An overview on microspheres

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Abstract

Microspheres are multiparticulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. They are made from polymeric waxy or other protective materials such as natural, semi synthetic and synthetic polymers. Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 µm consisting of proteins or synthetic polymers. . The present review highlights various types of microspheres, different methods of preparation, its applications and also various parameters to evaluate their efficiency. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, Radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres and are prepared by methods like Spray Drying, Solvent Evaporation, Single emulsion technique, Double emulsion technique, Phase separation coacervation technique, Spray drying and spray congealing, Solvent extraction. Microspheres have wide range of applications because of controlled and sustained release. This article also focuses on the various drugs that can be formulated into microspheres for controlled and sustained release.

Keywords: Microspheres, controlled, polymer, multiparticulate.

Introduction

Microspheres are small spherical particles with diameters from 1 to 1000µm (or 50nm to 2mm) [1]. In some cases, microspheres are also known as microparticles. Microspheres can be produced from several natural and synthetic polymeric materials or even from inorganic materials For example, microspheres can be produced from commercially available polymers or ceramics. Depending on the method, solid or porous microspheres can be obtained for specific intended applications.

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The variety of methods for the production of microspheres offers a myriad of opportunities to control the aspects of administration of the pharmaceutical compound. This focus facilitates the precise release of the desired amount of a component at the site of action and its reduction at non-target sites. Similarly, this factor guarantees the protection of the compounds before and after administration. Additionally, the vectorization of pharmaceutical compounds can be manipulated by coupling a recognition molecule to the microsphere. The exploitation of these changes in pharmacokinetic behavior can lead to an improved therapeutic effect. The aim of any pharmaceutical compound administration system is to provide a therapeutic amount of the compound at the correct site in the body to quickly achieve an effective concentration and then maintain it for a given time. A well-designed modified release system for the compound can overcome some of the problems of conventional

therapy and improve the therapeutic efficiency, thus improving the patient's quality of life. [2]

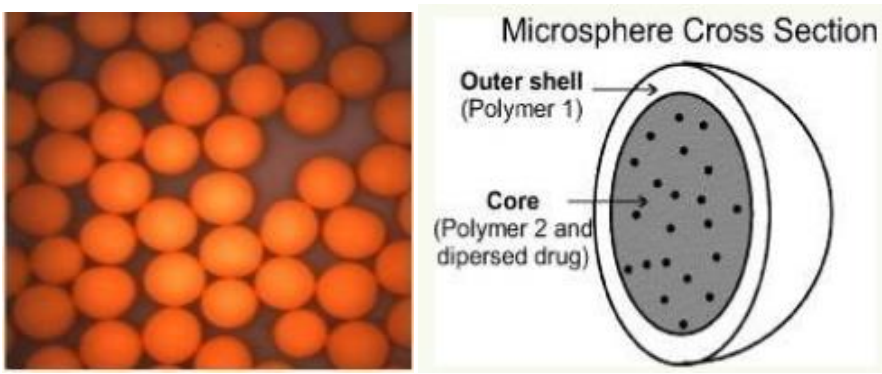

Fig 1:Microspheres

History and development

The concept of drug delivery has been revolutionized. The strides have been made to lend the patient derive maximum benefits of drug. The drug should be delivered to specific target sites at a rate and concentration that permit optimum therapeutic efficacy while reducing side effects to minimum. Another aspect to be considered in drug delivery is patient compliance during drug therapy. [1] The concept of the advanced drug delivery system especially those offering a sustained and controlled action of drug to desired area of effect, attained great appeal for nearly half a century. However, actual practice of controlled release began with advent of timed release coating of the pills or solid drug particles in order to mask their unacceptable taste or make them more palatable. [1] Between **1940** and **1960s,** the concept of microencapsulation technology began as an alternative means of delivering drugs. In continued quest for more refined systems, in **1980s,** polymer/membrane technology came to be known at forefront. Further, the process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposomes, bioerodible polymer, implants, monoclonal antibodies and various particulate carriers (e.g., nanoparticles and microspheres, etc). The microparticle delivery systems are considered and accepted as reliable means to deliver the drug to the target site with specificity. [1]A very good example of the development of one of the microspheres is microspheres intended for the Treatment of Vascular Complications of the Eye.The objective of this study was to design 1, 3, and 6 month sustained-release poly lactide-co-glycolide (PLGA) microspheres of SAR 1118, a lymphocyte function-associated antigen-1 antagonist, using Design of Experiments. A full-factorial design was used to identify the polymers suitable for degradation in 1, 3, and 6 months and the Box-Behnken design was used to study the influence of the polymer type, polymer concentration, and drug to polymer ratio on drug loading, burst release, and particle size. From the full-factorial design, PLGA (50:50), PLGA (75:25), and PLGA (85:15) with an inherent viscosity of 0.3–0.5 dL/g were identified as polymers suitable for degradation in 1, 3, and 6 months, respectively. From the Box-Behnken design, the optimized polymer concentration (12% w/v) and drug to polymer ratio (0.15) were identified and used to prepare the SAR 1118-encapsulated microspheres with the above 3 polymers and evaluated for drug loading, burst release, and sustained drug release. The burst release in these 3 batches was less than 20% and the drug loading ranged from 15%–18%. More than 90% of SAR 1118 release from PLGA (50:50), PLGA (75:25), and PLGA (85:15) microspheres occurred in 1, 3, and 6 months, respectively. Thus, the **in vitro** cumulative release data are remarkably close to the predicted values. The results demonstrated the potential of the Design of Experiments in designing theSAR 1118 microspheres with a high loading efficiency, low burst release, and sustained release for a desired duration. [3]

Material Used

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. These materials include the polymers of natural and synthetic origin and also modified natural substances.

Classification of Polymers

Synthetic Polymers

Non biodegradable

- PMMA
- Acrolein
- Glycidyl methacrylate
- Epoxy polymers
- Lactides and glycolides and their copolymers
- Polyalkylcyano acrylates
- Polyanhydrides

Natural Materials

Proteins

- Albumins
- Gelatin
- Collagen

Carbohydrates

- Starch
- Agarose
- Carrageenan
- Chitosan

Chemically modified carbohydrates

- DEAE cellulose
- Poly(acryl) dextran
- Poly(acryl) starch
- Targetability
- Polyvalent [1]

Types of microspheres[4]

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

i. Biodegradable polymeric microspheres
ii. Synthetic polymeric microspheres

Bioadhesive microspheres

The sticking of drug to membrane by using the sticking property can be defined Adhesion of water soluble polymers. This type of microsphere exhibits a prolonged residence time at the site of application. E.g. adhesion of the drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc.

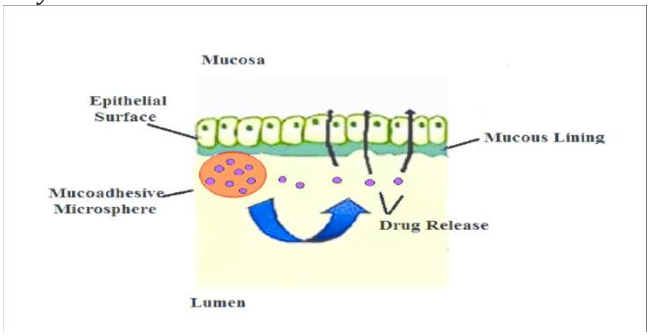

Fig 2: Bioadhesive microspheres

Magnetic microspheres

This type of delivery system is very much important for localizing the drug to the disease site in which larger amount of freely circulating drug can be replaced by small amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field.

Fig 3:Magnetic microspheres

Floating microspheres

In floating microspheres the bulk density is less than the gastric fluid therefore it remains buoyant in stomach without affecting on gastric emptying rate. Drug is released slowly at the desired rate of the site. it also reduces chances of striking and dose dumping Produces.

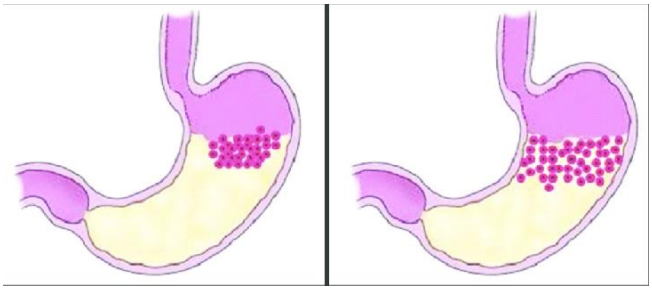

Fig 4: Floating microspheres

Radioactive microspheres

Radio imobilisation therapy microspheres having sized 10- 30 nm are of larger than capillaries. They are injected to arteries which lead to tumor of interest. These radioactive microspheres deliver high radiation dose to targeted areas without damaging the normal tissues. Different types of radioactive microspheres are α emitters, β emitters, γ emitters.

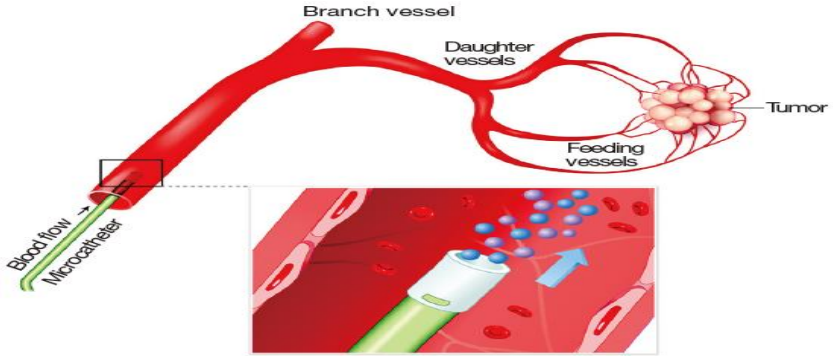

Fig 5: Radioactive microspheres

Polymeric microspheres The different types of polymeric microspheres classified as

i. **Biodegradable polymeric microspheres** Natural polymers such as starch are used as concept that they are biodegradable, biocompatible, and also Bioadhesive in nature. These polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results get gel formation.

ii. **Synthetic polymeric microspheres** Synthetic polymeric microspheres are widely used in clinical application, that are also used as bulking agent, fillers, embolic particles and drug delivery vehicles etc. and proved to be safe and biocompatible but the disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism ,further organ damage.

General methods of Preparation[1]

The microspheres can be prepared by using any of the several techniques discussed in the following sections, but the choice of technique mainly depends on the nature of polymer used, the drug, the intended use and the duration of therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below:

1. The particle size requirement
2. The drug or the protein should not be adversely affected by the process
3. Reproducibility of the release profile and the method
4. No stability problem

5. There should be no toxic product(s) associated with the final product.

Simple Emulsion Technique

The microparticulate carriers of natural polymers, i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g., oil. In the second step of preparation, cross-linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross-linking agents used include glutaraldehyde, formaldehyde, terephthaloyl chloride, diacid chloride, etc. Cross-linking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

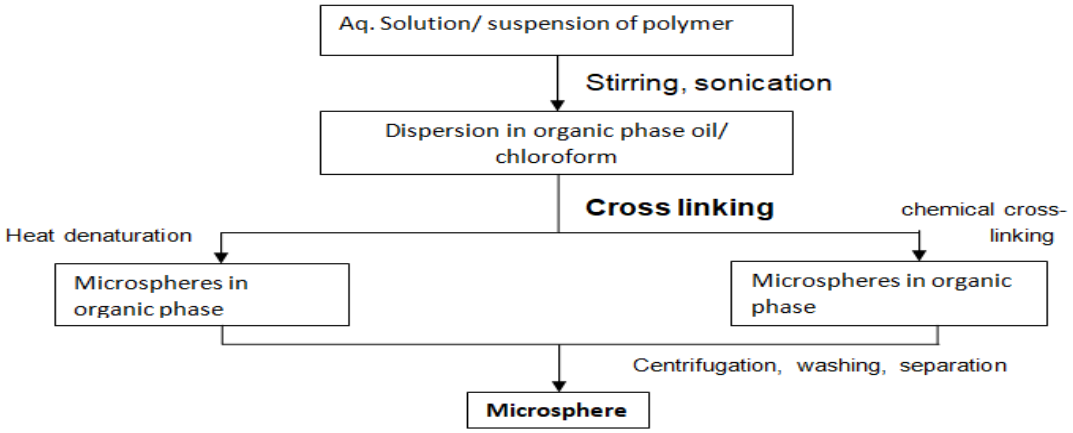

Fig 6: Schematic representation of simple emulsion based method of Microspheres preparation

Double emulsion technique

Briefly, double emulsion method of microspheres preparation involves the formation of multiple emulsions or double emulsion of type w/o/w and is best suited to the water- soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction process.

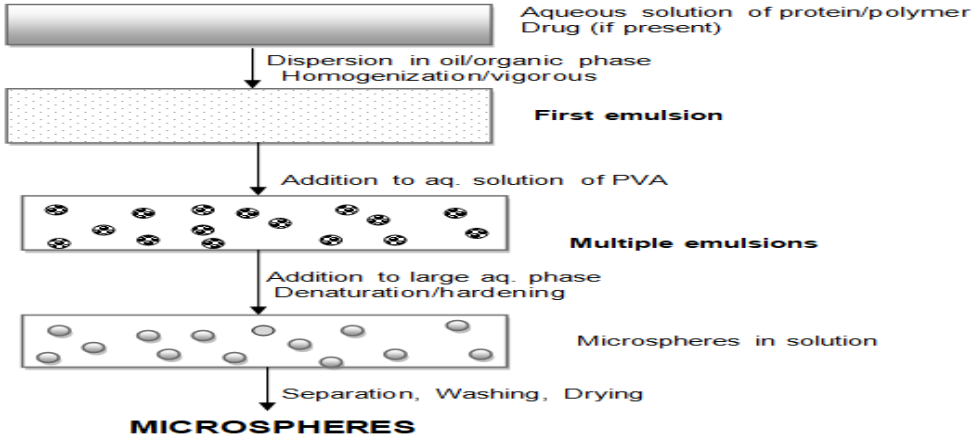

Fig 7: Schematic representation of double Emulsion Method of Microspheres Preparation

The solvent evaporation is carried out by maintaining emulsion at reduced pressure or by stirring the emulsion so that the organic phase evaporates out. In the later case, the emulsion is added to the large quantity of water (with or without surfactant) into which organic phase diffuses out. The solid microspheres are subsequently obtained by filtration and washing. A number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonists, vaccines, protein/ peptides and conventional molecules are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction.

Polymerization Techniques

The polymerization techniques conventionally used for the preparation of the microspheres are normally classified as:

1. Normal polymerization
2. Interfacial polymerization

Normal polymerization

The two processes are carried out in a liquid phase. Normal polymerization proceeds and carried out using different techniques as bulk, suspension, precipitation, emulsion and miceller polymerization process. The bulk polymerization, a monomer or a mixture of monomer along with the initiator is usually heated to initiate the polymerization and carry out the process. The catalyst or the initiator is added to the reaction mixture to facilitate or accelerate the rate of the reaction. The polymer so obtained may be moulded or fragmented as microspheres. For loading of drug, absorptive drug loading or adding drug during the process of polymerization may be opted.

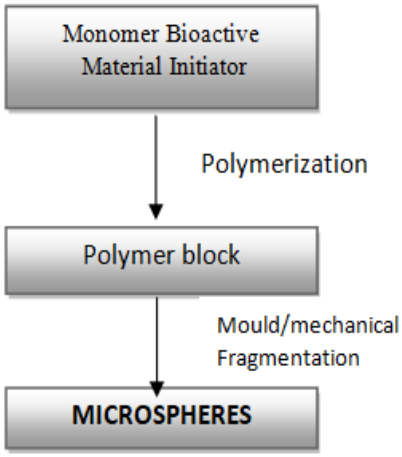

Fig: bulk polymerization

Fig 8:Bulk polymerization

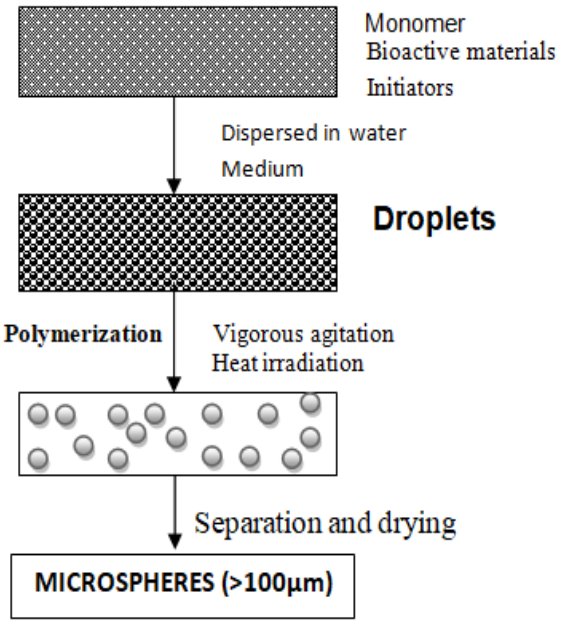

Fig 9:Suspension polymerization

The suspension polymerization which is also referred as the bead or pearl polymerization is carried out by heating the monomer or mixture of monomer with active principle as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives.The emulsion polymerization however differs from the suspension polymerization as due to presence of initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules. The bulk polymerization has an advantage of formation of the pure polymer, but it also suffers a disadvantage, as it is very difficult to dissipate the heat of reaction, which can adversely affect the thermolabile active ingredients. On the other hand suspension and emulsion polymerization can be carried out at lower temperature, since continuous external phase is normally water through which heat can easily dissipate. The two processes also lead to the formation of the higher molecular weight polymer at relatively faster rate. The major disadvantage of suspension and emulsion polymerization is,

association of polymer with the unreacted monomer and other additives.

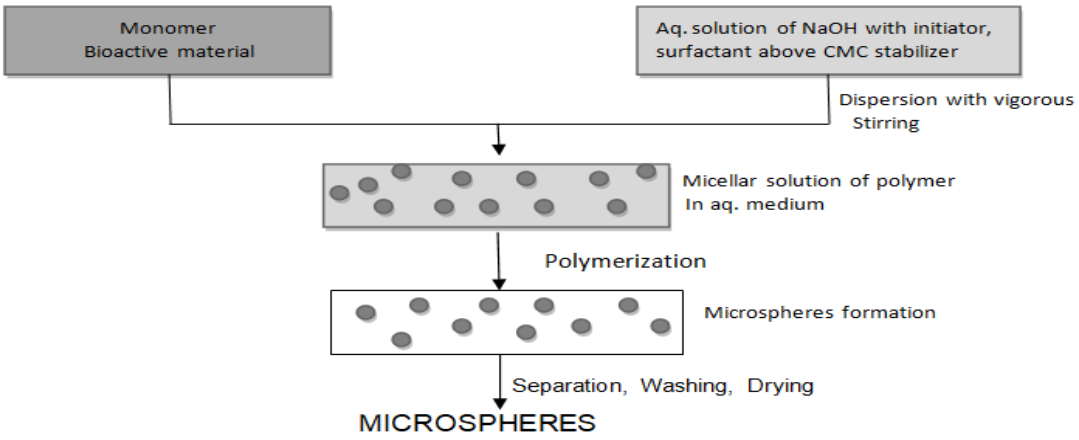

Fig 10: Schematic Representation of Emulsion Polymerization

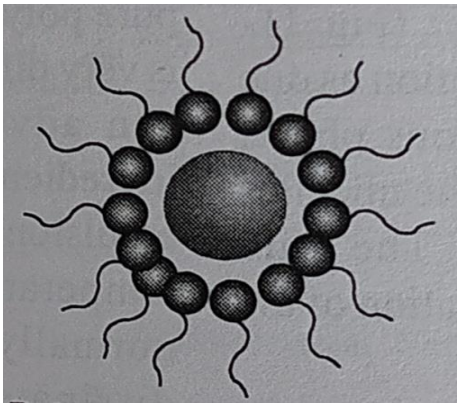

Fig 11: Polymerization in micelles having monomer globules

Interfacial polymerization

Interfacial polymerization essentially proceeds, involving reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one of which is dissolved in the continuous phase while the other being dispersed in continuous phase. The monomers present in either phases diffuse rapidly and polymerize rapidly at interface. Two conditions arise depending upon the solubility of formed polymer in the emulsion droplet. If the polymer is soluble in droplet it will lead to the formation of the monolithic type of carrier on the other hand if the polymer is insoluble in the monomer droplet, the formed carrier is of capsular (reservoir) type. The interfacial polymerization is not widely used in the preparation of the microparticles because of certain drawbacks, which are associated with the process such as:

- Toxicity associated with the unreacted monomer
- High permeability of the film
- High degradation of the drug during polymerization
- Fragility of microcapsules
- Non-biodegradability of the microparticles

Phase Separation Coacervation Technique

Phase separation method is specially designed for preparing the reservoir type of the system, i.e. to encapsulate water soluble drugs e.g. peptides, proteins, however, some of the preparations are of matrix type particularly, when the drug is hydrophobic in nature e.g. steroids.

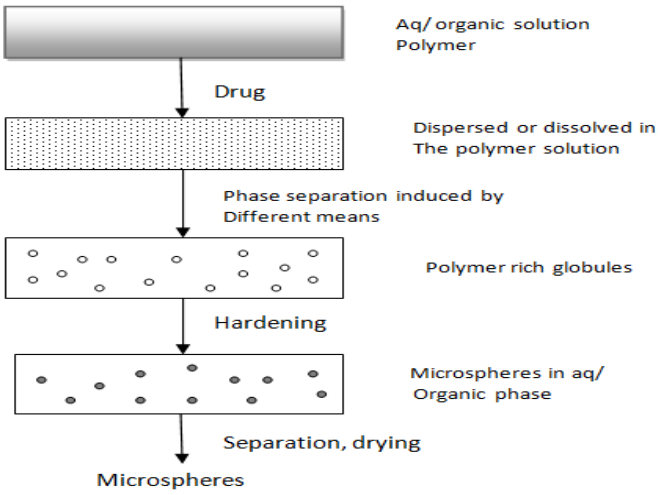

Fig 12: Schematic representation of Microspheres Formulation by Phase Separation Method

The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of polymer rich phase called the coacervates. In this technique, the polymer is first dissolved in a suitable solvent and then drug is dispersed by making its aqueous solution, if hydrophilic or dissolved in polymer solution itself, if hydrophobic. Phase separation is then accomplished by changing the solution conditions by using methods such as salt addition, non solvent addition, addition of the incompatible polymer or change in pH. The process is carried out under continuous stirring to control the size of the microparticles.

Spray drying and spray congealing

Spray drying and spray congealing methods are based on drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or the cooling of the solution, the two processes are named the spray drying spray congealing respectively. The polymer is first dissolved in the suitable volatile organic solvent such as dichloromethane, acetone, etc. the drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading to the formation of microspheres in a size range 1-100µm. microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying.

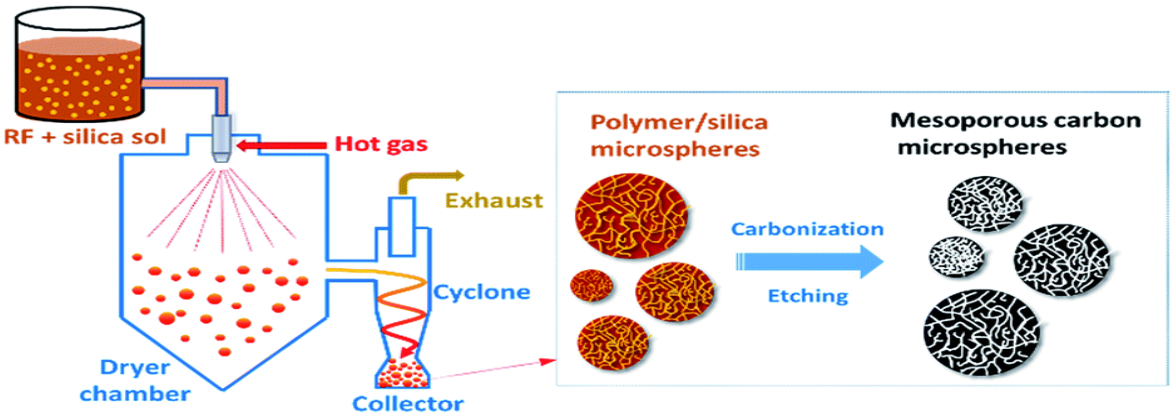

Fig 13:Solvent extraction

Solvent extraction method used for preparation of microparticles, involves removal of organic phase by extraction of organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction of water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

Advantages and disadvantages of microspheres

Advantages of Microspheres: [12]

• Size reduction leads to increase in surface area which can enhance solubility of the poorly soluble drug.
• Provide constant drug concentration in blood which can increase patent compliance,
• Decrease dose and toxicity.
• Coating of drug with polymers helps the drug from enzymatic cleavage hence found to be best for drug delivery.
• Less dosing frequency leads to better patient compliance.
• Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
• Protects the GIT from irritant effects of the drug.
• Convert liquid to solid form and to mask the bitter taste.
• Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
• Reduce the reactivity of the core in relation to the outside environment.
• Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
• Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections[10]

Limitation: [12]

Some of the disadvantages were found to be as follows [5]

1. The costs of the materials and processing of the controlled release preparation are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation /agitation may influence the stability of core particles to be encapsulated.

Application of Microspheres in Pharmaceutical Industry: [5]

Microspheres developed using polymer exhibits favourable biological behaviour such as bioadhesion, permeability-enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. e.g. Chitosan, Alginate, Gelatin

1. Oral Drug Delivery: The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make microspheres more suitable for oral drug delivery applications. e.g. Chitosan, Gelatin.
2. Gene Delivery: Microspheres could be a useful oral gene carrier be-cause of its adhesive and transport properties in the GI tract. e.g. Chitosan, Gelatin, viral vectors, cationic liposome, polycation complexes and Gene therapy with DNA plasmids and also delivery of insulin. It is also beneficial in vaccine delivery also as the prerequisite of a vaccine is protection against the microorganism or its toxic product. Biodegradable delivery system for vaccines that are given by Parenteral route may overcome the shortcoming of conventional vaccines. Several parenteral vaccines have been encapsulated in biodegradable polymeric microspheres, including the tetanus and diphtheria vaccine.
3. Nasal Drug Delivery: Polymer based drug delivery systems, such as micro-spheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. e.g. Starch, Dextran, Albumin, Chitosan + Gelatin
4. Intratumoral and Local Drug Delivery: In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films are fabricated. Mixture of drug has promising potential for use in controlled delivery in the oral cavity e.g. Gelatin, PLGA, Chitosan.
5. Buccal Drug Delivery: Polymer is an excellent polymer to be used for buccal delivery because it has muco / bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium alginate.
6. Gastrointestinal Drug Delivery: Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug

e.g. Eudragit, Ethyl cellulose + Carbopol BSA, Gelatin.

7. Transdermal Drug Delivery: Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. e.g. Chitosan, Alginate, PLGA.

9. Imaging: Diameter of microspheres plays an important role in determining the imaging of targeted sites using already labelled microspheres having radio activity. The microspheres injected via IV route apart from the portal vein will usually become entrapped in the area of lungs. This phenomenon is specifically used for scintigraphic imaging of tumour masses in lungs using human serum albumin microspheres.

10. Topical Porous Microspheres: Microsponges are porous microspheres having myriad of interconnected voids of size range 5 to 300µm. these sponges having capacity to engulf the various active ingredients such as emollients, fragrances, essential oils which is used for the topical application 40 .

11. Medical Application: • Release of proteins, peptides and hormones over the extended period of time. • Passive targeting of leaky tumor vessels, active targeting of tumor cells, antigens, by parenteral route. • Magnetic Microspheres can be used for used for stem cell extraction and bone marrow purging. • Used for Various diagnostic test for infectious disease like bacterial, viral and fungal.

12. Radioactive Application: It can be beneficial for the embolisation of various liver and spleen tumors which is used for radio synvectomy of local radiotherapy, arthritis, imaging of liver, bone marrow, local radiotherapy and even imaging of thrombus in deep vein thrombosis can be done.

13. Other Applications: Fluorescent microspheres can be used for membrane based technology flow cytometry, cell biology, fluorescent linked immunosorbent assay. Yttrium 90 can be used for primary treatment of carcinoma and also used for pre transplant management of HCC with promising results.

14. Colonic Drug Delivery: Polymer has been used for the specific delivery of insulin to the colon e.g. Chitosan.

15. Vaginal Drug Delivery: Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract e.g. Chitosan, Gelatin, PLGA.

16. Targeting by Using Micro Particulate Carriers: The concept of targeting is a well established dogma, which is gaining full attention now a days. The response produced by the drug depends on its access and interaction with receptor usually pellets method is reported which can be prepared by using extrusion / Spheronization technology e.g. microcrystalline cellulose (MCC) and chitosan.

Evaluation

Physiochemical Evaluation

Characterization Particle size and shape

Light microscopy (LM) provides a control over coating parameters in case of doublewalled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically[27].Scanning electron microscopy (SEM) allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems.

1.Attenuated total reflectance FT-IR Spectroscopy: FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The ATRFT-IR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.[28]

2.Density determination: The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the density of the microsphere carrier is determined.

3.Isoelectric point: The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different PH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined.

4.Entrapment efficiency: Microspheres containing of drug (5mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr., and was filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content[5]

% Entrapment = Actual content/Theoretical content x 100

5.Swelling index: This technique was used for Characterization of microspheres were performed with swelling index technique Different solution (100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and microspheres (100mg) were placed in a wire basket

and kept on the above solution and swelling was allowed at 37oC and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper

6.Angle of contact: The angle of contact is measured to determine thewetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water interface. The angle of contact is measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres.

***In Vitro* Methods**

Beaker method

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

Interface diffusion system

This method is developed by Dearden& Tomlinson. It consists of four compartments. The compartment A represents the oral cavity, and initially contained an appropriate concentration of drug in abuffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing body fluids, contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were with drawn and returned to compartment A with a syringe.

Modified Keshary Chien Cell

A specialized apparatus was designed in the laboratory. It comprised of a KesharyChien cell containing distilled water (50ml) at 370 C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using rotating elements, paddle 26 and basket 27 Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

Stability studies

By placing the microspheres in screw capped glass container and stored them at following conditions: ™

- Ambient humid condition ™
- Room temperature (27+/-2 0C) ™
- Oven temperature (40+/-2 0C) ™
- Refrigerator (5 0C -80C).

It was carried out of a 60 days and the drug content of the microsphere was analysed.

***In Vivo* Methods**

Animal models

Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the esophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed

Buccal absorption test

The buccal absorption test was developed by Beckett &Triggs in 1967. It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multi component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and Ph of the solution while the drug is held in the oral cavity[16-18]

Table 1:Various drugs for microspheres and their applications

Drugs	Method of preparation	Application	References
Risperidone	Double emulsion (o/w)	Antipsychotic Treatment of bipolar disorder and Schizophrenia	[10,11]
Naltrexone	Double emulsion (o/w)	Treatment of alcohol and opoid abuse	[10,11]
Leuprolide	Double emulsion (o/w/o)	Treatment of prostate cancer	[11]
Somatropin	Phase separation technique (cryogenic spray drying)	Treatment of growth hormone deficiency	[10,11]
Octreotide	Phase separation technique (cryogenic spray drying)	Treatment of severe watery diarrhea and Acromegaly	[10,11]
Triptorelin	Phase separation	Stimulates Gonadotrophin Releasing hormone(GnRH) i.e. LHRH	[11]
Buserelin	NA	Treatment of endometriosis	[11]
Lanreotide	Spray drying	Parkinsonism treatment	[11]
Minocycline	NA	Treatment of Gastroenteropancreatic neuroendocrine tumors (GEPNET)	[10,11]
Bromocriptine	Spray drying	Parkinsonism treatment	[10,11]
Goserelin acetate	NA	Treatment of prostate cancer	[11]
Recombinant bovine somatropin	NA	To increase milk product in cattle	[11]
Fluorouracil	Dry-in-oil	For targeted delivery to treat cerebral tumors Antitumor activity	[13]
Cisplatin	w/o emulsion system	Antitumor activity	[13]
Mitoxantrone	crosslinking technique	Antitumor	[13]
Oxantrazo	combined emulsion	Anticancer	[13]
Aceclofenac	By dissolving drug in polymer	Anti-inflammatory drug	[13]
Amoxicillin	Crosslinking	for helicobacter pylori infection eliminating infection	[13]
Indomethacin	Co-matrix method	Antiinflammatory	[13]
Nifedipine	Encapsulation	Calcium channel blockers	[13]
Propranolol	emulsification coacervation technique	Calcium channel blockers	[13]
Progesterone	Crosslinking	Steroid	[13]
Insulin	—	Antihyperglycemic effect	[13]
Furosemide	Crosslinking	Diuretics	[13]
Rifampicin	Double emulsion Solvent Evaporation	Treatment of Tuberculosis	[19]
Moxifloxacin	Spray Drying	Respiratory infection	[19]
Beclomethasone dipropionate	Spray Drying	Treatment of Asthma, COPD	[19]
Prostaglandin EI	W/O/W double emulsion solvent evaporation	Treatment of Pulmonary Arterial Hypertension	[19]
Ofloxacin	W/O emulsion solvent evaporation	Treatment of Pneumonia	[19]
Lysozyme	W/O/W double emulsion solvent evaporation	Treatment of pulmonary disorder	[19]

Table 2: Types of Microspheres

Types of Microsphere	Method of preparation	Application	References	Types of Microsphere
Therapeutic magnetic microspheres	Multiple emulsion method	Anticancer agent, Used in DNA analysis, cell isolation	[5], [8][20]	Therapeutic magnetic microspheres
Diagnostic microspheres	Emulsion solvent extraction method	Magnetic resonance imaging contrast enhancement, detoxification of biological fluids, immunoassay, liver metastases.	[5], [8]	Diagnostic microspheres
Bioadhesive microsphere	_	Buccal, oral, ocular, nasal, colonic drug delivery.	[5], [8]	Bioadhesive microsphere
Floating microspheres	_	Increases the gastric resistance time, Carriers for drugs like antiviral, antifungal and antibiotic agents	[5], [8]	Floating microspheres
Radioactive microspheres	_	Radioimmobilization of liver and spleen cancer Local radiotherapy, radiosynvectomy of arthritis joint	[5], [8]	Radioactive microspheres
Porous microsphere	Seed swelling method	Tissue regeneration scaffolds High speed protein chromatography Pulmonary drug delivery	[9]	Porous microsphere
Therapeutic magnetic microspheres	Multiple emulsion method	Anticancer agent, Used in DNA analysis, cell isolation	[5], [8]	Therapeutic magnetic microspheres

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