, which can negatively impact thermolabile active ingredients. On the other hand, suspension and emulsion polymerization can be conducted at lower temperatures [24].

b) Interfacial polymerization:

The procedure involves the reaction of various monomers at the interface of two immiscible liquid phases, leading to the creation of a polymer film that efficiently encapsulates the dispersed phase [18].

3. Solvent extraction:

The solvent evaporation technique is employed in the production of microparticles, which entails the elimination of the organic phase through the extraction of the non-aqueous solvent. This process employs a water-miscible organic solvent, specifically isopropanol [25].

4. Quassi Emulsion Solvent Diffusion: The literature has presented a distinctive quasi-emulsion solvent diffusion technique for the production of drug-controlled release microspheres composed of acrylic polymers. The Quassi emulsion solvent diffusion method can be utilized to generate micro

sponges by employing an external phase consisting of polyvinyl alcohol and distilled water. The interior phase is composed of the medication, ethanol, and polymers. Subsequently, the external phase is introduced to the internal phase after its initial formation at a temperature of 60oC. The resulting mixture is then continuously agitated for a duration of 2 hours to form an emulsion. Following filtration, the micro sponges can be extracted [13].

5. Ionic gelation method:

A precisely measured quantity of drug (w/v) was dissolved in a 1.2% (w/v) aqueous solution of sodium alginate. Subsequently, the mixture was continuously stirred until a homogeneous solution was obtained. This solution was then added drop by drop to a previously prepared solution of chitosan in acetic acid, which contained calcium and aluminum ions. The resulting mixture was allowed to undergo internal gelation by keeping it in its original solution for 24 hours. After this period, the mixture was filtered to obtain microspheres. The release of the drug was evaluated at pH 6.4-7.2 [26].

6. Hydroxyl appetite (HAP) microspheres in sphere morphology:

This method was utilized to produce microspheres with unique spherical morphology. The microspheres were prepared through an oil-in-water emulsion, followed by solvent evaporation. Initially, the oil-in-water emulsion was created by dispersing the organic phase (containing Diclofenac sodium at a concentration of 5% w/w of EVA and an appropriate amount of HAP) into the aqueous phase containing a surfactant. The organic phase was dispersed as small droplets, which were surrounded by surfactant molecules. This prevented the droplets from merging and allowed them to remain as individual droplets. While stirring, the DCM solvent was gradually evaporated, causing the droplets to solidify and transform into microspheres [19].

Evaluation of Microspheres:

Characterization:

The characterization of the microparticulate carrier is a crucial phenomenon that aids in the development of a suitable carrier for the delivery of proteins, drugs, or antigens. These microspheres exhibit diverse microstructures that dictate the stability and release of the carrier [27].

Particle size: [28]

The average particle size of recently prepared microsphere samples from each batch was determined using laser light scattering, specifically the Mastersizer 2000 model from Malvern Instruments in Malvern, UK.

Table no. 4 : Particle size

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

Optical microscopy:

Optical microscopy is employed to ascertain particle size through the utilization of an optical microscope, specifically the Meizer OPTIK. The measurement is conducted at a magnification of 450x, achieved by combining a 10x eyepiece with a 45x objective lens. A total of 100 particles are taken into account for calculation purposes.

Scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) is employed to determine surface morphology. In this method, microcapsules are directly mounted onto the SEM sample slab using double-sided adhesive tape. Subsequently, the samples are coated with a layer of gold film under reduced pressure and subjected to analysis [29].

Percentage yield:

The percentage yield was determined by weighing the microspheres obtained at the conclusion of the preparation process and applying the following formula: % Yield = (Practical yield / Theoretical yield) × 100 [28].

Angel of contact:

The angle of contact is utilized for the purpose of assessing the wetting characteristics of a micro particulate carrier. It serves to determine whether the microspheres possess hydrophilic or hydrophobic properties. This thermodynamic attribute is exclusive to solids and is influenced by the presence of the adsorbed component. The angle of contact is measured at the interface of the solid, air, and water. To measure the advancing and receding angles of contact, a droplet is placed within a circular cell that is positioned above the objective of an inverted microscope. The contact angle is measured promptly, within a minute of the deposition of the microspheres, at a temperature of 200°C [27].

Flow properties:

The flow properties can be analyzed by evaluating the Carr's compressibility index, Hausner ratio, and resting angle of repose. To assess bulk density and tapped density, a volumetric cylinder was employed [11].

Density determination:

The density of microspheres can be determined through the utilization of a multi-volume pycnometer [1]. A precisely measured sample contained in a cup is inserted into a multi-volume pycnometer. Helium is introduced into the chamber at a consistent pressure and permitted to expand, leading to a reduction in pressure within the chamber. Two successive readings of the pressure reduction at varying initial pressures are recorded. The volume and, as a result, the density of microsphere carriers are determined from the two pressure readings [15].

Bulk density:

Bulk density is determined by pouring a sample of microspheres with a known weight into a measuring cylinder without tapping and measuring its length. The weight is then divided by the volume to obtain the bulk density. The formula for bulk density is as follows: Bulk density = weight of microspheres / bulk volume.

Tapped density:

Tapped density, on the other hand, is determined by pouring a sample of microspheres with a known weight into a measuring cylinder and thoroughly tapping it before measuring its volume. The weight is then divided by the volume to obtain the tapped density. The formula for tapped density is as follows: Tapped density = weight of microspheres / volume after tapping.

Hausner's ratio:

Hausner's ratio is the ratio of the tapped density to the bulk density of microspheres. It can be used to predict the flow of microspheres. A low Hausner's ratio of less than 1.2 indicates a free-flowing microsphere. The formula for Hausner's ratio is as follows: Hausner's ratio = bulk density - tapped density [20].

Isoelectric point:

The micro electrophoresis technique is employed to quantify the electrophoretic mobility of microspheres, thereby enabling the determination of their isoelectric point [16]. The average velocity at various pH values ranging from 3 to 10 is determined through the measurement of the time taken for particle displacement over a distance of 1 nm [15].

Fourier transform infrared spectroscopy:

The assessment of drug polymer interaction and degradation of microspheres can be conducted through the use of Fourier Transform Infrared Spectroscopy (FTIR) [15]. The utilization of Fourier-transform infrared spectroscopy (FT-IR) indicates degradation of the polymeric structure of the transporter framework. The complete reflectance spectra of the microspheres are estimated through Attenuated Total Reflectance (ATR) rotation. The infrared (IR) beam is transmitted from the ATR cell and typically reflected through the sample to generate IR spectra primarily of the surface material. The ATR-FTIR technique furnishes information regarding the surface morphology of the microspheres, which is dependent on the assembly process and environmental factors [13].

Drug entrapment efficacy:

The efficacy of drug entrapment was assessed by dissolving a measured quantity of microspheres in methanol and subjecting it to sonication for a duration of 15 minutes. The resulting

solution was then filtered and appropriately diluted. The filtrate was subsequently analyzed for drug concentration using a spectrophotometer, employing the following equation:

%Entrapment =(Actual content/Theoretical content) ×100 [26].

Zeta potential:

The zeta potential of microspheres dispersed in a 0.0005M phosphate buffer with a pH of 6.8 was measured using a zeta meter. The movement of 200 microspheres from each formulation was observed in three separate determinations [26].

Swelling index:

This technique is employed to characterize sodium alginate microspheres. Various solutions, including distilled water and buffer solutions of pH 1.2, 4.5, and 7.4, are utilized in this process. Alginate microspheres weighing 100mg are placed in a wire basket and immersed in the aforementioned solutions, allowing for swelling to occur at a temperature of 37°C. The weight variation of the microspheres, from their initial weight to their weight after swelling, is measured periodically by taking their weight and soaking them with filter paper.

X-ray diffraction:

The determination of changes in the crystallinity of a drug can be achieved through the utilization of this technique. The XRD Instrument is employed to analyze micro particles and their individual components. The scanning range angle utilized for this analysis ranges between 80oC and 70oC.

Stability studies:

Stability studies were conducted by placing the microspheres in screw-capped glass containers and storing them under the following conditions: ambient humid condition, room temperature (27+/-2 oC), oven temperature (40+/-2 oC), and refrigerator (5 0+/-8 oC). The study was conducted over a period of 60 days, during which the drug content of the microspheres was analyzed [29].

Possible drugs to Formulate Microspheres:

1. Acetazolamide

2. Cefuroxime sodium

3. Diltiazem hydrochloride

4. Azithromycin

5. Refampicin (lipid microspheres)

6. Amoxicilline

7. Diclofenac sodium [30].

Application of Microspheres in drug delivery system:

1. Multiparticulate Drug Delivery:

The extrusion/spheronization technology was employed in this study. The additive used was micro-crystalline cellulose, which was present in concentrations ranging from 0 to 70%. To extrude the powder mixture, a combination of water and dilute acetic acid was utilized, with varying powder to liquid ratios. The findings of the study revealed that chitosan pellets could be produced with a maximum mass fraction of 50% (m/m) when demineralized water was used as the granulating fluid. However, by employing dilute acetic acid for the granulation step, the mass fraction of chitosan within the pellets could be increased to 100%[31].

2. Microspheres in vaccine delivery system:

The use of microspheres in vaccine delivery is essential for ensuring protection against microorganisms or their toxic products. An ideal vaccine must meet the criteria of efficacy, safety, convenience in application, and cost-effectiveness. The issue of safety and the reduction of adverse reactions is a complex matter that must be addressed. The safety aspect and the level of antibody production are closely linked to the method of administration. Biodegradable delivery systems for vaccines administered through the parenteral route can overcome the limitations of conventional vaccines. There is a growing interest in parenteral carriers (such as subcutaneous, intramuscular, and intradermal) due to their specific advantages, including [15].

1. Enhanced antigenicity through adjuvant-mediated mechanisms
2. Regulation of antigen release for improved efficacy
3. Preservation of antigen stability for enhanced immunogenicity [32].

3. Microspheres in oral drug delivery system:

The capacity of microspheres that encompass polymer to generate films allows for their utilization in the development of film dosage forms, serving as a substitute for pharmaceutical tablets.

The pH sensitivity, in conjunction with the reactivity of the primary amine groups, renders microspheres more appropriate for applications in oral drug delivery. For instance, materials such as Chitosan and Gelatin exhibit these desirable properties [16].

4. Microspheres in nasal drug delivery systems:

The nasal mucosa is considered an optimal location for the delivery of bioadhesive drug systems. Polymer-based drug delivery systems, such as microspheres, liposomes, and gels, have demonstrated favorable bioadhesive properties and readily swell upon contact with the nasal mucosa. This swelling enhances the bioavailability and duration of drug action when administered through the nasal route. Several polymer salts, including chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride, are suitable candidates for the sustained release of vancomycin hydrochloride via the nasal route. Incorporating Diphtheria Toxoid into chitosan microparticles for nasal administration results in a protective systemic and local immune response against Diphtheria Toxoid, accompanied by increased production of IgG antibodies. Nasal formulations have shown significant serum IgG responses comparable to secretory IgA levels, surpassing the effectiveness of parenteral administration of the vaccine [31].

5. Microspheres in occular drug delivery system:

The primary utilization of drug loaded ophthalmic delivery systems is in the treatment of glaucoma, particularly with cholinergic agonists such as pilocarpine16. The limited duration of action of aqueous eye drops, which typically lasts only 1-3 minutes, can be significantly prolonged to 15-20 minutes through the incorporation of microspheres possessing biodegradable properties, such as Poly alkyl cyanoacrylate [33].

6. Microspheres in gene delivery:

The utilization of microspheres in gene delivery is a topic of interest. Recombinant adenoviruses are commonly employed for gene delivery due to their high efficacy and broad cellular targets. However, there in vivo application can result in immune responses and oncogenicity, necessitating repeated gene therapy. In contrast, non-viral gene delivery via microspheres offers sustained gene delivery and several advantages, including stability, ease of preparation, targeted delivery to cells and tissues, low immune response generation, and the possibility of large-scale reproducible production [34].

7. Monoclonal Antibodies:

Monoclonal antibodies that target microspheres are considered to be immune microspheres. This targeting mechanism is utilized to achieve selective targeting to specific sites. Monoclonal antibodies are highly specific molecules that can be attached to microspheres through various methods, including non-specific and specific adsorption, direct coupling, and coupling via reagent [35].

8. Pulmonary Drug delivery system:

The role of polymers in pulmonary drug delivery systems is of great importance due to their bio-adhesive properties, which enhance the bioavailability and residence time of drugs. Microsphere formulations are particularly beneficial in this regard. To this end, microspheres loaded with doxorubicin and paclitaxel were prepared using PLGA, with a mean diameter and mass median aerodynamic diameter of 11.4±2.71µm and 3.52±0.82µm, respectively. Microspheres of this size range facilitate drug aerosolization in the lungs and exhibit superior efficacy in managing lung metastases through sustained release from porous PLGA microspheres containing doxorubicin and paclitaxel [36].

9. Microspheres in chemotherapy:

The utilization of microspheres as carriers for anti-tumor agents is a highly promising application. The microspheres exhibit enhanced endocytic activity and are administered through leaky vasculature. In order to prepare stealth microspheres, they are coated with
soluble polyoxy ethylene. Additionally, the accumulation of non-stealth microspheres in the Reticulo Endothelial System (RES) may be exploited for cancer chemotherapy [37].

Recent Advancement in Microspheres:

1) Significant Applications of Chitosan Polymer:

One important application of the chitosan polymer is its ability to lower cholesterol levels. In a study conducted on mice, it was observed that the serum cholesterol levels in a control group, which was fed a high fat/high cholesterol diet for 3 weeks, increased by approximately 2-fold to 4.3mM. However, when any of these fibers were included at a concentration of 7.5% in the diet, this increase was prevented.

The cholesterol-lowering effect of chitosan can be attributed to several mechanisms.

- It leads to a decrease in cholesterol intake from food.
- It reduces the efficiency of cholesterol absorption.

- It increases the excretion of bile acid and cholesterol through feces [38].

2) Wound healing properties:

The wound healing properties of chitosan were initially documented in 1978. Chitosan acetate films, known for their durability and protective nature, offer the added benefits of excellent oxygen permeability, high water absorptivity, and gradual enzymatic degradation [33].

3) Enhancing Drug Stability:

The utilization of chitosan polymer has been employed to enhance the stability of drugs. This involves the complexation of the drug with chitosan, followed by the creation of a slurry and kneading process lasting 45 minutes until a dough-like mass is formed. This mass is then passed through sieve no.16 to produce granules that exhibit complete stability under various conditions [31].

4) Application in Orthopaedic Patients:

Chitosan, a biopolymer, possesses osteoconductive properties, as well as enhanced wound healing and antimicrobial characteristics. These attributes make it an appealing option for use as a bioactive coating to enhance the integration of orthopedic and craniofacial implant devices with bone tissue. It has been scientifically proven to be effective in promoting tissue growth during repair and accelerating wound healing and bone regeneration [31].

5) In the Cosmetics Industry:

Cosmetic compositions have been developed for the treatment of hair or skin, which are distinguished by their inclusion of new quaternary chitosan derivatives. These derivatives, as exemplified by hair setting lotions, oxidation hair-coloring compositions, hair toning compositions, skin creams, hair treatment compositions, and gel-form products, exhibit substantial benefits, particularly in relation to hair keratin. They have been found to possess hair strengthening and conditioning properties [31].

Future challenges of Microspheres:

1. The development of a novel drug delivery system that incorporates drug molecules with multiple potential activities is being pursued.
2. The design of a drug delivery system that acts locally is being undertaken.
3. A more precise method for enhancing drug responsiveness and increasing sensitivity is being sought.

4. The oral delivery of insulin using body-friendly polymers with improved systemic absorption is being explored.
5. The reduction of costs can lead to increased commercial availability.

Currently, controlled drug delivery technologies have advanced to the point where they can incorporate drugs into newer delivery systems, resulting in maximum therapeutic effectiveness and safety. Numerous pharmaceutical companies are actively engaged in developing new delivery technologies and marketing a variety of products.

In conclusion, significant efforts are being made to design innovative drug delivery systems, enhance drug responsiveness, and reduce costs in order to improve therapeutic outcomes and increase availability in the market [39].

Conclusion:

The review concludes that this particular analysis primarily focuses on microspheres. It is evident that, when compared to other innovative methods of drug delivery, microspheres are a superior option. They are particularly advantageous in disease cell sorting, gene diagnostics, targeted delivery, and effective in vivo administration. Therefore, microspheres are expected to play a significant role in the future advancements of the medicinal field.

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