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### RESEARCH ARTICLE

#### MICROSPHERES: A NOVEL DRUG DELIVERY SYSTEM

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#### Abstract

Microspheres are freeflowing powders that are made up of proteins or synthetic polymers. They are little spherical particles with diameters ranging from a few millimetres to a few millimetres (typically from 1 to 100 micrometer). Microspheres are microparticles that are employed in applications that require a predictable and constant particle surface area. To achieve the desired impact, the drug should be delivered in an ideal amount at the right time to the target tissue with the least degree of adverse effects and maximal therapeutic efficacy. The microspheres drew a lot of attention because of their long-lasting release and ability to target anticancer medications to the tumor. Microspheres will play a key role in innovative medication delivery in the future, particularly in sick cell sorting, diagnostics, gene & genetic materials, and safe, targeted and precise delivery.

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#### Introduction:-

Microspheres are tiny spherical particles having dimensions in the micrometer range (usually 1 to 1000 micrometers). Microparticles are another name for microspheres. Natural and manmade materials can be used to create microspheres. Commercially accessible microspheres include glass, polymer, and ceramic microspheres. Solid and hollow microspheres have various densities and are utilised for different purposes. Hollow microspheres are commonly utilised as additions to reduce a material's density. Depending on the type of substance and size of the material, solid microspheres can be used for a variety of purposes. Microspheres are designed to address some of the issues with traditional therapy and to improve the therapeutic efficacy of a specific medicine.

#### Two most common types of polymer

1. Polyethylene microspheres
2. Polystyrene microspheres

#### Polyethylene microspheres:

Microspheres made of polyethylene are often employed as permanent or temporary fillers. Polyethylene microspheres with a lower melting point can generate porous architectures in ceramics and other materials. Polyethylene microspheres are very sought for flow visualisation and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting, and other research applications due to their high sphericity and availability of colourful and fluorescent microspheres. Electronic paper digital displays also use charged polyethylene microspheres.

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**Polystyrene microspheres:**

Polystyrene microspheres are frequently employed in biological applications because they make operations like cell sorting and antibody precipitation easier. Proteins and ligands rapidly and permanently adsorb onto polystyrene microspheres, making them ideal for medical research and biological laboratories.

**Theory****Types Of Microspheres****Bioadhesive microspheres:**

Adhesion is defined as the ability of a medication to adhere to a membrane using its sticking feature polymers that are water soluble. Drug delivery device adhesion to mucosal membrane. Bioadhesion can be described as buccal, ocular, rectal, nasal, and other types of adhesion. The term "bioadhesion" refers to the ability of cells to stick together. Materials that bind to biological substrates, such as mucosal membranes, are referred to as mucosal membranes. The ability to attach bioadhesive drug delivery devices to mucosal tissue allows for the creation of an implant. The frequency of administration was reduced, which increased patient compliance. By combining the two, it provides an intelligent way to drug delivery.

**Magnetic microspheres:**

This type of delivery mechanism is critical because it allows the drug to be delivered to the illness location. A higher amount of freely circulating medicine can be substituted with a smaller amount of magnetically focused drug in this situation. Magnetic carriers receive magnetic responses to a magnetic field from integrated components such as chitosan, dextran, and other materials utilized in magnetic microspheres. The many types are as follows: Magnetic microspheres are utilized to deliver therapeutic drugs.

To treat a liver tumour, a chemotherapeutic drug is used. This technique can also target drugs such as proteins and peptides. The magnetic drug transport technology is based on the fact that the drug can be encapsulated or conjugated on the surface of a magnetic microsphere. The carrier's accumulation at the target spot allows them to deliver the drug locally.

**Floating microspheres:**

Because floating types have a lower bulk density than gastric fluid, they float in the stomach without slowing down gastric emptying. When the system is floating on stomach content, the medicine is released slowly and at an ideal rate, resulting in increased gastric residence and plasma concentration oscillations. It also reduces the chances of striking and dose dumping while providing a long-term therapeutic impact. This is how the medication (ketoprofen) is given.

**Radioactive Microspheres:**

Microspheres used in radio embolisation therapy range in size from 10 to 30 nanometers, which are larger than capillaries. When they come across, they get trapped in the first capillary bed. They are injected into the arteries leading to the tumour. As a result, these radioactive microspheres give a substantial dosage of radiation to the body.

They are injected to the arteries that lead to tumour of interest. So, these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. 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  $\alpha$  emitters,  $\beta$  emitters,  $\gamma$  emitters.

**Mucoadhesive microspheres:**

Mucoadhesive microspheres with a diameter of 1-1000 $\mu$ m and made entirely of or coated with a mucoadhesive polymer have additional advantages, including efficient drug absorption and increased bioavailability due to a high surface to volume ratio, much closer contact with the mucus layer, and specific drug targeting to the absorption site achieved by anchoring plant lectins. Mucoadhesive microspheres can be modified to adhere to any mucosal tissue, such as that present in the eye, nasal cavity, urinary tract, and gastrointestinal tract, allowing for both localised and systemic controlled pharmaceutical release.

**Material:-**

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

**Synthetic Polymers****Natural polymers**

Synthetic polymers are divided into two types.

a) Non-biodegradable polymers

Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b) Biodegradable polymers

Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, Collagen

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Chemically modified carbohydrates: Poly dextran, Poly starch.

**Method of Preparation**

The choice of technique depends upon the nature of polymer as well nature of drug and the duration of therapy. The most important physical chemical factors that may be controlled in microsphere manufacture are: -

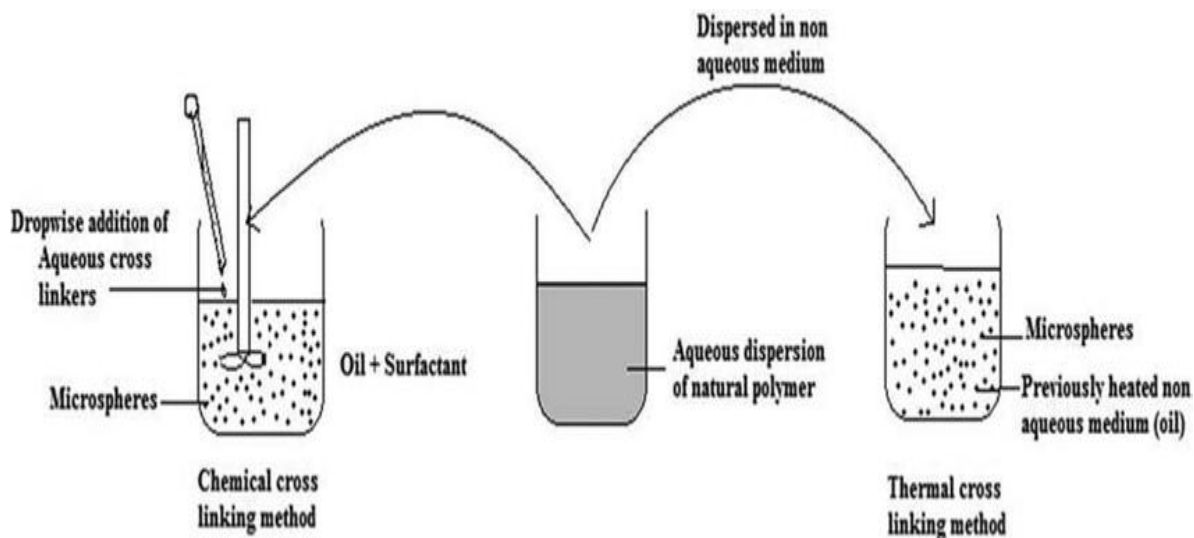
1. The particle size requirement
2. Molecular weight of polymer
3. Polymer to drug ratio
4. No stability problem
5. Final product should be non-toxic.
6. Total mass of drug and polymer
7. Reproducibility
8. Controlled particle size and dispersibility in aqueous vehicles for injection
9. Release of active reagent with a good control over a wide time scale

**Techniques for microsphere preparation**

1. Single emulsion techniques
2. Double emulsion techniques
3. Polymerization
  - a. Normal polymerization
    1. Bulk
    2. Suspension
    3. Emulsion
  - b. Inter-facial polymerization
4. Phase separation coacervation technique
5. Spray drying
6. Solvent extraction
7. Solution-enhancement dispersion method
8. Wax coating Hot-melt method

**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.



### Double emulsion technique

It is the preparation of multiple emulsions, i.e. W/O/W, by pouring the primary w/o emulsion into aqueous poly vinyl alcohol solution. This w/o/w emulsion required 30 minutes of steady churning. Over the course of 30 minutes, gradually add some water to the emulsion. Microcapsules are collected through filtration and dried under vacuum. Water soluble medicines, peptides, proteins, and vaccinations are the best candidates. This approach can be used with both natural and synthetic polymers. A lipophilic organic continuous phase disperses the aqueous protein solution. The active components may be present in this protein solution. Disperse in oil/organic phase homogenization/vigorous, i.e. production of first emulsion followed by addition to an aqueous solution of PVA (Poly Vinyl Alcohol), resulting in several emulsions.

### Polymerization techniques

Mainly two techniques are using for the preparation of microsphere are classified as:

#### (a) Normal polymerization

To commence polymerization in bulk polymerization, a monomer or a combination of monomers, as well as the initiator or catalyst, is commonly heated. The resulting polymer can be moulded into microspheres. Drug loading can be accomplished by adding the drug during the polymerization process.

It is particularly difficult to dissipate the heat of reaction, which impacts thermo labile active components, even if it is a pure polymer synthesis process. Suspension polymerization, also known as pearl polymerization, involves heating the monomer mixture with active medication as droplets dispersion in a continuous aqueous phase at a lower temperature. Microspheres having a diameter of less than 100 m are created through suspension methods.

#### (b) Interfacial polymerization

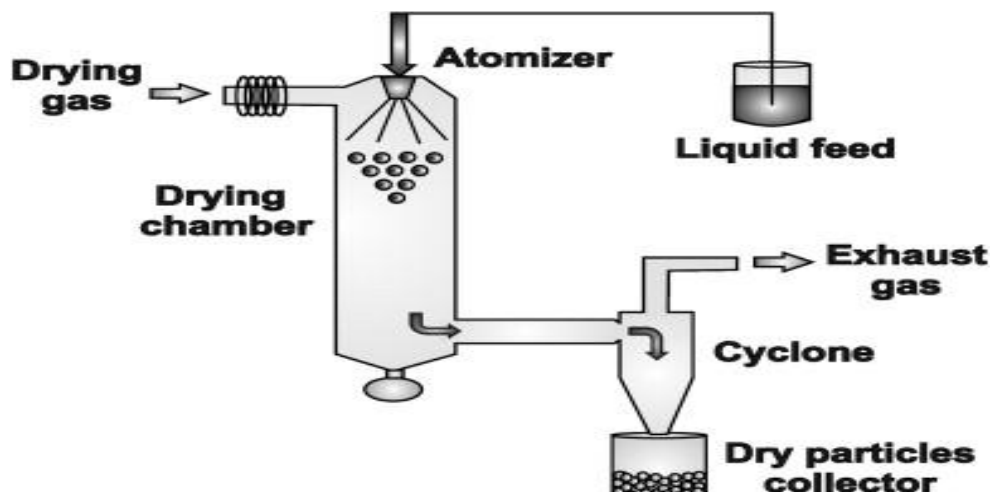
The creation of a polymer film that effectively envelops the dispersed phase is caused by the interaction of various monomers at the interface between the two immiscible liquid phases. In this method, two reactive monomers are used: one is dissolved in continuous phase, while the other is disseminated in continuous phase (aqueous in nature) and emulsified throughout. Two situations arise due to the solubility of the generated polymer in the emulsion droplet. The carrier will be monolithic if the polymer is soluble in the droplet. The capsular kind is formed when the polymer is insoluble in the droplet.

### Spray drying and spray congealing

Concept of spray drying technique depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray congealing is shown in the figure below. Evaporation is the basic mechanism in spray drying, whereas in spray congealing it is that of a phase inversion from a liquid to a solid. Both processes are similar, except for energy flow. Spray drying is the most widely used industrial process involving particle formation and drying.

Therefore, spray drying is an ideal process where the endproduct must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.

Spray drying technique is also useful for preparing chitosan microsphere, In 1999 He et.al. Used formaldehyde as a crosslinking and also reported a novel method in which cimetidine and famotidine were entrapped in microspheres prepared by spray drying of multiple emulsion (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.

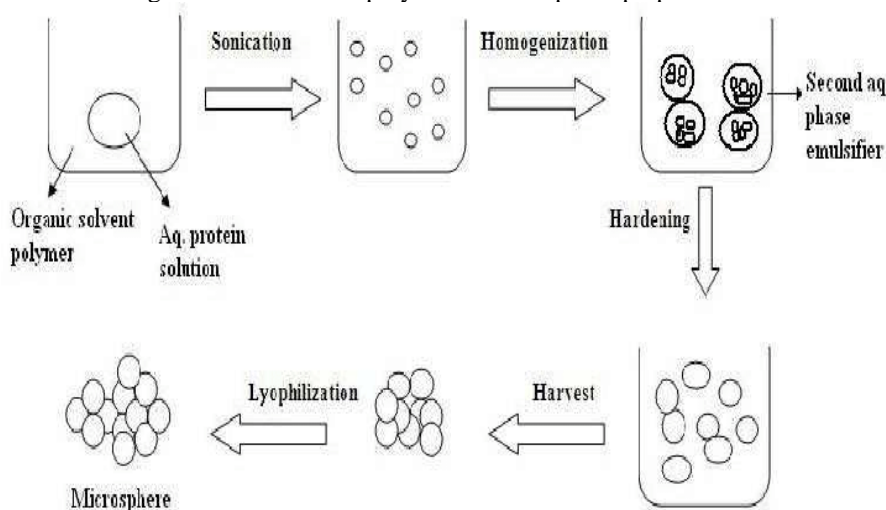


### Wax Coating and Hot Melt

Polymer is dispersed in a suitable dispersion media and then slowly cooled to generate microspheres in this procedure. This technology can easily manufacture polymers with low melting points into microspheres. Particle wax is mostly used for coating and coring. In which the medication is encapsulated by dispersion in moulded wax. High-speed mixing disperses the wax suspension in a cold solution, such as liquid paraffin. For one hour, agitate the mixture. The exterior phase was then decanted, and suspended microspheres were collected from the solvent. Allow it to dry in the open air. It is a less expensive way than others, and the medicine is released faster. Carnauba wax and beeswax are the most common coating ingredients, and they can be blended to create custom coatings in order to achieve desired characteristics.

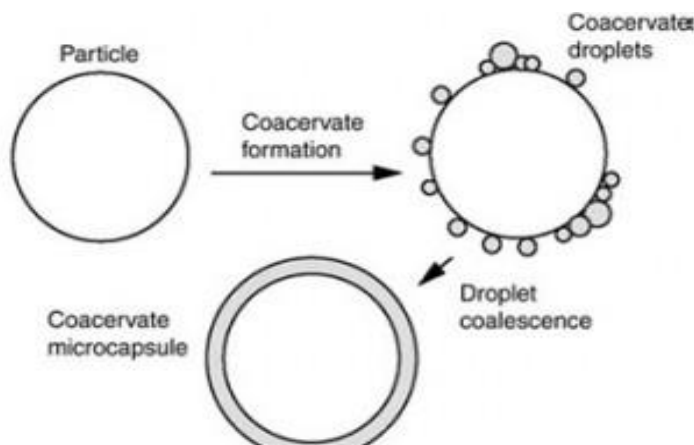
### Solvent evaporation method

For the generation of emulsions between a polymer solution and an immiscible continuous phase in both aqueous (o/w) and non-aqueous (w/o) environments. Bogataj et al. (2000) used the evaporation method to manufacture microspheres using liquid paraffin/acetone as the solvents. The drug solution (in acetone) was distributed in chitosan solution, which was then emulsified and mixed in liquid paraffin. The microsphere suspension was filtered, washed, and dried. Magnesium stearate was also used as an agglomeration-preventative agent. The average particle size decreased as the amount of magnesium stearate employed for microsphere preparation increased.



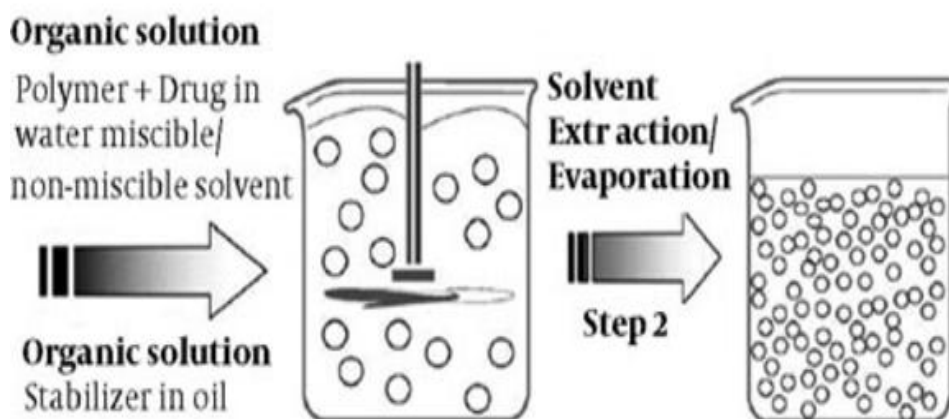
### Phase separation coacervation technique

It is the straightforward separation of two immiscible liquid phases from a micromolecular solution. The polymer is solubilized in this process to create a solution. This method is used to produce reservoir-type systems, such as encapsulating water-soluble medicines like peptides and proteins. The objective of coacervation is to reduce the polymer's solubility in the organic phase in order to affect the creation of polymer-rich phases known as coacervates. In this approach, drug particles are dispersed in a polymer solution, and an incompatible polymer is added to the system, causing the first polymer to phase separate and swallow the drug particles. This process can also be used to make matrix-type preparations for hydrophilic drugs such as steroids. Adding non-solvent results in matrix-type preparations.



### Solvent extraction

The organic phase is removed by extraction of the organic solvent in this process of microparticle production. Isopropanol can be used as an organic solvent that is water miscible. Organic phase is removed by water extraction. This procedure can shorten the time it takes for a microsphere to harden. Direct addition of the medication or protein to the polymer organic solution is one version of the method. The rate of solvent removal by extraction relies on the temperature of the water, the emulsion volume to water ratio, and the polymer's solubility profile.



### Emulsification method

Multiple emulsions may also be formed for example; a heated aqueous drug solution can be dispersed in molten wax to form a water-in-oil emulsion, which is emulsified in a heated external aqueous phase to form a water-in-oil-in-water emulsion. The system is cooled and the microcapsules collected. For highly aqueous soluble drugs, a nonaqueous phase can be used to prevent loss of drug to the external phase. Another alternative is to rapidly reduce the temperature when the primary emulsion is placed in the external aqueous phase.

### Mechanism of Drug Release

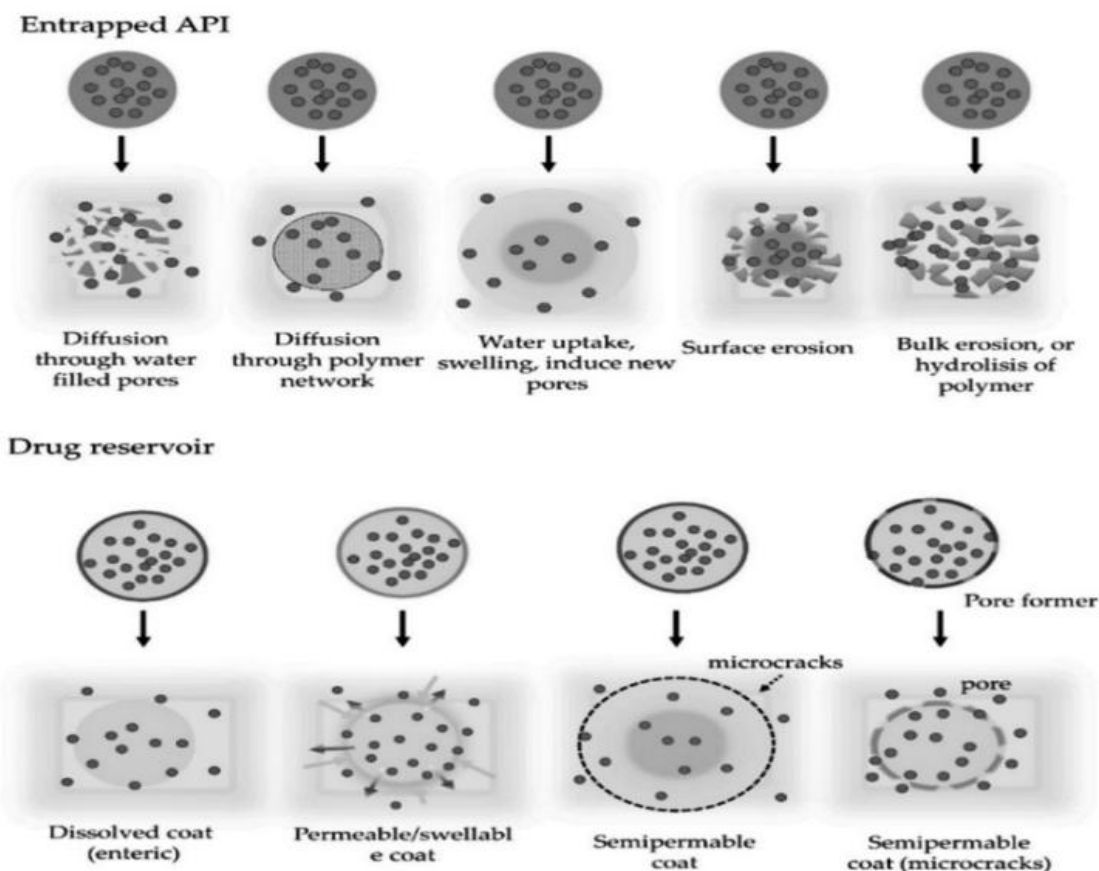
Various events and mechanisms (dissolution/diffusion, osmotically driven release, erosion) contribute to the drug release of microparticulates manufactured by particular manufacturing technologies and/or possibly incorporating

special excipient(s). In most cases, these processes operate in tandem, with one playing a larger role during drug release than the other.

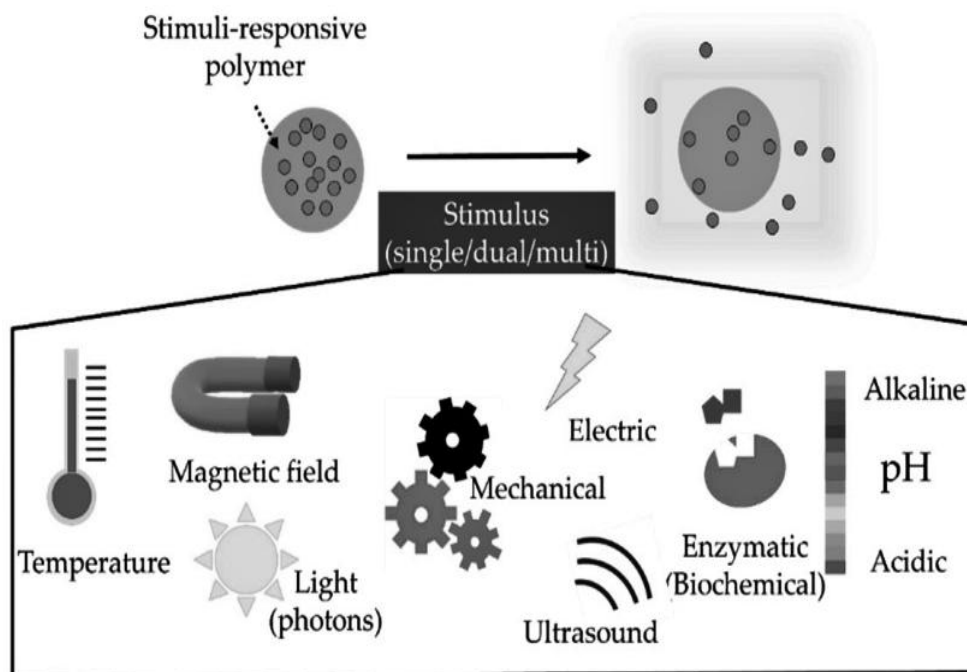
The behaviour of the polymer system during dissolution is crucial when the active medicinal ingredient is incorporated in a polymer matrix in a microparticulate, but it is reliant on a number of characteristics (drug properties, formulation, release medium, etc.)

In the case of a polymer matrix, the active ingredient can diffuse across the entire polymer network or through the holes filled with water. Aqueous pore networks may dissolve drugs that dissolve in water.

Polymer chains swell as a result of water absorption, indicating the creation of new holes and/or osmotic pressure. Swelling raises the volume, the drug's effective diffusion coefficient rises, and more pharmacokinetic molecules enter the watery component. It's also conceivable for the polymer matrix (bulk/surface) to erode.



The initial "burst" of drug, which can be as much as 10–50 percent of the drug load, is followed by a "lag" phase of delayed release, and then a period of steady release for macromolecules. The first wave of protein-based therapies has been linked to their proclivity for partitioning to the surface of the microsphere during the process of encapsulation. Attempts have been made to alleviate the burst using a variety of methods.



To minimize the affinity of the encapsulated pharmaceuticals for the bulk phase, add excipients to the polymer phase, employ innovative polymers, encapsulate particulate versions of the drugs, or replace the non-solvent aqueous phase used in the construction process with non-polar oils or alcohols. The explosion is frequently followed by a period of restricted dissemination and little activity.

**Formulation and Manufacturing  
Composition and Excipients**

Plant, animal, and microbial-origin biopolymers are advantageous, as are semi-synthetic cellulose derivatives and biodegradable or non-biodegradable synthetic polymers. Polysaccharides and proteins are commonly included in the formulation, but waxes and lipids also play a role. Non-polymer excipients help construct and solidify the polymer network of drug delivery systems by crosslinking polymer chains (CaCl<sub>2</sub>, glutaraldehyde, poly-l-lysine, etc.).

The most commonly used polymers and their important microencapsulation-related properties are summarized in Table.

Excipient	Physiochemical Properties	Applications and Benefits	Limitations	Ref.
Gelatine	Amphoteric gelatin A (isoelectric point (IEP) pH: 7–9.4) Swells, then dissolves in water	At low pH coacervation with negatively charged polymers, high potential of crosslinking emulsifier, stabilizer (high viscosity), binder Thermoreversible gelling, implantable pulmonary delivery	Influence of pH and ionic strength on behavior Need for preservation against possible prion (BSE) contamination	20,21



		pH-dependent, swelling, dissolution, erosion		
Caesin	Hydrophilic, metal binding Insoluble in water at its IEP (pH 4.6)	calcium caseinate –reversible thermal gelation solubility increase (coenzyme Q10)	Anaphylactic Reactions	22
Whey Protein	Insoluble at its IEP (pH 5.2)	Thermal gelation, encapsulation of oils film formation: gas barrier, good tensile strength	Thermally irreversible gel formation above 70 °C Denatures at higher salt conc.	23
Albumin	IEP: 4.7 Freely soluble in water negative charge at pH 7.4	Pulmonary delivery Alginate-albumin	Chemical degradation, denaturation at high salt conc., enzymes, heat	24
Zein	$\alpha$ , $\beta$ , $\gamma$ , $\delta$ , zein with different Mw amphiphilic character.	Oral controlled release matrix and wall	Brittle, rigid wall, complex with a gelling component to plasticize	25,26
Soy Protein	Partly Soluble in water depending on extraction process	Oral control release matrix and wall emulsifier, foaming agent	Sensitivity	27
Gluten	Water insoluble	Wall material, good elastic and thermoplastic properties	Gluten sensitivity	28
Bees-wax (Apismellifera)	Melting point 62-64 C HLB = 12	Edible, easy use, smooth surface, hot melt extrusion prolonged release for hydrophilic substances, protection from chemical degradation	Oxidation	29
Carnauba wax (Copernicacerifera)	mp: 78–85 °C HLBrequired = 12	Good compatibility hot melt extrusion, embedding water soluble components, taste masking	Oxidation	30,31
Paraffin (hard mineral)	mp: 50-60 C	Embedding water soluble components liquid paraffin in the emulsification	Sensitivity	32

		process		
Chitosan	Soluble in weak acids Mucoadhesive reacts with negatively charged surfaces	Antifungal, antibacterial, reduces LDL (low-density lipoprotein), tissue regenerative, pulmonary delivery Ionotropic gelation, coacervation with anions, modified emulsification	pH dependence (insoluble above pH 6.5) Addition of electrolytes precipitates chitosan in solution, hygroscopic	33-35
Sodium hyaluronate	Anionic character, soluble in water, high viscosity at low concentration	In microspheres nasal, vaginal, ophthalmic delivery systems	Very hygroscopic, when heated, emits Na <sub>2</sub> O	36,37
Starch (wheat, corn, potato, rice, tapioca)	Starch from different origins Differ in particle size and shape Soluble in hot water after a time of gelatinization	Spray drying, extrusion, molecular inclusion, coacervation with proteins, hydrocolloid-forming, release via swelling, diffusion, erosion	Hygroscopic	38
Gaur gum	Water soluble, nonionic, galactomannan forms a thixotropic solution, stable at pH 4–10.5	Controlled-release, colon-targeted release, appetite suppressant, thermoreversible	Needs preservation, borate hinders swelling	39
Locust bean gum (LBG)/carob, ceratonia	Nonionic, galactomannan, dispersible in hot water, soluble at higher temperature	Controlled release in combination pseudoplastic, gelling with the addition of borate, solubility not affected by pH or ionic concentration	Low water solubility, hypersensitivity	40
Konjac Gum	Water soluble	Elevation of temperature, increase gelation, antioxidant properties	Indigestible	41,42
Carrageenan	Anionic polymer, $\iota$ -Carrageenan: shear thinning thixotropic gel forming	$\lambda$ -Carrageenan: highest anionic charge, high solubility, but no gelling, $\kappa$ , $\iota$ -Carrageenan:	Acid-catalyzed hydrolyses, especially at higher temperature and pH < 3	43,44

		elastic gel is formed with K <sup>+</sup> ,Ca <sup>2+</sup> , thermoreversible gel forming Release by erosion (physicalcontact- Scentcaps®), effective against HPV(human papilloma virus)	Administration of >2 g/kg orally Induces intestinal ulcers, not biodegradable.	
Agarose	Soluble in hot water	swelling, Thermoreversible gelation (at ≈37 °C) with hysteresis	Poor biodegradability	45

### Evaluation of Microspheres

#### Particle size and shape

Considering the microspheres, the traditional SEM (scanning electron microscopy) and LM (light microscopy) approaches are the most extensively employed. Both approaches can be used to identify the shape and exterior structure of microspheres. In the case of double walled microspheres, light microscopy allows for precise control of coating conditions. The architecture of the microspheres may be seen before and after coating, and the alterations can be assessed microscopically. In comparison to light microscopy, scanning electron microscopy has a better resolution

#### Angle of contact

The angle of contact is measured to determine the wetting property of the micro particle carrier. The nature of the microspheres is determined by their hydrophobicity or hydrophilicity. This thermodynamic feature is unique to the solid and is influenced by the adsorbed component's existence. The angle of contact is measured at the solid/air/water interface.

#### Isoelectric point

The device used to assess the electrophoretic mobility of the microspheres is micro electrophoresis, from which the isoelectric point can be calculated. The mean velocity at different Ph values ranging from 3 to 10 is computed by monitoring the time of travel of a particle across a distance of 1 mm. This information can be used to determine the particle's electrical mobility. The electrophoretic mobility of microspheres can be linked to the surface charge, ionizable behavior, or ion absorption nature of the microspheres.

#### Density determination

The density of the microspheres can be determined using the multi volume pycnometer. The correctly weighted sample in a cup is inserted into the multi volume pycnometer. Helium is put into the chamber at a steady pressure and allowed to expand. The pressure within the chamber decreases as a result of this expansion. The two successive readings of the pressure reduction at various beginning pressures are documented. The density and volume of the microsphere's carrier are calculated using two pressure readings.

#### Density of the bulk:

With the use of a funnel, a precisely weighed sample of microspheres is gently placed into a 10 ml graduated cylinder. The original volume is usually noted. If required, carefully level the microspheres without compacting them, and read the apparent volume V<sub>0</sub>, which is still unsettled.

to the nearest graduated unit. Calculate the bulk density in g/cm<sup>3</sup> by the formula.

$$D_f M = V_0$$

Where D<sub>f</sub> is bulk density, M is weight of samples in grams and V<sub>0</sub> is volumes of sample in cm<sup>3</sup>.

**Tapped Density:**

The tapped density is obtained by dividing the mass of a powder by the tapped volume in  $\text{cm}^3$ . The sample of microspheres is carefully introduced into a 10 ml graduated cylinder. The cylinder is dropped at 2- second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped density of each formulation is then obtained by dividing the weight of sample in grams by the final tapped volume in  $\text{cm}^3$  of the sample contained in the cylinder. It is calculated by using equation given below

$$D M o = Vp$$

Where  $D_o$  is bulk density,  $M$  is weight of samples in grams and  $V_p$  is final tapped volumes of granules in  $\text{cm}^3$ .

**Compressibility index**

It is also calculated through consolidation index of Carr using this formula:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

**Physical appearance**

All the prepared microspheres were observed visually for color and uniformity of size.

**Percent yield**

Percentage yield of the prepared microsphere is calculated using the following equation.

$$\% \text{ yield} = \frac{\text{Weight of dried microspheres}}{\text{Amount of drug} + \text{Amount of polymer}}$$

**Swelling index**

Swelling index of dried microspheres was calculated by this formula:

$$\text{Swelling Index} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

**Fourier Transform-Infrared Spectroscopy**

Fourier Transform Infrared Spectroscopy is utilized to determine the deterioration of the carrier system's polymeric matrix. ATR [alternated total reflectance] is used to investigate the surface of the microspheres. The IR beam travelling through the alternating total reflectance cell reflected multiple times through the sample, resulting in mostly surface material IR spectra. The alternating total reflectance-Fourier Transform-Infrared Spectroscopy gives information about the surface composition of the microspheres depending on the manufacturing techniques and conditions.

**Chemical analysis using electron spectroscopy**

The surface chemistry of the object was studied using ESCA [Electron spectroscopy for chemical analysis]. It is possible to identify microspheres. Electron spectroscopy for chemical analysis gives a method for determining the atomic composition of a surface. Identifying the surficial degradation of the biodegradable microspheres, the spectra obtained using electron spectroscopy for chemical analysis can be used.

**Entrapment efficiency**

By allowing the washed microspheres to lyse the capture efficiency of the microspheres or the percent entrapment can be determined. To the determination of active constituents as per monograph requirement the lysate is then subjected. By using the following equation, the percent encapsulation efficiency is calculated by the formula:

$$\% \text{ Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

**Applications****Medical application**

1. Release of proteins, hormones and peptides over extended period of time.
2. Gene therapy with DNA plasmids and also delivery of insulin.
3. Vaccine delivery for treatment of diseases like hepatitis, diphtheria, birth control.
4. Targeting tumor vessels, targeting of tumor cells, antigens, by intra-arterial application.
5. Tumor targeting with doxorubicin and also treatments of leishmaniasis.
6. Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
7. Used in isolation of antibodies, toxin extraction by affinity chromatography.
8. Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal

**Microspheres in vaccine delivery**

Protection against the microorganism or its harmful product is a requirement of a vaccination. An ideal vaccine must meet the following criteria: efficacy, safety, ease of use, and cost. The question of safety and minimizing adverse reactions is a difficult one. The degree of antibody response generation and the issue of safety are both intimately related to the technique of application. Biodegradable vaccine delivery technologies for parenteral vaccinations may be able to address the shortcomings of traditional vaccines. Parenteral (subcutaneous, intramuscular, intradermal) carriers are appealing because they provide a number of benefits, including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.
4. Targeting using micro particulate carriers

**Surface modified microspheres**

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. The most studied surface modifiers are:

1. Antibodies and their fragments
2. Proteins
3. Mono-, oligo- and polysaccharides
4. Chelating compounds (EDTA, DTPA or Desferroxamine)
5. Synthetic soluble polymers

Such modifications are provided on surface of microspheres in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

**Monoclonal antibodies mediated microspheres**

Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. The Mabs can be attached to microspheres by any of the following methods

1. Nonspecific adsorption
2. Specific
3. Direct coupling
4. Coupling via reagents

**Imaging**

Microspheres have been examined extensively and have been employed for targeted applications. Radio-labeled microspheres can be used to imaging a variety of cells, cell lines, tissues, and organs. The particle size range of microspheres is a key component in deciding which sites can be imaged. The particles injected intravenously in a vein other than the portal vein will become caught in the lungs' capillary bed. Using tagged human serum albumin microspheres, this phenomenon is used for scientific graphic imaging of tumour masses in the lungs.

**Topical porous microspheres**

Microsponges are porous microspheres with a network of linked voids ranging in size from 5 to 300 micrometers. These micro sponges can entrap a wide range of active compounds, including emollients, perfumes, and essential oils, among others. These porous microspheres with active chemicals can be used in creams, lotions, and powder formulations. Microsponges are non-collapsible structures with a porous surface that allows active substances to be released gradually.

**Microspheres in Gene delivery:**

Viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems are all examples of gene delivery systems. Because viral vectors are very effective and have a large range of cell targets, they are ideal for gene delivery. When employed in vivo, however, they produce immunological responses as well as carcinogenic consequences. Non-viral delivery techniques are being studied for gene therapy to address the limitations of viral vectors. The advantages of a non-viral delivery system are ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale, repeatable production. For gene delivery applications, polymer has been employed as a carrier of DNA.

### Microspheres for Oral drug delivery

Rabbits were used to test the possibility of polymer films containing diazepam as an oral medication delivery system. The findings suggested that a film made up of a 1:0.5 drug-polymer mixture could be a useful dosage form comparable to existing tablet dosage forms. Polymer's capacity to form films may allow it to be used in the manufacture of film dosage forms as a substitute for pharmaceutical tablets. Polymer is a unique polymer for oral drug administration applications because of its pH sensitivity and the reactivity of the major amine groups.

### Ophthalmic Drug Delivery

Polymer has favourable biological qualities such as bio adhesive, permeability-enhancing capabilities, and unique physico-chemical properties, making it a remarkable material for the construction of ocular drug delivery vehicles. Polymer hydrogels offer better acceptability for ophthalmic delivery, such as suspensions or ointments, due to their elastic properties. Ophthalmic chitosan gels improve adhesion to the mucin that coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, slowing drug elimination by the lachrymal flow.

### Nasal drug delivery:

The mucosa of the nose is an excellent location for bio adhesive medication delivery systems. Polymer-based drug delivery systems, such as micro spheres and gels, have been shown to have high bio adhesion properties and to swell easily when in contact with the nasal mucosa, enhancing drug bioavailability and residence time. For nasal sustained release of vancomycin hydrochloride, various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride are good choices. Nasal delivery of Diphtheria Toxoid encased in chitosan microparticles induces a protective systemic and local immune response against Diphtheria Toxoid, as well as increased IgG production. Nasal formulations have elicited strong serum IgG responses that are comparable to secretory IgA levels, which are superior to parenteral administration of the antibody.

**Table:-** Microspheres for Nasal Drug Delivery.

Drug	Polymer Use	Result
Gentamicin	Degradable starch microspheres and lysophosphatidicholine	Increased nasal absorption
Insulin	Degradable starch microspheres and lysophosphatidicholine	Increased efficiency to nasal route
Human growth hormone	Degradable starch microspheres and lysophosphatidicholine	Rapid and increased absorption
Desmopressin	Starch	Addition of LPC causes a five folds increase in C <sub>max</sub> and two folds increase in bioavailability
Haemagglutinin (HA)	Hyaluronic acid esters	With mucosal adjuvant serum IgG antibody response ascompared to i.m. immunization

### Recent Applications of Controlled Release Microspheres

Microspheres with controlled release are being developed for a variety of purposes, including the delivery of big, fragile medicines like proteins and nucleic acids. The following are a few recent examples.

Vaccines with a Limited-Release Period Vaccination has been extremely effective in managing or even eradicating several key forms of infectious diseases, and new or improved vaccines for AIDS, hepatitis B, anthrax, and SARS are all being studied extensively. The requirement for many administrations is a common issue.

Single-shot vaccine delivery systems should deliver the antigen(s) and adjuvant on a predetermined schedule and retain the antigen's bioactivity throughout the production process and the device's frequently lengthy stay in the body.

### Drugs Formulated as Microspheres for Novel Drug Delivery

**Table:-** List of Drugs Formulated as Microspheres for Novel Drug Delivery

Category	Drug	References
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Anticancer	Fluorouracil	86
	Cisplastin	87
	Mitoxantrone	88
	Oxantrazol	89
NSAID	Acelofenac	90
	Ibuprofen	91
	Piroxicam	92
	Flurbiprofen	93
Antibiotic	Cefdinir	94
	Amoxicillin	95
	Gentamicin	96
Anti-inflammatory	Indomethacin	97
	Diclofenac sodium	98
	Ketoprofen	99
Cardiac agent	Telmisartan	100
	Nifedipine	99,100
	Propranolol	99,100
	Diltiazem	101
Steroidal	Progesterone	102
Anti-diabetic	Insulin	103
Diuretics	Furosemide	104
Hypoglycemic agents	Glipizide	105
	Vidagliptin	105
Anti-tuberculosis agent	Rifabutin	106
Anti- HIV	AbacavirSulphate	107
Bipolar Disorder	Lithium Carbonate	108
SNRIs	Venlafaxine hydrochloride	109
Bronchodilators	Salbutamol	110
K <sup>+</sup> channel activator	Nicorandil	111
Hypolipidemic agents	Fluvastatin Sodium	112
Proton pump inhibitors	Rabeprazole Sodium	113
Xanthines	Theophylline	110

### Marketed Products of Microspheres:

**Table:-** List of Marketed Microspheres Drug Products.

Sr. No.	Drug	Technology	Commercial Name
1	Bromocriptine	Spray drying	Parlodel LARTM
2	Triptorelin	Phase separation	Trelstar Depot, DecapeptylR SR
3	Octreotide	Phase separation	SandostatinR LAR
4	Nalrexon	Double emulsion	Vivitrol
5	Lanreotide	Phase separation	Somatuline
6	Somatropin	Spray drying	Nutropin
7	Leuprolide	Double emulsion	Leupron Depot
8	Resperidone	Double emulsion	Risperdal, Consta
9	Pantoprazole		Prantonix
10	Sulphur Hexafluoride		Lumason
11	Human Albumin		Optison
12	Tretinoin		Altinac
13	Perflutren		Definity
14	Triamcinolone Acteonid		Zilretta
15	Minocycline		Arestin

**Conclusion:-**

Microspheres have been identified as one of the best innovative drug delivery systems, with the benefit of target selectivity and improved patient compliance. Its applications are vast, as it is employed not only for drug delivery but also for imaging malignancies, detecting biomolecular interactions, and so on.

Microspheres will play a central role in novel drug delivery in the future, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, and effective in vivo delivery, and supplements as miniature versions of diseased organs and tissues in the body, thanks to the combination of various other strategies.

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