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A PERSPECTIVE REVIEW OF MICROSPHERES: IN DRUG DELIVERY

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ABSTRACT:

Drug distribution management has undergone substantial advancements over the past thirty years, establishing itself as a crucial component of pharmaceutical development. Traditional medications present certain limitations, particularly the necessity for frequent monitoring of plasma drug concentrations, especially for those with short half-lives. The regular administration of these medications can lead to decreased patient adherence and fluctuations in plasma levels. These issues can be mitigated through the development of innovative drugs, especially those utilizing controlled drug delivery systems, which maintain stable plasma concentrations by gradually releasing the drug over an extended duration. Effective management of drug distribution can also enhance the bioavailability of medications, thereby improving both treatment outcomes and patient adherence. Various methods exist for controlled delivery, including liposomes, ethosomes, phytosomes, microemulsions, and microspheres. Among these, microspheres are particularly advantageous as they facilitate the slow release of drugs from polymer matrices, with the polymers typically being biodegradable and devoid of adverse effects. Consequently, microspheres find applications across numerous medical disciplines, including oncology, radiology, gynaecology, cardiology, pulmonology, and diabetes management. This review article provides an overview of the different types of microspheres and the latest advancements in their design. Furthermore, microspheres can be analysed and functionalized through a range of techniques.

Keywords: Controlled release, Microspheres, Bío adhesion, constant drug plasma levels, micron size particles, biodegradable.

1. INTRODUCTION :

The oral route is generally regarded as the preferred method for administering medication. However, the therapeutic effectiveness of numerous medications is often constrained by their short half-lives in the bloodstream and their restricted absorption in specific segments of the intestine. In many cases, such pharmacokinetic limitations require multiple doses of the medication to attain the desired therapeutic outcomes. Microspheres are tiny, spherical particles that range in size from 1 to 1,000 μm in diameter. They can be made from a variety of materials, including polymers, ceramics, and inorganic materials.

Microspheres are crucial in enhancing the bioavailability of traditional pharmaceuticals while also reducing adverse effects. The process of microencapsulation is employed to alter and slow down the release of the drug. Owing to their diminutive particle size, microspheres are extensively dispersed throughout the gastrointestinal tract, which facilitates improved drug absorption and diminishes side effects.

1.1 ADVANTAGES

- Particle size reduction enhances the solubility of the poorly soluble drug.
- Microspheres aid in conversion of oils and other liquids to solids for ease of handling
- Provide constant drug concentration in blood thereby increasing patient compliance.
  Decrease dose and toxicity.
- Microspheres have decreased enzymatic and proteolytic degradation.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreases the toxicity.

1.2 DISADVANTAGES

- The cost of production is high.
- Dose dumping takes place.
- The release of drug may be influenced by various factors like food and transient time.

- There is no uniformity in the release of drug.
- Reproducibility is less.
- Environmental factors like temperature, pH, oxidation, change in solvent, heat influences the release of drug.

2. POLYMERS :

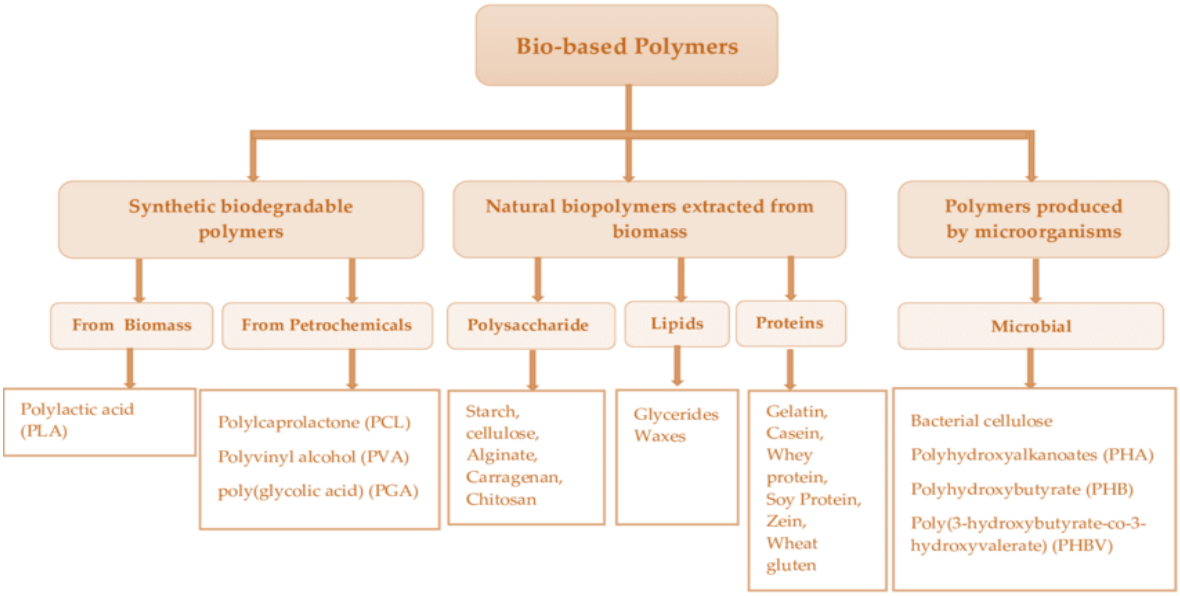

Fig:1-Types of polymers

3.TYPES OF MICROSPHERES :

- Bio adhesive
- microspheres
- Magnetic microspheres
- Floating microspheres
- Radioactive microspheres
- Polymeric microspheres

3.1 BIO ADHESIVE MICROSPHERES

The medicine adhering to the membrane by utilizing the water-soluble polymers' sticking ability is known as adhesion. Bio-adhesion is the process by which medication delivery devices adhere to mucous membranes, such as those in the mouth, eyes, throat, and nose. This kind of microspheres provides release of drug at targeted site for a prolonged period.

3.2 MAGNETIC MICROSPHERES

Microspheres are typically free-moving, tiny, spherical particles that range in size from 1 to 1000 μm and are made of proteins or synthetic polymers that are biodegradable. This are of two types

I. Therapeutic magnetic microspheres – These are used for chemotherapy for liver treatment. It is mostly used for delivery for proteins and peptides.
II. Diagnostic magnetic microspheres – These types of microspheres are used for detecting of tumours

3.3 FLOATING MICROSPHERES

The bulk density of the floating type is lower than that of the gastric fluid, it floats in the stomach without influencing the rate of gastric emptying. The system is observed to be floating on stomach contents, decreasing gastric residency, and increasing variability in plasma concentration as the drug is released gradually at the intended rate.

3.4 RADIOACTIVE MICROSPHERES

These microspheres, which are larger than capillaries and have sizes between 10 and 30 nm, are utilized in radioembolization therapy. They cause tumours of interest when they are injected into arteries. High radiation doses are delivered to specific regions by these radioactive microspheres without endangering healthy tissues.

3.5 POLYMERIC MICROSPHERES

The polymeric microspheres are of two types. They are biodegradable and synthetic polymeric microspheres.

I. **Bio degradable microspheres -** These consists of natural polymers like starch as it is biocompatible bio degradable and bio sticky.

II. **Synthetic polymeric Microspheres** – The synthetic polymers are used as bulking agent, fillers, embolic particles, and vehicles for delivering drug. The main disadvantage is potential risks, embolism, and further organ damage.

4.METHOD OF PREPARATIONS :

1. 1.Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Solvent extraction
7. Quassi emulsion solvent diffusion

4.1 SPRAY DRYING

In the process of spray drying, the polymer is initially dissolved in a volatile organic solvent such as acetone or dichloromethane. The medication is subsequently homogenized at high speeds and incorporated into a polymeric solution. Following this, a heated air stream atomizes the mixture. Atomization involves creating small droplets from which the solvent quickly evaporates, resulting in microspheres that vary in size from 1 to 100 micrometres. A cyclone separator is employed to remove micro particles from the hot air, while vacuum drying is used to eliminate any residual liquid.

4.2 SOLVENT EVAPORATION

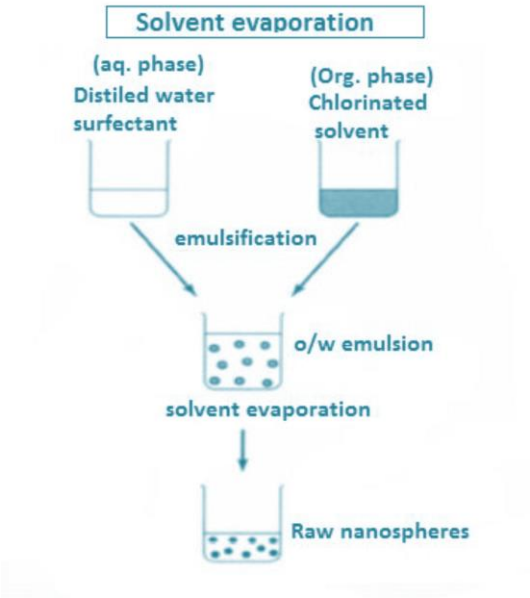

Fig:2- Solvent evaporation technique

SINGLE EMULSION TECHNIQUE

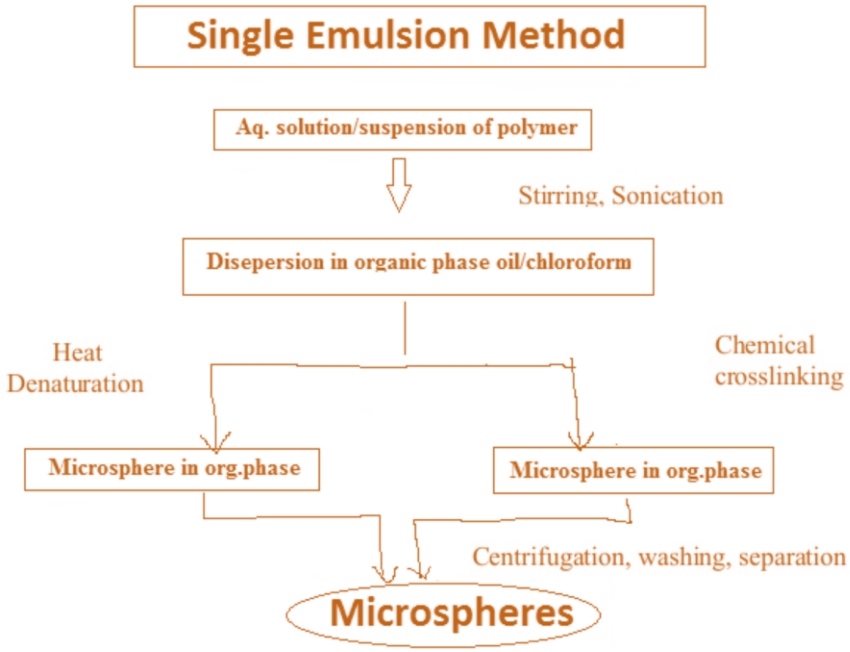

Fig:3- Single emulsion technique

DOUBLE EMULSION TECHNIQUE

This technique involves the formation of multiple emulsions or double emulsions of W/O/W

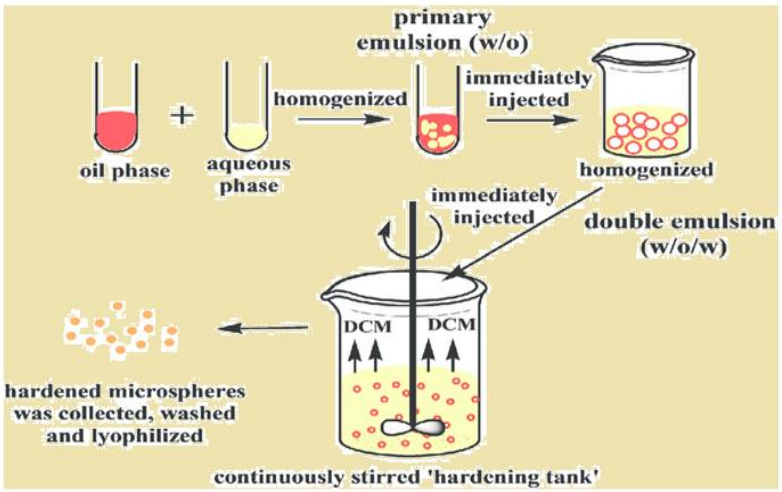

Fig:4- Double emulsion technique

4.4 PHASE SEPERATION COACERVATION TECHNIQUE

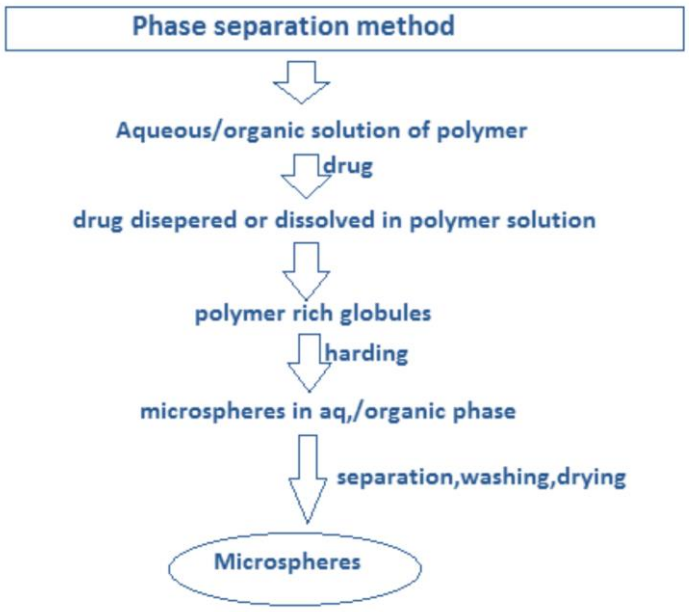

Fig:5- Phase separation coacervation technique

SOLVENT EXTRACTION

The medication and polymer used in solvent extraction must dissolve in organic solvent to generate an aqueous solution. To create a microsphere in aqueous medium, phase and extract this solution using an organic solvent that is water soluble

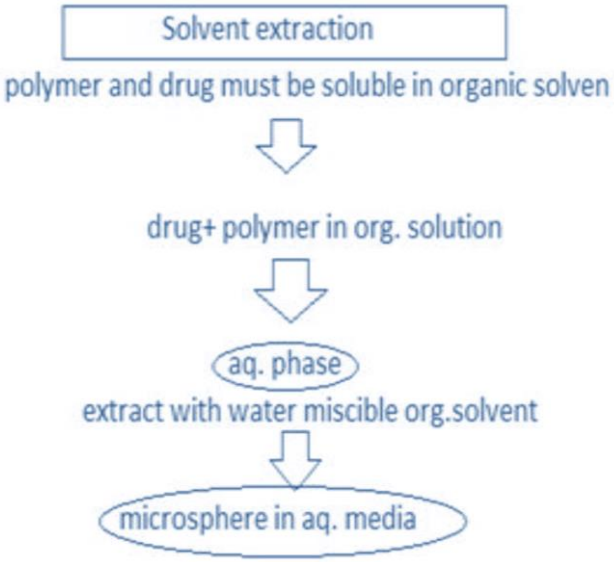

Fig:6- Solvent extraction

QUASSI EMULSION DIFUSSION TECHNIQUE

The quasi-emulsion solvent diffusion technique for the fabrication of drug-controlled release microspheres composed of acrylic polymers. This quasi-emulsion solvent diffusion approach can also be utilized to produce micro sponges by incorporating an external phase that consists of polyvinyl alcohol and distilled water. The internal phase is comprised of the drug, ethanol, and polymers. Following the preparation of the internal phase at a temperature of 60°C, the external phase is introduced. The resulting mixture is then stirred continuously for a duration of two hours to form an emulsion. After filtration, the micro sponges can be extracted.

5. EVALUATION OF MICROSPHERES :

PHYSICOCHEMICAL CHARACTERIZATION

1. **Particle size and shape** - The particle size and shape are mostly determined by light microscopy (LM) and scanning electron microscopy (SEM). The microspheres are visualized before and after coating. This method is used to identify the shape, size, and morphology of microspheres.
2. **Density determination** – The density of microspheres is measured by a device called multi volume pycnometer. The sample to be analysed is placed in the device and then helium gas is introduced at a constant pressure and allowed to expand. This results in decrease in pressure within the chamber. The pressure difference is calculated. Thus, the density is determined.
3. **Electron spectroscopy for chemical analysis** – The surface chemistry of microspheres is determined by electron spectroscopy for chemical analysis.
4. **Fourier transform- infrared spectroscopy** – This technique is used to determine the polymeric degradation within the microspheres.
5. **Swelling index** – The swelling index is determined by measuring the weight of microspheres when placed in specific solvent. Swelling degree is calculated by allowing 5mg of dried microspheres to swell overnight in beaker containing 5ml of buffer solution.

$$\text{Swelling Index} = \frac{wf - wo}{wo} \times 10 \quad (1)$$

IN VIVO METHODS

1. **Animal models-** Animals are used to determine the effectiveness of the formulation. The animals used are dogs, rats, rabbits, cats, etc. The animal is anesthetized and the formulation injected to it. The pharmacokinetic and pharmacodynamic data is analysed by taking blood samples.
2. **Buccal absorption-** This method is used to detect drug loss by oral cavity. The characteristics of drugs like pH, contact time, initial concentration can be determined in oral cavity.
3. **Corneal perfusion chambers -**This test is used for developing ophthalmic formulations. The corneal chamber is made up of poly carbonate, stainless steel making it easier for topical drug delivery.

IN VITRO METHODS

1. **Beaker test –** In this method the formulation is dissolved in a medium uniformly by using stirrer. The capacity of fluid contained in beaker is 50 -500ml and stirrer speed is 60-300rpm.The amount drug dissolved in medium is calculated.
2. **Dissolution apparatus test**-This test is conducted to determine the dissolution time of microspheres. This test is carried out according to USP and BP standards. The dissolution medium used in evaluation contains 100-500ml and has a rotational speed of 50-100rpm.
3. **Interface diffusion system -**The four-compartment interface diffusion system was created by Dearden and Tomlinson. The medication is in a buffer in Compartment A, which stands in for the mouth cavity. 1-octanol is present in Compartment B, which stands in for the buccal membrane. 0.2 M HCl is found in Compartment C, which stands for bodily fluids. 1-octanol is also present in Compartment D, which stands for protein binding. The aqueous phase and 1-octanol are saturated with one another before to usage. Using a syringe, samples are extracted and brought back to compartment A. Through the analysis of samples from all four body compartments, this technique enables the measurement of drug dissolution in each one.

Table 1- Marketed Formulations of Microspheres

MARKETED NAMES	COMPANY NAMES	DISEASE	DRUG
Asacol	Win Medicare pharma	Ulcerative colitis	Mesalamine
Intazide	Intas, India	Ulcerative colitis	Balsalazide
Colospa	Solavay, India	Irritable colon syndromes	Mabeverine
Decapeptyl	Ferring pharmaceuticals	Advanced prostate cancer	Triptorelin
Sazo	Wallac India	Ulcerative colitis, Crohn's disease	Sulphasalazine
Nutropin	Genetech	Growth hormone deficiency	Somatropin
Arestin	OraPharma	Periodontitis	Minocycline
Risperdal	Apollo	Schizophrenia	Risperidone
Mesacol tablet	Sun pharma	Ulcerative colitis	Mesalamine
Sandostatin® LAR	Novartis	Acromegaly, Neuroendocrine tumours	Octreotide LAR
Vivitrol	Alkermes	Alcohol dependence, Opioid dependence prevention	Naltrexone

CONCLUSION-

Compared to traditional drug delivery methods, the idea of microsphere drug delivery systems has some benefits, such as regulated and prolonged distribution. In view to meet a variety of needs, including oral, targeted, sustained, topical, and even biotechnological applications like gene therapy, they enable the exact and regulated delivery of drugs. Microsphere formulations are proven to be efficient carriers for the novel drug delivery system and exhibit greater potency and effectiveness in in-vivo drug delivery systems. Therefore, production of microspheres has been increased all over the global market.

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