

The Current Trends in Microspheres: A Review

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Abstract

The idea of targeted drug delivery is to concentrate the treatment in the target tissues while lowering the relative concentration of the drug in the non-target tissues. As a result, the medication is concentrated at the desired location. As a result, the medication has no effect on the tissues nearby. Therefore, by combining the drug with a carrier particle like microspheres, nanoparticles, liposomes, niosomes, etc. that regulates the release and absorption characteristics of the drug, carrier technology offers an intelligent way for drug delivery. Microspheres are naturally biodegradable powders made of proteins or synthetic polymers that flow freely and preferably have a particle size of less than 200 m. If improved, it is the trustworthy method for maintaining the desired concentration at the site of interest without unfavourable effects and reliably delivering the drug to the target site with specificity. Microspheres attracted a lot of interest for their sustained release as well as their ability to direct anti-cancer medications to the tumour. Microspheres will play a key role in novel drug delivery in the future by fusing together a variety of other strategies, especially in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, and efficient in vivo delivery, and supplements as miniature representations of diseased organs and tissues in the body.

Keywords: Microspheres, controlled release, Types of microspheres, Methods of preparation, characterisation of microspheres, applications.

INTRODUCTION

To have the greatest therapeutic efficiency, the drug must be delivered to the target tissue in the ideal quantity and at the proper time, generating the least amount of toxicity and side effects¹. In order to deliver a medicinal chemical to the target region with a continuous regulated release, there are several different methods. Using microspheres as medication carriers is one such strategy. One of the most intriguing areas of study in pharmaceutical sciences is the creation of innovative delivery systems for the controlled release of medications. Some of the drawbacks of traditional therapy can be avoided, and the therapeutic effectiveness of a specific drug can be improved, with the help of a well-designed controlled drug delivery system. The agent must be delivered to the target tissue in the ideal quantity and at the proper time in order to achieve optimum therapeutic efficiency while causing the least amount of toxicity and side effects possible. In order to deliver a medicinal chemical to the target region with a continuous regulated release, there are several different methods. Attaching bioactive molecules to liposomes, bio-erodible polymers, implants, monoclonal antibodies, and other particulates would enable precise targeting and site-specific delivery. Using microspheres as medication carriers is one such strategy. Drugs, vaccinations, antibiotics, and hormones can all be released under regulated conditions using microsphere. For instance, by utilising the properties of microspheres, in addition to the fundamental advantages, the microspheres might offer a greater surface area and have an easier time estimating diffusion and mass transfer behaviour.

As a "monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) as a "structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level," microspheres are defined as either. Microspheres are tiny, spherical particles that typically have dimensions between 1 and 1000 micrometres. Microparticles are another name for microspheres. manmade polymers that degrade naturally and naturally modified materials like starches, gums, proteins, lipids, and waxes. Albumin and gelatin are examples of natural polymers, while poly lactic acid and polyglycolic acid are examples of manmade polymers. The solubility and stabilities of the polymers and drugs, process safety, and economic considerations were taken into account when choosing the solvents used to dissolve the polymeric components². To maintain drug release and lessen or eliminate gastrointestinal tract discomfort, oral microspheres have been used. Multiparticulate delivery techniques also disperse more evenly throughout the digestive system. Compared to single-unit dosage forms such polymeric matrix tablets with no disintegration, this leads to more consistent drug absorption and lessens local discomfort. It is also possible to prevent unwanted intestinal retention of the polymeric substance, which might happen when taking matrix tablets on a regular basis³. Drug release can be modified and delayed via microencapsulation. As a result of their small particle size, they are broadly dispersed throughout the digestive system, improving drug absorption and lowering side effects brought

on by a localised build-up of irritating substances against the gastrointestinal mucosa⁴.

Advantages of Microspheres:

1. The poorly soluble medication becomes more soluble after particle size reduction.
2. The therapeutic impact of microsphere is continuous and lasting.
3. Maintain a steady drug level in the blood to improve patient compliance.
4. Reduce toxicity and dosage.
5. They are excellent for drug distribution because they prevent enzymatic and photolytic cleavage of the medication.
6. Decrease the dosage frequency to increase patient compliance.
7. More effective medicine use will increase bioavailability and lessen the frequency or severity of side effects.
8. Guards against the drug's irritating effects on the GIT.
9. Compared to big polymer implants, biodegradable microspheres offer the benefit of not requiring surgery for installation or removal.
10. Deliveries with controlled release Biodegradable microspheres are utilised to regulate drug release rates, reducing toxicity and the issues associated with repeated injections.
11. Masking of taste and odour.
12. The solidification of oils and other liquids for handling.
13. Drugs that protect the environment (moisture, light etc.).
14. Powder flow has been improved.
15. Assists or facilitates the dispersion of compounds that are water-insoluble in aqueous media⁵.

Disadvantages of Microspheres:

1. Compared to ordinary formulations, the prices of the components and processing for the controlled release preparation are significantly greater.
2. How polymer matrix decays and how it affects the environment.
3. What happens to polymer additives such fillers, stabilisers, antioxidants, and plasticizers.
4. There is less reproducibility.
5. Process variables such as temperature variation, pH changes, solvent addition, and agitation/evaporation may have an impact on the stability of the core particles to be encapsulated.
6. The effects of polymer degradation products on the environment caused by heat, hydrolysis, oxidation, solar radiation, or biological agents⁶.

Ideal Properties of Microspheres:

1. The capability of incorporating medication concentrations that are reasonably high.
2. After synthesis, the preparation must be stable and have a shelf life that is therapeutically acceptable.
3. Particle size and dispersibility in aqueous injection vehicles are controlled.

4. Biocompatibility with regulated biodegradability; Release of active reagent with good control over a broad time scale.
5. Chemical modification susceptibility⁵.

CRITERIA FOR MICROSPHERE PREPARATION

The micro encapsulation technique can be used to include solid, liquid, or gas components into one or more polymeric coverings⁷. Particle size, route of administration, length of drug release, and all aforementioned characteristics connected to rpm, technique of cross-linking, drug of cross-linking, evaporation time, coprecipitation, etc⁸, are all factors that affect the numerous procedures used to prepare distinct microspheres. Preparation of microspheres should satisfy certain criteria⁹:

1. The capability of incorporating medication concentrations that are reasonably high.
2. After synthesis, the preparation must be stable and have a shelf life that is therapeutically acceptable.
3. Particle size and dispersibility in aqueous injection vehicles are controlled.
4. Controlled release of the active reagent over a broad time frame.
5. Susceptibility to chemical manipulation and. Biocompatibility with regulated biodegradability.

Materials Used for the Formulation of Microspheres:

The microspheres used usually are polymers. They are classified into 2 types¹⁰:

- A. Natural polymers
 - B. Synthetic Polymers
- A] Natural polymers:

The natural polymers that are obtained from the different sources like carbohydrates, chemically modified carbohydrates & proteins.

- Carbohydrates: E.g.: Starch, Agarose, Chitosan, Carrageenan.
- Chemically modified carbohydrates: E.g.: Poly search, Poly dextran,
- Proteins: E.g.: Collagen, Albumin & Gelatine¹¹.

B] Synthetic polymers:

Into 2 types the synthetic polymers are divided as

- Biodegradable polymers
- For e.g. Poly anhydrides, Lactides, Poly alkyl cyanoacrylates, Glycolides & their copolymers,

- Non-biodegradable polymers

For e.g. PMMA [Polymethylmethacrylate], Epoxy polymers, Acrolein, Glycidyl methacrylate¹².

Types of Microspheres:

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Diagnostic microspheres
4. Floating microspheres
5. Radioactive microspheres

6. Mucoadhesive microspheres
7. Polymeric microspheres
- i) Biodegradable polymeric microspheres
- ii) Synthetic polymeric microspheres

1. Bioadhesive microspheres

Adhesion is the attaching of a substance to a membrane using the adhesive properties of water soluble polymers. Bioadhesion is the attachment of a medication delivery device to a mucosal membrane, such as the buccal, ocular, rectal, nasal, etc. Materials that adhere to biological substrates, such as mucosal members, are referred to as having "bioadhesion." The ability of establishing a close and persistent contact at the site of administration exists due to the adhesion of bioadhesive drug delivery devices to the mucosal tissue. By reducing the frequency of delivery, this extended residence time can improve patient compliance while also enhancing absorption when combined with a controlled drug release. By affixing the drug to a carrier particle such microspheres, nanospheres, liposomes, nanoparticles, etc., which controls the release and absorption of the medication, carrier technology offers an intelligent method for drug delivery. These particulate drug delivery techniques rely heavily on microspheres due to their small size and effective carrier capacity¹³.

2. Magnetic microspheres

This type of delivery mechanism is crucial for directing the drug to the site of the sickness. In this case, a smaller amount of a medicine that is magnetically targeted can replace a larger amount of a drug that is freely circulating. Materials utilised for magnetic microspheres such as chitosan and dextran are integrated into magnetic carriers, which receive magnetic responses to a magnetic field¹⁴. The various types are Chemotherapeutic agents are delivered to liver tumours using therapeutic magnetic microspheres. Through this technique, drugs like proteins and peptides can also be targeted¹⁵.

3. Diagnostic microspheres

The principle behind the magnetic drug delivery method is that the medication can either be conjugated on the surface of a magnetic microsphere or enclosed within one. They are able to locally distribute the medication due to the carrier's buildup at the target site¹⁶.

4. Floating microspheres

The bulk density of floating kinds is lower than that of gastric fluid, they float unaffected by the rate at which the stomach empties. If the system is floating on stomach content, the drug is released slowly at the desired rate, which increases gastric residence and causes plasma concentration to fluctuate. Additionally, it lessens the likelihood of striking and dose dumping and generates a sustained therapeutic impact¹⁷.

5. Radioactive microspheres

Microspheres used in radio embolization therapy range in size from 10 to 30 nm, which are larger than capillaries and are tapped into the first capillary bed upon contact. They are injected into the arteries that supply the target tumour. As a result, these radioactive microspheres deliver a high radiation dose to the desired locations while sparing the healthy tissues around them. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters¹⁸.

6. Mucoadhesive microspheres

The addition of mucoadhesive properties to microspheres has additional benefits, such as efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, much more intimate contact with the mucus layer, and specific targeting of drug to the absorption site achieved by anchoring plant l. In order to provide the possibility of both localised and systemic controlled medication release, mucoadhesive microspheres can be designed to stick to any mucosal tissue, including those present in the eye, nasal cavity, urinary, and gastrointestinal tract¹⁹.

7. Polymeric microspheres

The different types of polymeric microspheres can be classified as:

i) Biodegradable polymeric microspheres

The idea behind the usage of natural polymers like starch is that they are biodegradable, biocompatible, and bioadhesive by nature. Due to their extreme swelling capacity in aqueous media, biodegradable polymers extend the residence time when in contact with mucous membranes, causing gel formation. The concentration of the polymer and the sustained release pattern regulate the rate and degree of medication release. The key disadvantage is that biodegradable microspheres' drug loading efficiency in clinical settings is complex, making it challenging to regulate drug release²⁰.

ii) Synthetic polymeric microspheres

In addition to being employed as bulking agents, fillers, embolic particles, drug delivery vehicles, etc., synthetic polymeric microspheres are also frequently used in clinical applications and have proven to be both safe and biocompatible. The main drawback of these microspheres is that they have a propensity to migrate away from the injection site, increasing the risk of embolism and subsequent organ damage²¹.

METHODS OF PREPARATION:

Microspheres can be prepared by following methods,

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
8. Quassi emulsion solvent diffusion

1. Spray Drying:

In the spray drying process, the polymer is first dissolved in a volatile organic solvent like acetone or dichloromethane. The medication is then homogenised at a high speed and disseminated in a polymeric solution. Then, a heated air stream atomizes this dispersion. When a substance is atomized, it creates tiny droplets from which the solvent rapidly evaporates, creating microspheres that range in size from 1 to 100 m. The cyclone separator separates micro particles from hot air while vacuum drying eliminates any remaining liquid. One of this procedure' main benefits is its ability to operate under aseptic environments²².

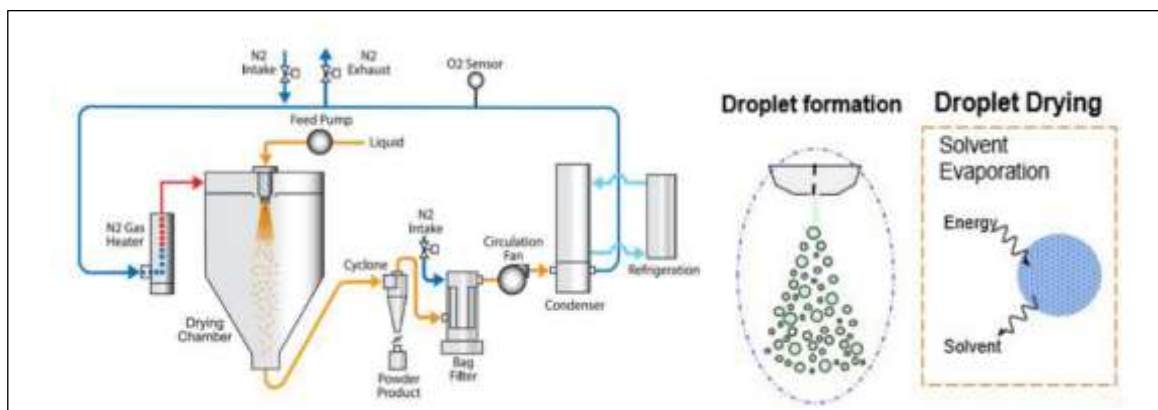


Fig1. Diagrammatic representation of Spray Drying Technique²³

2. Solvent Evaporation:

This procedure is carried out during the liquid manufacturing phase of the vehicle. The microcapsule coating is distributed in a volatile solvent that can mix with the liquid manufacturing process' vehicle phase. In the coating polymer solution, a microencapsulated core material is dissolved. Agitation To create the proper size microcapsule, the core material mixture

is dissolved in the liquid manufacturing vehicle phase. The solvent for the polymer of the core material is then dissolved in the polymer solution, and if additional heating is required to cause the mixture to evaporate, the polymer around the core shrinks. Matrix-type microcapsules are created when the covering polymer solution dissolves the core material. Either water-soluble or soluble elements make up the essential components²⁴.

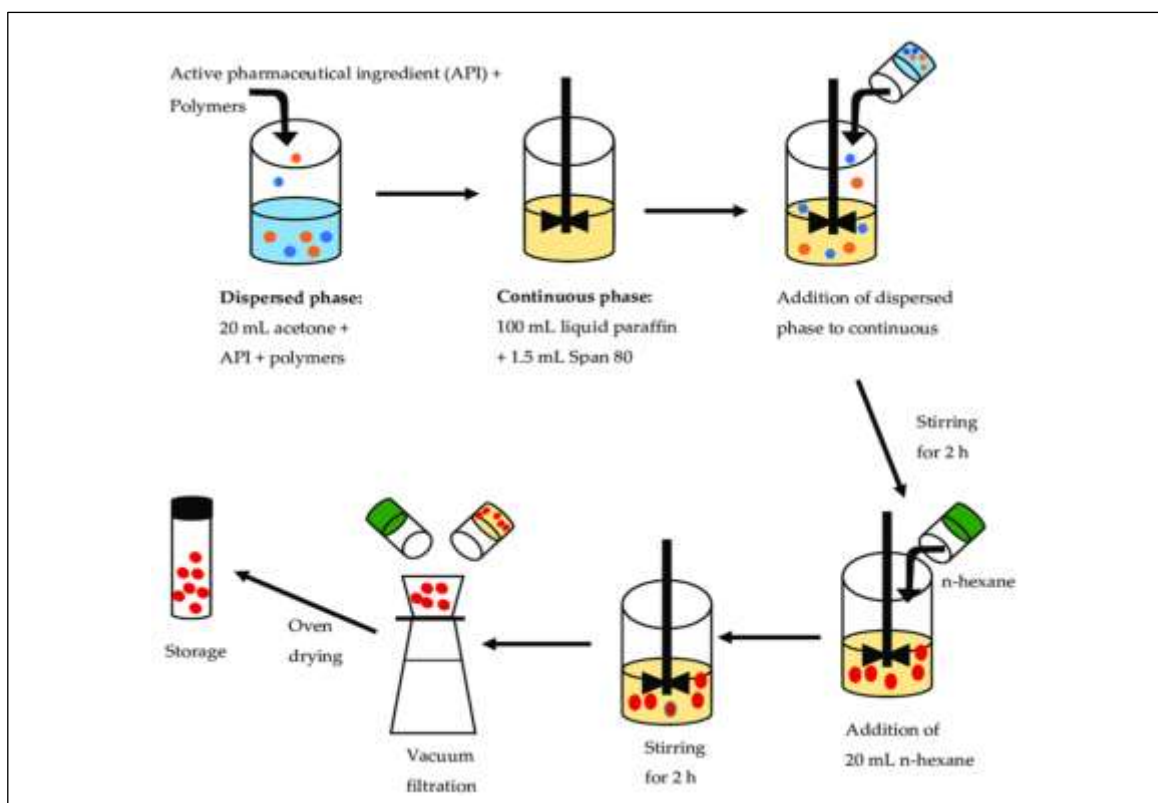


Figure 2: Schematic representation of the solvent evaporation process²⁵.

3. Single emulsion technique:

The single emulsion approach is used to create the micro particle carriers for the natural polymers, such as proteins and carbohydrates. After being dissolved in an aqueous media, natural polymers are then dispersed in a non-aqueous liquid, such as oil. The cross connecting of dispersed globules is done in the following step. Heat or chemical cross linkers can be used to create the cross connecting. Acid chloride, formaldehyde, and glutaraldehyde are the chemical cross-

linking agents used. The thermolabile material is not suited for heat denaturation. If added at the time of preparation and then subjected to centrifugation, washing, and separation, chemical cross-linking has the drawback of exposing the active ingredient to chemicals more than is necessary. In addition, the nature of the surfactants used to stabilise the emulsion phases can greatly affect the size, size distribution, surface morphology and loading drug release, and bio performance of the final multiarticulate product²².

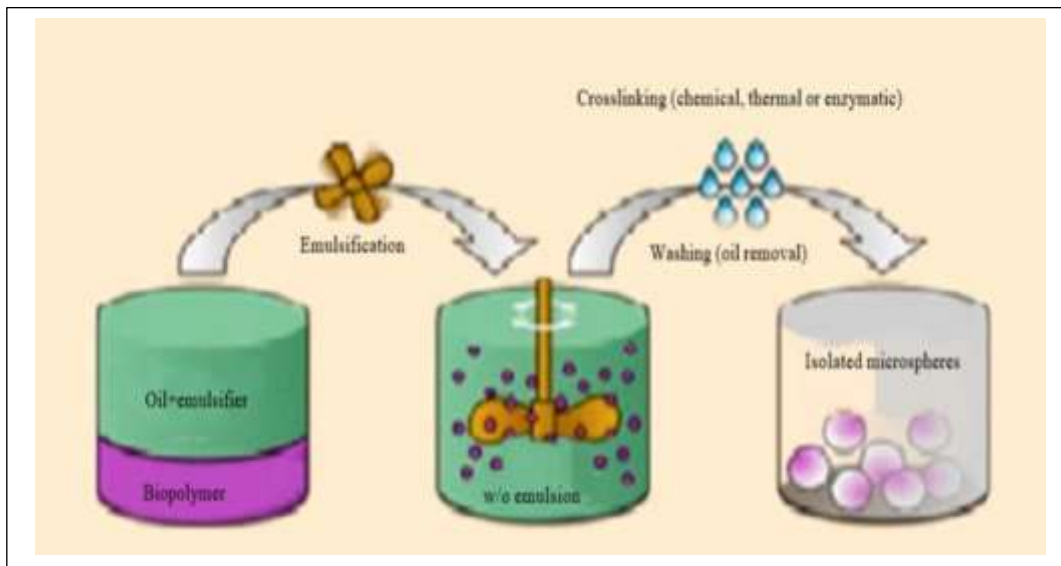


Figure 3: Single emulsion technique²⁶

4. Double emulsion technique:

The ideal candidates for this method of microsphere preparation include water soluble medications, peptides, proteins, and vaccines. It involves the formation of multiple

emulsions or double emulsions of type w/o/w. Both natural and synthetic polymers can be employed using this technique. The lipophilic organic continuous phase contains a dispersion of the aqueous protein solution. The active ingredients could be present in this protein solution²⁷.

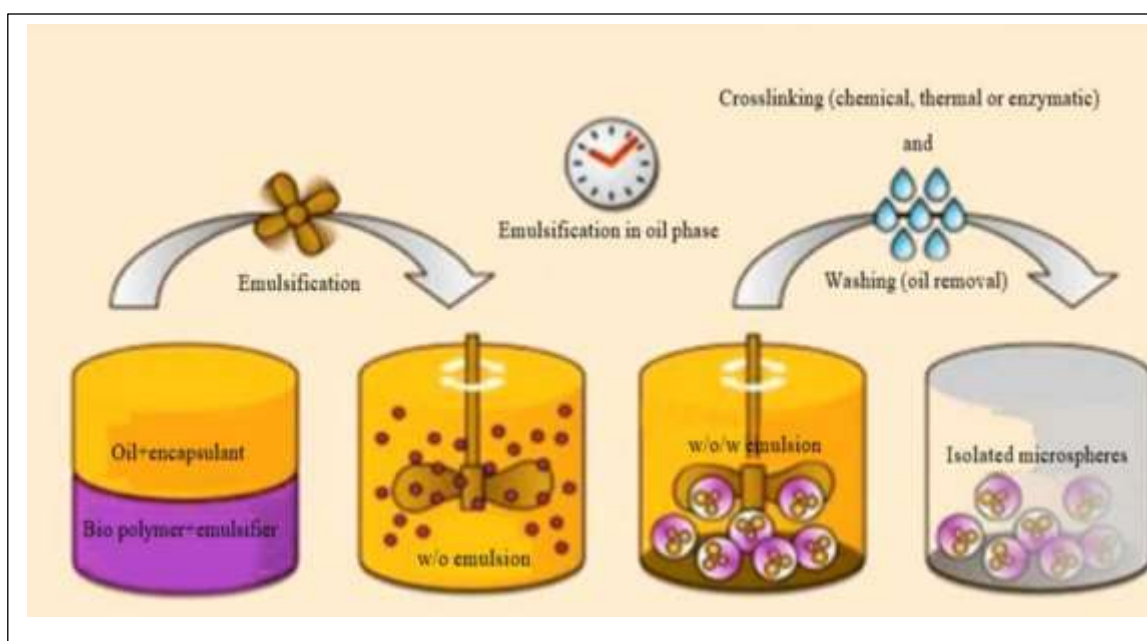


Figure 4: Double emulsion technique²⁸

5. Phase separation coacervation technique:

This method is based on the idea that when polymers become less soluble in organic phases, coacervates—a phase rich in

polymers—become more likely to develop. This method involves dispersing drug particles in a polymer solution before adding an incompatible polymer to create the first polymer needed for phase separation²².

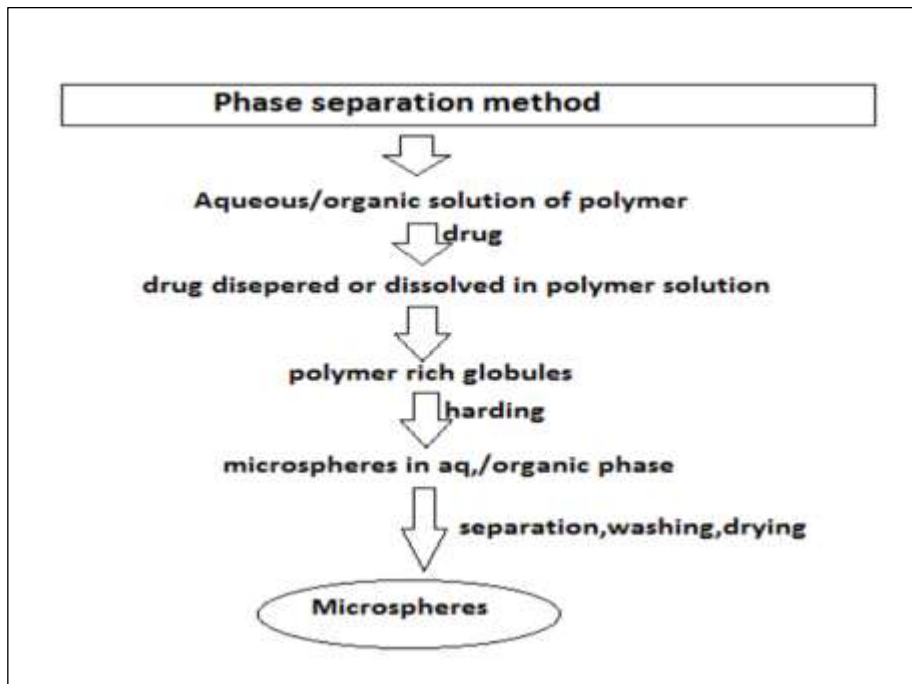


Figure 5: Phase separation method.

6. Spray drying and spray congealing:

These techniques rely on the polymer and medication mist in the air drying. Both spray drying and spray congealing depend

on the elimination of the solvent or the cooling of the solution²⁹.

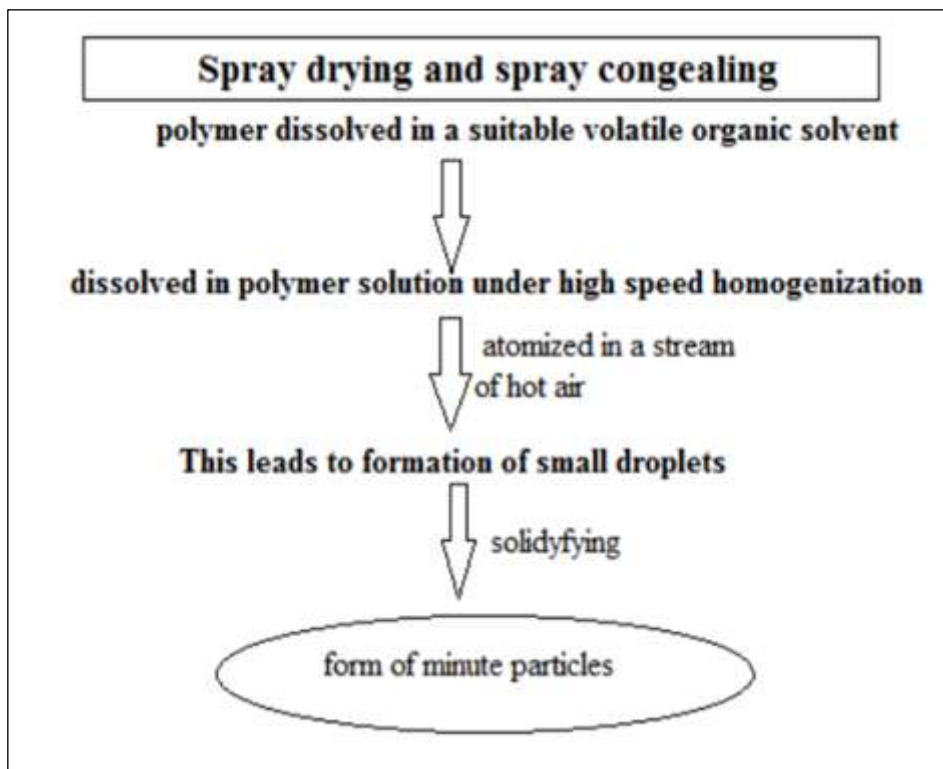


Figure 6: Spray drying and spray congealing.

7. Solvent extraction:

The process of making microparticles by solvent evaporation entails removing the organic phase by extracting the non-

aqueous solvent. Isopropanol, an organic solvent that is water miscible, is used in this procedure²².

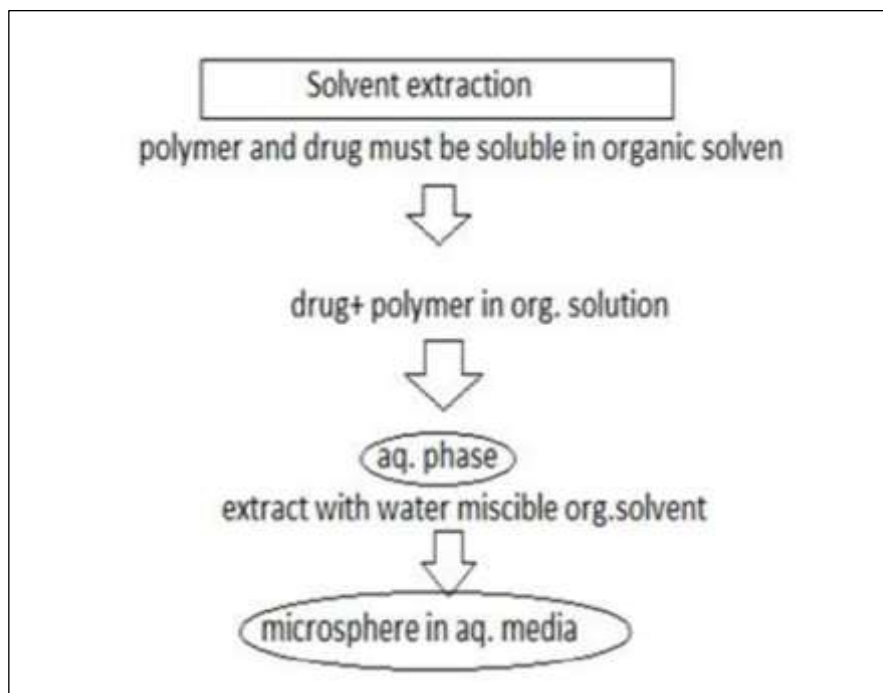


Figure 7: Solvent extraction.

8. Quassi emulsion solvent diffusion:

The literature has described a unique quasi-emulsion solvent diffusion process for creating drug-controlled release microspheres made of acrylic polymers. The Quassi emulsion solvent diffusion method can be used to create micro sponges by employing an external phase that contains polyvinyl alcohol and distilled water²⁹. The medication, ethanol, and polymers make up the interior phase. The external phase is added to the internal phase after the internal phase has first been created at 60°C. After that, the mixture is continuously stirred for 2 hours to create an emulsion. Once the mixture has been filtered, the micro sponges can be removed³⁰.

EVALUATIONS:

A. Physiochemical Evaluation

I. Molecular size and shape:

The Scanning Electron Microscopy (SEM) and Light Microscopy (LM) systems are the most widely used for routine representation of microspheres. Both may have the option of determining the microspheres' external structure and condition. The cost of a covering boundary is managed using light microscopy (LM) in a two-walled microsphere. When the covering is present, it is estimated that the structures of the microspheres are infinitesimally small. SEM can be used to evaluate the surface of a microsphere and cross-separate after the particles (SEM). Scanning electron microscopy can be used to evaluate double-walled frameworks³¹.

II. Density estimation:

The thickness of the microspheres is calculated using a multi-volume pycnometer. The example is precisely stated in a cup, and then something is entered into the multi-volume pyrometer. Helium is started in the chamber at a constant weight, and they allow extension. Results carry less weight within the group in this development. When two successive readings of weight fall in a different proportion, that is when initial weight is noted. The volume can determine the thickness of the microsphere's transporter based on two weight readings³².

III. Angle of contact:

An angle of contact is used to determine if a microparticle channel will moisten. Examining the propensity of microspheres, the word hydrophobicity or hydrophilicity is used. It is important to estimate the point of contact at the strong/air/water interaction. The attachment of a bead to a roundabout cell mounted over an upgraded magnifying instrument's objective allows for the estimation of the point of contact that is moving and retreating. The contact locations are expected to be at 20°C inside a microsphere's moment of transition³³.

IV. Electron spectroscopy for chemical analysis:

The surface science of the microsphere's assurance requires the application of electron spectroscopy for substance research (ESCA). The electron spectroscopy for the compound evaluation approach is a standard for the nuclear organisation of the surface these stocks (ESCA). The spectra provide proof of the biodegradable microsphere's surface deterioration. ESCA was used to obtain these spectra³⁴.

V. Fourier transform-infrared spectroscopy:

The use of FT-IR dictates corruption of the polymeric lattice of the transporter framework. Rotated complete reflectances (ATR) estimate the microspheres' explored surface. The IR bar is passed from the ATR cell and usually reflected through the example to provide IR spectra primarily of surface material. The ATR-FTIR provides information about the microspheres' surface layout based on the assembly process and environmental factors³⁵.

VI. Entrapment efficiency:

By allowing wash microspheres, lysate can determine the microspheres' ability to capture or the percentage of capture. The lysate is next exposed to the assurance of dynamic elements in accordance with monograph need. Encapsulation efficiency is determined using the following equation³⁶:

$$\% DEE = \frac{\text{Estimated drug content}}{\text{Theoretical percent drug content}} \times 100$$

VII. Isoelectric point:

Micro electrophoresis equipment can be used to measure the isoelectric point by monitoring the electrophoretic mobility of microspheres. The time it takes for particles to move across a distance of 1 nm is used to compute the mean velocity at various pH values between 3 and 10³⁷.

VIII. Percentage yield:

It is computed by dividing the total weight of the medication and polymer required to prepare each batch by the weight of the microspheres that were obtained from that batch, then multiplying that result by 100³⁷.

IX. Swelling index:

It is calculated by measuring how much microspheres swell when placed in a specific solvent. The equilibrium swelling degree of microspheres is assessed by overnight swelling in a measuring cylinder of 5 mg of dried microspheres in 5 ml of buffer solution. It is computed using the provided formula³⁷.

$$\text{Swelling index} = \frac{\text{Mass of swollen microsphere} - \text{Mass of dried microspheres}}{\text{Mass of dried microspheres}} \times 100$$

B. In vitro Method:

The following method are used to determine drug release

I. Beaker method:

Using an overhead stirrer, the dosage form is consistently agitated while being forced to attach to the bottom of the beaker containing the medium. The amount of medium utilised in the research described in the literature ranges from 50 to 500 ml, and the stirrer speed ranges from 60 to 300 rpm³⁷.

II. Interface diffusion method:

Dearden and Tomlinson were the ones who created this technique. There are four sections in it. Compartment A, which initially has a suitable medication concentration in buffer, mimics the oral cavity. the buccal membrane compartment B, which contains 1-octanol, and the bodily fluids compartment C, which contains 0.2M HCl. Protein binding is represented by compartment D, which also includes 1-octanol. The 1-octanol and aqueous phases must be saturated with one another prior to usage. Samples are taken out and syringed back into compartment A³⁷.

III. Modified Keshary Chien cell method:

It makes use of equipment created especially for laboratories. It consists of a Keshary Chien cell with 50 cc of distilled water and a dissolving media of 37 °C. In a glass tube with a 10# sieve at the bottom that reciprocates in the medium at a rate of 30 strokes per minute, TMDDS (Trans Membrane Drug Delivery System) is put³⁷.

IV. Dissolution apparatus method:

Both rotating parts, the paddle and the basket, have been utilised in standard USP or BP dissolution apparatus to evaluate in vitro release characteristics. The study's dissolution medium ranges from 100 to 500 ml, and the rotational speed ranges from 50 to 100 rpm³⁷.

C. In vivo method:

Techniques for determining the biological reaction of the organism locally or systemically, as well as those that involve direct local assessment of uptake or accumulation of substances at their surface, are used to evaluate the permeability of intact mucosa. The most popular in vivo study

techniques involve the use of animal models and buccal absorption assays³⁷.

Applications of Microspheres:**Microspheres used for vaccine delivery:**

Immune system development against infectious diseases is how vaccines offer protection. The tetanus, diphtheria, and cholera vaccines are a few examples of vaccinations that are enclosed in microspheres³⁸. By extending the antigen release for weeks or months, microspheres containing vaccinations enhance immunologic response^{39,40}. Encapsulating the vaccine in a suitable carrier and holding it there until it is released stops the vaccine from degrading. Controlled vaccination administration can contain numerous antigenic epitopes or both the antigen and the adjuvant in a single carrier, which may reduce systemic side effects. In order to provide a continuous release of an encapsulated antigen, biodegradable polymers are utilised, which break down to harmless, low-molecular-weight compounds in the body⁴¹. A variety of antigens can be encapsulated by chitosan microspheres. The best choice is synthetic biodegradable polymers, like polylactic-coglycolic acid, which is frequently used to encapsulate antigen in single-dose vaccines⁴².

Microspheres containing monoclonal antibodies:

For antigen molecules that are present at the target site, monoclonal antibodies exhibit a high level of specificity⁴³. Microspheres delivering pharmacologically active substances to target areas are targeted using the specificity of monoclonal antibodies. Monoclonal antibodies are joined with microspheres through covalent coupling, nonspecific adsorption, coupling via chemicals, and selective adsorption. The antibodies may be attached to the free carboxyl group, aldehyde group, amino group, or hydroxyl group on the surface of the microspheres⁴⁴. Anti-vascular endothelial factor formulation microspheres that contained monoclonal antibodies displayed release for up to six months⁴⁵.

Microspheres in gene delivery:

Recombinant adenoviruses are frequently utilised for gene delivery because of their high efficiency and wide range of cell targets, even if when used in vivo they can elicit immunological reactions and oncogenicity. When using viral vectors, gene therapy must be administered repeatedly. Microspheres are employed to encapsulate genes in non-viral gene delivery, enabling continuous gene delivery. Microspheres may be produced on a large scale with high levels of reproducibility, are stable, simple to make, and target the cells or tissue⁴⁶.

Ophthalmic drug delivery through microspheres:

Bio adhesive and permeability-improving qualities are imparted by polymers utilised for ocular medication administration. In comparison to alternative drug delivery formulations for the eye, such as ointments or solutions, polymer hydrogels are more effective because of their elasticity⁴⁴. A chitosan gel increases precorneal drug residence durations by inhibiting the drug's escape through lachrymal flow, distributes over the conjunctiva, and strengthens adhesion to the mucus membrane of the eye. To provide regulated or sustained drug delivery in the eye, drug-loaded microspheres can be suspended in a system of polymer hydrogel⁴⁷.

Nasal drug delivery though microspheres: (51-54)

An excellent location for bioadhesive drug delivery devices is the nasal mucosa. In order to increase the bioavailability and residence time of the medications in the nasal route, microspheres are designed to have high bioadhesive

characteristics and swell easily when in contact with the nasal mucosa. For nasal sustained release of vancomycin hydrochloride, a number of polymer salts, including chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride, are suitable choices. By promoting the formation of IgG antibodies, nasal administration of chitosan microspheres containing diphtheria toxoid causes a protective local and systemic immune response against the toxoid⁴⁸. Microspheres absorb the moisture from the mucosa, which causes the nasal cells to contract and shorten the tight junctions, increasing medication absorption⁴⁹. For nasal medication delivery, dextran and starch microspheres are regarded as safe⁵⁰. Ondansetron-containing alginate microspheres made using the ionic-gelation technique are utilised to prolong the drug's release via the nasal mucosa⁵¹.

Microspheres for delivery of protein and peptides:

The controlled release of proteins and peptides from microspheres constructed of biodegradable polymers has been investigated. Long-term steady-state plasma protein or peptide concentrations can be maintained with the aid of microspheres⁵². In the microsphere formulation of protein/peptide medicines, biodegradable polylactic acid, polylactic-co-glycolic acid, and chitosan microspheres are appropriate⁵³. The microsphere-based delivery mechanism is used by commercially available peptide medications such as triptorelin, lanreotide, buserelin, and abarelix⁵⁴.

Microspheres used in cancer treatment:

Yttrium-90 or other β -emitter-containing radioactive microspheres are utilised to treat liver cancers. A 30 micron-diameter suspension of radioactive microspheres is injected into the hepatic artery, where they enter the tumour vasculature. Radiation exposure causes tumour cells to die off without harming nearby healthy cells. To treat colon cancer, polymeric microspheres carrying the medication 5-fluorouracil may be utilised. These polymeric microspheres guard against the drug's degradation in the stomach⁵⁵.

Topical porous microspheres:

These porous microspheres, which have the ability to entrap a variety of active compounds including emollients, perfumes, volatile oils, and others, are utilised as topical delivery systems and can also be integrated into formulations like creams, lotions, and powders^{56,57}.

Vaginal drug delivery:

A polymer that has had its major amino groups changed by the addition of thioglycolic acid embeds clotrimazole, an imidazole derivative, which is frequently used to treat mycotic infections of the genitourinary tract. By adding thiol groups, the polymer's mucoadhesive qualities are significantly enhanced, increasing the vaginal mucosa tissue's residence period (26 times longer than the corresponding unmodified polymer), and ensuring a controlled medication release in the treatment of mycotic infections. Metronidazole and acriflavine-containing polymer vaginal tablets have demonstrated acceptable release and good adhesion characteristics⁵⁸.

Transdermal drug delivery:

The ability of polymer to create films is strong. The membrane thickness and cross-linking of the film have an impact on the drug release from the devices. In-situ preparation of the chitosan alginate polyelectrolyte complex in the form of beads and microspheres has been done for potential use in packaging, controlled release systems, and wound dressings. For the treatment of local inflammation, polymer gel beads are a promising biocompatible and biodegradable delivery system for medications like prednisolone, which exhibited sustained

release action that increased therapeutic efficacy. It was discovered that the sort of membrane being employed affected how quickly the medicine was released. For regulated drug distribution and release kinetics, a chitosan hydrogel and membrane combination containing the local anaesthetic lidocaine hydrochloride works well⁵⁸.

Colonic drug delivery:

Insulin has been delivered specifically to the colon via polymer. The enteric coating (Hydroxy propyl methyl cellulose phthalate) on the chitosan capsules contained, in addition to insulin, many other absorption enhancers and enzyme inhibitors. It was discovered that the colonic region was where capsules specifically dissolved. It was proposed that this disintegration was caused by either the presence of bacterial enzymes that can degrade the polymer or the lower pH in the ascending colon compared to the terminal ileum⁵⁸.

Intratumoral and local drug delivery:

Strategies for local and intratumoral medication administration have gained popularity recently as a possible treatment option for cancer. Polymer films were created in order to deliver paclitaxel at the tumour location in a therapeutically effective concentration. The amount of paclitaxel that could be put into flexible, translucent films was 31% (w/w). According to the study, polymer films containing paclitaxels were produced using a casting method with high loading efficiencies, maintaining the chemical integrity of the molecules throughout the process⁵⁸.

Buccal drug delivery:

Because it has muco/bio adhesive characteristics and can improve absorption, polymer is a great polymer to utilise for buccal distribution. The antibacterial efficacy of buccal tablets based on chitosan microspheres and chlorhexidine diacetate is improved by the prolonged release of the medication in the buccal cavity. Drug-free polymer microparticles nevertheless exhibit antibacterial properties because of the polymer. The buccal bilayer devices (bilaminated films, palavered tablets) with or without anionic crosslinking polymers (polycarbophil, sodium alginate, gellan gum) have intriguing potential for use in controlled distribution in the oral cavity. These medications include nifedipine and propranolol hydrochloride⁵⁸.

Gastrointestinal drug delivery:

When added to acidic and neutral environments, polymer granules with interior voids created by deacidification are buoyant and allow a controlled release of the medication prednisolone. Melatonin was delivered in floating hollow microcapsules with a gastroretentive, controlled-release mechanism. These microcapsules considerably slow down the release of the medication, with release lasting 1.75 to 6.7 hours in simulated gastric juice. The majority of mucoadhesive microcapsules, such as methoclamide and glipizide-loaded chitosan microspheres, remain in the stomach for more than 10 hours⁵⁸.

Peroral drug delivery:

A presystemic metabolism of peptides can be significantly reduced by polymer and the majority of its derivatives, which significantly improves the bioavailability of several perorally administered peptide medications like buserelin, calcitonin, and insulin. Chitosan that hasn't been changed increases the penetration of peptide medicines. By immobilising enzyme inhibitors on the polymer, peptides incorporated in polymers can be protected from being broken down by intestine peptidases. By adding chitosanglycerol mono-oleate, the mucoadhesive property of polymer gel can be increased by three to seven times. Drug release from the gel was regulated

by matrix diffusion. When taken as beads contained in a chitosan matrix, nifedipine releases its medication more slowly than when taken as granules⁵⁸.

Multiparticulate delivery system:

Chitosan pellets were created by H.Steckel and F. Mindermann-Nogly utilising the extrusion/spheronization method. From 0% to 70% of microcrystalline cellulose was utilised as an ingredient. Different powder to liquid ratios were used to extrude the powder mixture, which dilutes acetic acid. The study demonstrated that using demineralized water as the granulating fluid, chitosan pellets with a maximum of

50% (m/m) could be manufactured. Using diluted acetic acid for the granulation process would enhance the bulk fraction of chitosan in the pellets to 100%⁵⁸.

Other potential applications include

- Conversion of oil and other liquids to solids for ease of handling
- Taste and odour masking
- To delay the volatilization
- Safe handling of toxic substances

Marketed Formulations Of Microspheres:

MARKETED NAME	COMPANY NAME	DISEASE	DRUG	Ref
Mesacol tablet	Sunpharma	Ulcerative colitis	Mesalamine	59
Asacol	Win Medicare pharma	Ulcerative colitis, Crohn's disease	Mesalamine	60
SAZO	Wallac India	Ulcerative colitis, Crohn's disease	Sulphasalazine	61
Intazide	Intas,India	Ulcerative colitis	Balsalazide	62
COLOSPA	Solvay, India	Irritable colon syndrome	Mabeverine	63
CYCLOMINOL	Neol India	Irritable colon syndrome	Dicyclomine	64
Decapeptyl	Ferring pharmaceuticals	Advanced prostate cancer	Triptorelin	65
Arestin	OraPharma	Periodontitis	Minocycline	66
Risperdal	Apollo	Schizophrenia	Respiridone	67
Nutropin	Genentech	Growth hormone deficiency	Somatropin	68

Conclusion

The most widely used drug delivery method is microspheres because of their benefits of sustained and controlled release action, better stability, decreased dosing frequency, dissolving rate, and bioavailability. The spherical microspheres are used to deliver the medicine precisely to the target site and to keep the desired concentration at the place of interest without producing any unwanted side effects. The medicine is contained within the microspheres' unique polymeric membrane, which is positioned in the particle's centre. In comparison to many other kinds of drug delivery systems, microspheres are a preferable option for DDS. The microspheres will play a significant and central role in novel drug delivery in the future by combining various other strategies, particularly in diagnostics, diseased cell sorting, gene & genetic materials, targeted, safe, effective & specific in vitro delivery & supplements as the miniature versions of the diseased tissues & organ in the body.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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