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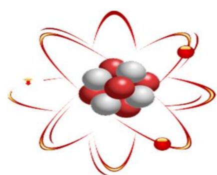

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MICROPARTICULATE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microsphere, nanoparticles etc, which modulates the release and absorption characteristics of the drug. Microspheres/microparticles constitute an important part of this particulate drug delivery system by virtue of their small size and efficient carrier characteristics. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs. The present review highlights several carriers used in the preparation of microparticles, preparation methods of microparticles, their release mechanisms, evaluation parameters, their advantages and applications. Therefore microparticles open up new vistas of research in the development of novel drug delivery systems. Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microsphere, nanoparticles etc, which modulates the release and absorption characteristics of the drug. Microspheres/microparticles constitute an important part of this particulate drug delivery system by virtue of their small size and efficient carrier characteristics. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs. The present review highlights several carriers used in the preparation of microparticles, preparation methods of microparticles, their release mechanisms, evaluation parameters, their advantages and applications. Therefore microparticles open up new vistas of research in the development of novel drug delivery systems.

KEY WORDS: Microparticles, Controlled drug delivery, Polymers, Microencapsulation techniques.

INTRODUCTION

Oral drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. This results in pill burden and consequently, patient complains. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profile is to release the drug in a controlled manner and site specific manner.

Microparticles are a type of drug delivery systems where the particle size ranges from one micron (one thousandth of a mm) to few mm. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Hence, they play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects [1].

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MORPHOLOGY OF MICROPARITCLE

Microencapsulation is a technology used to entrap solids, liquids, or gases inside a polymeric matrix or shell. Microparticles are particulate dispersions or solid particles. Two general micromorphologies of microparticles can be distinguished- microcapsules and microspheres.

Microcapsule (figure: 2) is a system in which drug containing core is completely surrounded by a polymer shell. The core can be solid, liquid or gas; the shell is a continuous, porous or non-porous polymeric layer.

Microcapsules are classified into three basis categories as monocored, polycored and matrix type as shown in figure.3;
Monocored microcapsules have a single hollow chamber within the capsule.

Polycore microcapsules have a number of different sized chambers with in the shell. *Matrix* type micro particle has the active ingredients integrated within the matrix of the shell.

However, the morphology of the internal structure of a micro particle depends on the shell materials and the micro encapsulation methods that are employed.

Microsphere (figure: 4) is a system in which the drug substance is either homogenously dissolved or dispersed in a polymeric matrix. Microspheres show different release properties compared to true microcapsules [2-4].

IMPORTANT FEATURES OF MICROCAPSULES

The most significant feature of microcapsules is their microscopic size that allows for a huge surface area, for example the total surface area of 1µm has been reported to be about 60m^2. The total surface area is inversely proportional to the diameter. This large surface area is available for sites of adsorption and desorption, chemical reactions, light scattering etc [2].

ADVANTAGES

This type of drug delivery systems mainly provides the encapsulated material to reach the area of action without getting adversely affected by the environment through which it passes. Pharmaceutical and biomedical advantages of microparticle include:

1. Taste and odor masking. Eg: Fish oils, sulfa drugs.
2. Protection of drugs from environment.
3. Particle size reduction for enhancing solubility of the poorly soluble drug.
4. Sustained or controlled drug delivery Eg: KCl, Ibuprofen.
5. Targeted release of encapsulated material.
6. Live cell encapsulation. Eg: Resealed erythrocytes (figure: 5).
7. Conversion of liquid to free flowing solids.
8. Delay of volatilization.
9. Separation of incompatible components Eg: Excipients, buffers and other drugs.
10. Improvement of flow of powder.
11. Safe handling of toxic substances.
12. Aid in dispersion of water insoluble substance in aqueous media [2,5,6].

DISADVANTAGES

Although the advantages of microparticles are impressive there are certain limitations. These include:

1. The costs of the materials and processing of the controlled release preparation, which may be 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, p^H, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents and

The cost, time probability of success in securing government registration of the product, if required [7].

APPLICATIONS

Microparticulate drug delivery offers several applications for drugs having poor bioavailability. A number of pharmaceutical encapsulated products are currently on the market, Such as aspirin, theophylline and its derivatives, vitamins, antihypertensive, potassium chloride, progesterone and contraceptive hormone combinations [8].

Sustained drug delivery

By encapsulating a drug in a polymer matrix, which limits access of the biological fluid into the drug

until the time of degradation, microparticles maintain the blood level of the drug within a therapeutic window for a prolonged period. Toxic side effects can be improved by reducing the frequency of administration. For example novel sustained release microspheres of Glipizide are quite beneficial for diabetic patient [5.9].

Controlled drug delivery

Here, the drug is delivered at a predetermined rate, locally or systemically for a specified period of time. Depot formulation of short acting peptide have been successfully developed using microparticle technology (figure: 6) e.g. leuprorelin acetate and triptoreline, both are luteinizing hormone releasing hormone agonists [5].

Local drug delivery

Subcutaneously or intramuscularly applied microparticles can maintain a therapeutically effective concentration at the site of action for a desirable duration. The local delivery system obviates systemic drug administration for local therapeutic affects and can reduce the related systemic side effects. It is proven beneficial for delivery of local anesthetics [5].

Pulsatile drug delivery

While burst and pulsatile release is not considered for sustained delivery application, their release pattern proves to the useful for delivery of antibiotics and vaccines pulsatile release of antibiotics can alleviate evolution of the bacterial resistance. In the vaccine delivery, initial burst followed by delayed release pulsed can mimic an initial and boost injection respectively.

Potential application of this drug delivery system is replacement of therapeutic agents, gene therapy, and in use of vaccine for treating AIDS, tumors, cancer, and diabetes. The spheres are engineered to stick tightly to and even penetrate linings in the GIT before transferring their contents over time into circulatory system.

Based on this novel drug delivery technique, Quinidine gluconate CR tablets are used for treating and preventing abnormal heart rhythm. Glucotrol (Glipizide SR) is an ant diabetic drug used to control high blood sugar levels [5].

Targeted drug delivery

Drugs can be targeted in different ways.

Drug is delivery to a tissue:

a. Antitumor microparticles are administered intra-arterially and target an organ
b. or body cavity i.e., peritoneum.
c. Therapeutic drug delivery of Anti cancer drugs. e.g. .doxorubicin and 5-fluorouracil. *c.* Markers for analysis/detection. E.g. Detect tumours; infected cells; anti-pathogen lymphocytes.

Intracellular delivery:

a. Gene delivery e.g. delivery of plasmid DNA
b. Anti-sense therapy e.g. Closing production of certain proteins by delivery of anti-sense oligonucleotides to bind ribosomal mRNA
c. Intracellular toxins for cancer therapy
d. Ribozyme delivery
e. Drug delivery to cell organelles e.g. mitochondria
f. Vaccine adjuvant i.e. biodegradable polylactic acid and polylactic acid co-glycolic acid microspheres also act as immune adjuvant by providing a depot formulation of the antigen at the site of administration. The antigen is thus continuously released to antigen presenting cells [5,10].

RELEASE MECHANISM

Different release mechanisms (figure: 7) of encapsulated material provide controlled, sustained or targeted release of core material. Generally there are three different mechanisms by which the core material is released from a microcapsule-mechanical rupture of the capsule wall dissolution or melting of the wall and diffusion through the wall less common release mechanisms include ablation (slow erosion of shell) and biodegradation.

Drug release from the microsphere occurs by general mechanism including diffusion, polymer degradation, and hydrolysis/erosion.

Diffusion:

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior as shown in figure: 8.

Erosion:

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as the water

penetrates within it leading to the plasticization of the matrix [2,11].

CARRIERS USED IN PREPARATION OF MICROPARTICLES

Polymers remain the most versatile class of biomaterials being extensively applied in medicine and biotechnology, as well as in food and cosmetic industries.

A broad range of polymers can be used to form microcapsules. The polymer is judiciously combined with the drug/other active ingredient in such a way that the active agent is released from the material in a predetermined fashion and released the drug at a constant rate for a desired time period. Hence, encapsulating the drug in a polymer matrix provides ideal pharmacokinetic profile for drugs, where the drug concentration reaches therapeutic levels without exceeding the max tolerable dose and maintains the concentrations for extended periods of time till the desired therapeutic effect is reached. The five key advantages that polymeric drug delivery products can offer are localized delivery of drug, sustained delivery of drugs, stabilization of drugs, release rate which is less dependent of the drug properties and steadier release rate with time.

A wide array of polymers has been employed as drug retarding agents, each of which presents a different approach to matrix concept. Polymers that primarily form insoluble or skeleton matrices are considered as the "1st category of retarding materials" The second class represents hydrophobic and water insoluble materials which are potentially erodible and the third group exhibits hydrophilic properties.
The following classes of polymers are generally used:

Non biodegradable polymers:

These materials are inert in environment of use and include polyethylene vinyl acetate (PVA) polydimethyl siloxam (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene & PVC.

Hydrogels:

They swell but do not dissolve when brought in contact with water. Eg: polyhydroxy ethyl methyl acrylate, cross linked polyvinyl alcohol (PVA), PVP, Polyacrylamide & natural substances like dextran.

Soluble polymers:

These include PEG.APMC, Copolymer of methacrylic acid and acrylic acid methyl ester (Eudragit L)

Biodegradable Polymers:

These include PLA, PGA, Polycaprolactone (PCL), PLGA, etc,.
In the manufacture of controlled release dosage forms, these polymers are used separately or in combination to obtain dosage forms that release drugs over various durations. For example, soluble polymers are commonly used to produce tablets for oral delivery that erode over a period of hours. When combined with hydrophobic polymers such as EC, the soluble polymers are used to form coating for controlled release tablets or multiparticulates, which release drugs over relatively short times. In contrast, biodegradable polymers such as PLA or PCL have been utilized to produce devices that release a drug over several months or years when used as sub dermal implants. PGA, PLA & PLGA are used in controlled drug delivery because these polymers are used extensively as biodegradable suture material. Some of the biodegradable polymer used in Drug Delivery Systems includes: Table-1

All these polymers will eventually be interesting relative to their safety, for the design of microparticulate drug carriers. The type of technique used affect factors such as porosity, size distribution, and surface morphology of the microsphere and may subsequently affect the performance of drug delivery product. The preparation condition of microsphere, drug-polymer compatibility, expected drug release behavior, and the final purpose of the formulator should be taken into account for the final choice of the polymer carrier.

TECHNIQUES OF MICROENCAPSULATION:

A variety of techniques are employed for the entrapment of solids or liquids within polymer coatings or matrices as shown in table: 2. The choice of preparation method essentially depends on the raw material intended to be used and on the solubility characteristics of the active compound to be associated with the particles. The preparation method can be broadly divided into 2 categories: Chemical methods and physical methods [12-14].

Chemical Methods

This method uses monomers/prepolymers as starting materials. These methods involve chemical reactions along with microsphere formation. These include

suspension polymerization, emulsion polymerization, dispersion and interfacial methods. Among them emulsion polymerization method is widely used in drug delivery [2].

Emulsion Polymerization

According to this technique the monomer (alkyl acrylates) is added drop wise to the stored aqueous polymerization medium containing the material to be encapsulated (core material) and a suitable emulsifier. The polymerization begins and initially produced polymer molecules precipitate in the aq. medium to form primary nuclei. As the polymerization proceeds, these nuclei grow gradually and simultaneously entrap the core material to form the final microcapsules as shown in figure: 9 [2,16].

Interfacial Polymerization (IFP)

In this technique the capsule shell will be formed at or on the surface of the droplet or particle by polymerization of the reactive monomers. The substances used are multifunctional monomers. Generally used monomers include multifunctional isocyanates and multifunctional acid chlorides. These will be used either individually on in combination. The multifunctional monomer dissolved in liquid core material and it will be dispersed in aqueous phase containing dispersing agent. A coreactant multifunctional amine will be added to the mixture. This results in rapid polymerization at interface and generation of capsuleshell takes place. A polyurea shell will be formed when isocyanate reacts with amine, poly nylon or polyamide shell will be formed when acid chloride reacts with amine. When isocyanate reacts with hydroxyl containing monomer produces polyurethane shell.

D. Saihi et al., encapsulated di-ammonium hydrogen phosphate (DAHP) by polyurethane-urea membrane using an interfacial polymerization method. An elevated yield of synthesis (22%) of a powder of microcapsules was produced with a fill content of 62 wt% of DAHP as determined by elementary analysis. This can be explained by the high quantity of DAHP introduced in the aqueous phase. The mean size of DAHP microcapsules is 13.35μm. Besides, 95% of the sized particles have a diameter lower than 30.1μm [5,17].

In situ polymerization

Like IFP the capsule shell formation occurs because of polymerization monomers added to the encapsulation reactor. In this process no reactive agents are added to the core material, polymerization occurs exclusively in the continuous phase and on the continuous phase side of the interface formed by the dispersed core material and continuous phase. Initially a low molecular weight prepolymer will be formed, as time goes on the prepolymer grows in size, it deposits on the surface of the dispersed core material there by generating solid capsule shell. E.g. encapsulation of various water immiscible liquids with shells formed by the reaction at acidic pHof urea with formaldehyde in aqueous media[8]. Wang Qiangbin et al., prepared Carboxyl-functionalized magnetic microspheres by in situ polymerization of styrene and methyacrylic acid at 85°C in the presence of nano-Fe_3O_4 in styrene, using lauroyl peroxide as an initiator [17].

Physical/Mechanical Methods

They use polymers as starting materials. Hence no chemical reactions are involved and only shape fabrication takes place. These methods include suspension cross linking, solvent evaporation/extraction, coacervation/phase separation, spray drying, Fluidized bed coating, melt solidification, precipitation, co-extrusion, layer by layer deposition.

Suspension Cross Linking

It is a method of choice for the preparation of protein and polysaccharide microcapsules. This involves dispersion of an aq. solution of the polymer containing core material is an immiscible organic solvent (suspension/dispersion medium), in the form of small droplet. The suspension medium contains a suitable stabilizer to maintain the individuality of the droplet/microcapsules. The cross linking process is accomplished either thermally (at>500^0c) or by the use of a cross linking agent (formaldehyde, terephthaloyl chloride etc.) It is a versatile method and can be adopted for microencapsulation of solution, insoluble, liquid or solid materials, and for the production of microcapsules [2].

Solvent evaporation/Solvent Extraction

It is the most commonly used technique to prepare microsphere/microcapsules (fig. 10). Microencapsulation by solvent evaporation is conceptually a simple oil-in-water (O/W) procedure. It involves, first, the emulsification of polymer solution containing drug which is either dissolved or suspended in an immiscible liquid phase containing a surfactant to form a dispersion of drug. Polymer-solvent droplet. Second, the solvent is removed

from the dispersed droplet by application of heat, vacuum or by allowing evaporation at room temperature to leave a suspension of drug-containing polymeric microsphere that can be separated by centrifugation. Finally the microsphere are washed and dried, forming free flowing microsphere. It is extensively employed in the encapsulation of active ingredients [3,18].

Hot Melt Microencapsulation

The polymer is first melted and then mixed acid solid drug particle or liquid drugs. This mixture is suspended in an immiscible solvent and heated to 5^0c above the melting point of the polymer under continuous stirring. The emulsion is then cooled below the melting point until the droplets solidify [5].

Coacervation/Phase Separation

Bungenberg and colleagues defined as, partial desolvation of a homogeneous polymer solution into a polymer-rich phase (coacervate) and the poor polymer phase (coacervation medium). The term originated from the Latin ›acervus‹ , meaning “heap”. This was the first reported process to be adapted for the industrial production of microcapsules. Currently, two methods for coacervation are available, namely simple and complex processes. The mechanism of microcapsule formation for both processes is identical, except for the way in which the phase separation is carried out. In simple coacervation a desolvation agent is added for phase separation, whereas complex coacervation involves complexation between two oppositely charged polymers. The three basic steps in complex coacervation are: (i) formation of three immiscible phases; (ii) deposition of the coating; and (iii) rigidization of the coating [2,5,18].

First step include formation of three immiscible phases; liquid manufacturing vehicle, core material, coating material. The core material is dispersed in a solution of the coating polymer. The coating material phase, an immiscible polymer in liquid state is formed by (i) changing temperature of polymer solution, e.g. ethyl cellulose in cyclohexane(N-acetyl P-amino phenol as core), (ii) addition of salt, e.g. addition of sodium sulphate solution to gelatine solution in vitamin encapsulation, (iii) addition of nonsolvent, e.g. addition of isopropyl ether to methyl ethyl ketone solution of cellulose acetate butyrate (methylscopalamine hydrobromide is core), (iv) addition of incompatible polymer to the polymer solution, e.g. addition of polybutadiene to the solution of ethylcellulose in toluene (methylene blue as core material), (v) inducing polymer – polymer interaction, e.g. interaction of gum Arabic and gelatine at their iso-electric point. Second step, includes deposition of liquid polymer upon the core material. Finally, the prepared microcapsules are stabilized by crosslinking, desolvation or thermal treatment (figure: 11).

Crosslinking is the formation of chemical links between molecular chains to form a three-dimensional network of connected molecules. The degree of crosslinking, quantified in terms of the crosslink density, together with the details of the molecular structure, have a profound impact on the swelling characteristics of the crosslinked system. E.g. Derivatives of ethylene glycol di(meth)acrylate like, Ethylene glycol diacrylate, Di(ethylene glycol) diacrylate, Tetra(ethylene glycol) diacrylate, Ethylene glycol dimethacrylate,Di(ethylene glycol) dimethacrylate, Tri(ethylene glycol) dimethacrylate; Derivatives of methylenebisacrylamide like N,N.- Methylenebisacrylamide, N,N.- Methylenebisacrylamide, N,N.- (1,2-Dihydroxyethylene)bisacrylamide, glutaraldehyde, sodium tripolyphosphate etc.

Spray Drying

Spray drying (figure:12) is a single step closed-system process applicable to wide variety of materials. The drug is dissolved or suspended in a suitable (either aq. or non-aqueous) solvent containing polymer materials. The solution or suspension is atomized into a drying chamber, and microparticles form as the atomized droplets are dried by heated carrier gas. The result of this process is heavily dependent on the material properties. The instrument settings such as inlet temperature, rate of feed flow, spray air flow and aspirator flow can together influence the product parameters such as particle size, yield, temperature load and content of residual solvents.

Optimization of these parameters is usually made through trial and error.Spray drying leads to broad distribution of particle size, with a Gaussian shape centered on 10µm.

Bodmeier and Chen used poly (D, L-lactic acid) as polymer and encapsulated different substances e.g. Progesterone and Theophylline. Microparticles containing Captopril were prepared by spray drying using PLGA as polymer. In the year 1992, the pharmaceutical company Hoechst AG(Germany), now Sanofi-Aventis, patented “long acting biodegradable peptide drug microparticles” with Buserelin acetate as drug substance, which was spray dried with PLGA as matrix polymer and is currently

available on the market as Profact®. Recombinant hepatitis B surface antigen was encapsulated using oligosaccharide ester derivatives by a spray drying method [5,18,20].

Fluidized Bed Coating (Air Suspension Technique)

There are three commonly used fluid-bed process: top, tangential and bottom spray methods. When the granules are coated by the top-spray granulator system, granules usually have a porous surface and an interstitial void space, therefore, the bulk density of produced granules is usually lower than that attainable by granulation techniques. A rotating-disk method (tangential-spray coating method), which combines centrifugal, high-density mixing and the efficiency of fluid bed drying, yields a product that has higher bulk density but still has some interstitial void space. It yields particle that are less friable and more spherical in shape.

In the wurster process (bottom spray as shown in figure: 13) the solid core particle are fluidized by air pressure and a solution of wall materials is sprayed on to the particles from the bottom of the fluidization chamber parallel to the air stream. At the spraying nozzle is immersed in the airflow and sprays the coating materials concurrently into the fluidized particles, the coating solution droplets travel only a short distance before contacting the solid particles.

As a result the film is applied more evenly and the coated film is more homogenous. The coated particles are lifted on the air stream, which dries the coating as the particles are carried away from the nozzle. The particles rise on the air stream, the settle down, and then begin another cycle.

The cycles until the desired film thickness are achieved. It is well suited for uniform coating of particle with a polymeric membrane in a single operation [5].

Impregnation

Substrates soluble in supercritical CO_2 ($ScCO_2$) can be easily impregnated inside porous system to prepare controlled drug delivery systems as demonstrated by Domingo et.al. In the work carried out by Domingo et.al, an amorphous inorganic mesophore and a polymeric matrix (amberlite) were impregnated with various thermolabile organic compounds (benzoic acid, salicylic acid, aspirin, triflusal and ketoprofen) by diffusion from saturated $ScCO_2$. This technique of microencapsulation is promising because it is performed in room temperature, without organic solvents and with a precise control of the particle size owing to the separation of the process of particle creation and the process of encapsulation.

Controlled coating

It is a new process developed by Benoit et al., Here the coating materials are dissolved in $ScCO_2$ and then time/pressure (T/P) conditions are slowly adjusted in the autoclave to precipitate it onto the surface of the suspended particles. This process has been applied to coat bovine serum albumin (BSA) and sugar granules, with trimyristin (Dynasan®114) or Gelucire® 50-02, a mixture of glycerides and glyceride esters of PEG. Different coating morphologies were obtained depending upon the material used. This process allowed good control of the particle structure (composition and thickness). Furthermore, it was shown that BSA did not undergo any degradation after $ScCO_2$ treatment, indicating that this process could be useful for encapsulation of proteins.

Encapsulation by Rapid Expansion of Supercritical Fluids

Supercritical fluids are highly compressed gasses that possess several advantageous properties of both liquids and gases. The most widely used being supercritical carbon dioxide(CO_2), alkanes ($C_2$to C_4), and nitrous oxide (N_2O). A small change in temperature or pressure causes a large change in the density of supercritical fluids near the critical point. Supercritical CO2 is widely used for its low critical temperature value, in addition to its nontoxic, non flammable properties; it is also readily available, highly pure and cost-effective. This technology also applicable to prepare nanoparticles also.

The most widely used methods are as follows:

a. Rapid expansion of supercritical solution (RESS)
b. Gas anti-solvent (GAS)
c. Particles from gas-saturated solution (PGSS)

Rapid expansion of supercritical solution (figure:14):

In this process, supercritical fluid containing the active ingredient and the shell material are maintained at high pressure and then released at atmospheric pressure through a small nozzle. The sudden drop in pressure causes desolvation of the shell material, which is then deposited around the active ingredient (core) and forms a coating layer. The disadvantage of this process is that both the active ingredient and the shell material must be very soluble in supercritical fluids. In general, very few

polymers with low cohesive energy densities (e.g., polydimethylsiloxanes, polymethacrylates) are soluble in supercritical fluids such as CO2. The solubility of polymers can be enhanced by using co-solvents. In some cases nonsolvents are used; this increases the solubility in supercritical fluids, but the shell materials do not dissolve at atmospheric pressure. Kiyoshi et al. had very recently carried out microencapsulation of TiO_2 nanoparticles with polymer by RESS using ethanol as a nonsolvent for the polymer shell such as polyethylene glycol (PEG), poly(styrene)-b-(poly(methylmethacrylate)-copoly (glycidal methacrylate) copolymer (PS-b-(PMMA-co-PGMA) and poly(methyl methacrylate)

Gas anti-solvent (GAS) process:

This process is also called supercritical fluid anti-solvent (SAS). Here, supercritical fluid is added to a solution of shell material and the active ingredients and maintained at high pressure. This leads to a volume expansion of the solution that causes super saturation such that precipitation of the solute occurs. Thus, the solute must be soluble in the liquid solvent, but should not dissolve in the mixture of solvent and supercritical fluid. On the other hand, the liquid solvent must be miscible with the supercritical fluid. This process is unsuitable for the encapsulation of water-soluble ingredients as water has low solubility in supercritical fluids. It is also possible to produce submicron particles using this method.

Particles from a gas-saturated solution (PGSS):

This process is carried out by mixing core and shell materials in supercritical fluid at high pressure. During this process supercritical fluid penetrates the shell material, causing swelling. When the mixture is heated above the glass transition temperature (Tg), the polymer liquefies. Upon releasing the pressure, the shell material is allowed to deposit onto the active ingredient. In this process, the core and shell materials may not be soluble in the supercritical fluid.

Other Techniques:

In addition to the microencapsulation techniques described above, microencapsulation can also be carried out by spray coating, melt solidification, polymer precipitation, co-extrusion, layer-by-layer deposition, supercritical fluid expansion and spinning disk [7].

Selection of microencapsulation methods

A single microencapsulation method cannot be universally applied for a variety of drugs on developing a new microparticle system for a given drug, it is important to understand the physicochemical properties of the drug and find an encapsulation method and polymeric materials that best match the properties. Since water is the most widely used solvent system, solubility of the drug in water often serves a good starting point of the survey. Physical status of the drug can also limit the selection. The microencapsulation methods that have widely been used for drugs of different properties are summarized in table:3.

The requirements to be considered to select a method for encapsulation are:

1. The yield and drug encapsulation efficiency should be high.
2. The stability and biological activity of the drug should not be effected during the microencapsulation process.
3. Microsphere quality and drug release profile should be within specified limits.
4. Microspheres should not exhibit aggregation or adherence.
5. The process should be usable at industrial scale.

The method is selected mainly based on the nature of the polymer used [6,13].

FACTORS INFLUENCING ENCAPSULATION EFFICIENCY

The encapsulation efficiency of the microparticle or microcapsule or microsphere will be affected by different parameters, Figure.15 illustrate the factors influencing encapsulation efficiency.

Solubility of polymer in the organic solvent

Mehta et al., 1996, studied the effect of solubilities of the polymers of different PLGAs in methylene chloride were compared by measuring the methanol cloud point (Cs): Higher Cs meant that the polymer was more soluble in methylene chloride and, thus, required a greater amount of methanol to precipitate from the polymer solution. The PLGA polymer of a relatively high L/G ratio (75/25) had a higher solubility in methylene chloride than the other PLGA (L/G ratio=50/50). A lower molecular weight polymer had a higher solubility in methylene chloride than a higher molecular weight polymer. End-capped polymers, which were more hydrophobic than non-end-capped polymers of the same molecular weight and component ratio, were more soluble in methylene chloride.

Diffusion of drugs into the continuous phase mostly occurred during the first 10 minutes of emulsification; therefore, as the time the polymer phase stayed in the non-solidified (semi-solid) state was extended, encapsulation efficiency became relatively low. In Mehta's study, polymers having relatively high solubilities in methylene chloride took longer to solidify and resulted in low encapsulation efficiencies, and vice versa. Particle size and bulk density also varied according to the polymer. Since polymers having higher solubilities in methylene chloride stayed longer in the semi-solid state, the dispersed phase became more concentrated before it completely solidified, resulting in denser microparticles.

Johansen et al., 1998 shown that the use of relatively hydrophilic PLGA which carried free carboxylic end groups resulted in a significantly higher encapsulation efficiency compared to that of an end-capped polymer. A similar explanation as above applies to this observation: Hydrophilic PLGA is relatively less soluble in the solvent, methylene chloride, and precipitates more quickly than the end-capped one. High solidification rate might have increased the encapsulation efficiency. On the other hand, the authors attribute the increase to the enhanced interaction between PLGA and the protein through hydrogen bonding and polar interactions[32]. Walter et al[33]. also observed an increased encapsulation efficiency from using relatively hydrophilic PLGA in DNA microencapsulation. The hydrophilicity of the polymer enhanced the stability of the primary emulsion, and it contributed to such an increase.

Solubility of organic solvent in water

Bodmeier et al. found that methylene chloride resulted in a higher encapsulation efficiency as compared with chloroform or benzene, even though methylene chloride was a better solvent for poly (lactic acid) (PLA) than the others. Methylene chloride is more soluble in water than chloroform or benzene. The 'high' solubility allowed relatively fast mass-transfer between the dispersed and the continuous phases and led to fast precipitation of the polymer. The significance of solubility of the organic solvent in water was also confirmed by the fact that the addition of water-miscible co-solvents such as acetone, methanol, ethyl acetate, or dimethyl sulfoxide (DMSO), contributed to increase of the encapsulation efficiency. Knowing that the methanol is a non-solvent for PLA and a water-miscible solvent, it can be assumed that methanol played a dual function in facilitating the polymer precipitation: First, the presence of methanol in the dispersed phase decreased the polymer solubility in the dispersed phase. Second, as a water-miscible solvent, methanol facilitated diffusion of water into the dispersed phase.

In order to explain the low encapsulation efficiency obtained with benzene, the authors mention that the benzene required a larger amount of water (non-solvent) than methylene chloride for precipitation of the polymer, and the drug was lost due to the delayed solidification. However, given that benzene is a poorer solvent than methylene chloride for a PLA polymer, this argument does not agree with the widely spread idea that a poor solvent requires a smaller amount of non-solvent to precipitate a polymer. In fact, there could have been a better explanation if they had considered that the delayed solidification was due to the low solubility of benzene in water: As a poor solvent for a PLA polymer, benzene requires only a small amount of non-solvent for complete solidification of the polymer. However, since benzene can dissolve only a tiny fraction of water, it takes much longer to uptake water into the dispersed phase. That is, while solubility of a polymer in an organic solvent governs the quantity of a nonsolvent required in precipitating a polymer, solubility of the organic solvent in the non-solvent limits diffusion of the non-solvent into the polymer phase. Thus, when a cosolvent system is involved, both solubility of a polymer in a solvent and solubility of the solvent in a non-solvent participate in determining the solidification rate of the dispersed phase [21].

Lysozyme-loaded PLGA microparticles were prepared using the oil in water (o/w) single emulsion technique. Here, the authors used a co-solvent system, varying the ratio of the component solvents. DMSO was used for solubilization of lysozyme and PLGA, and methylene chloride was used for generation of emulsion drops as well as solubilization of PLGA. Encapsulation efficiency increased, and initial burst decreased as the volume fraction of DMSO in the co-solvent system increased. Particle size increased, and density of the microparticle matrix decreased with increasing DMSO. Overall, these results indicate that the presence of DMSO increased the hydrophilicity of the solvent system and allowed fast extraction of the solvent into the continuous phase, which led to higher encapsulation efficiency and larger particle size.

Concentration of the polymer

Encapsulation efficiency increases with increasing polymer. For example, the encapsulation efficiency increased from 53.1 to 70.9% when concentration of the polymer increased from 20.0 to 32.5%. High viscosity and fast solidification of the dispersed phase contributed to reducing porosity of the microparticles as well. The contribution of a high polymer concentration to the encapsulation efficiency can be interpreted in two ways. First, when highly concentrated, the polymer precipitates faster on the surface of the dispersed phase and prevents drug diffusion across the phase boundary. Second, the high concentration increases viscosity of the solution and delays the drug diffusion within the polymer droplets.

Ratio of dispersed phase to continuous phase (DP/ CP ratio)

Encapsulation efficiency and particle size increase as the volume of the continuous phase increases. For example, the encapsulation efficiency increased more than twice as the ratio of the dispersed phase to the continuous phase (DP/CP ratio) decreased from 1/50 to 1/300. It is likely that a large volume of continuous phase provides a high concentration gradient of the organic solvent across the phase boundary by diluting the solvent, leading to fast solidification of the microparticles. A relevant observation is described in the literature. In this example, which utilized ethyl acetate as a solvent, the formation of microparticles was dependent on the volume of the continuous phase. When 8 mL of PLGA solution (o) was poured into 20 or 50 mL of water phase (w), the polymer solution was well disintegrated into dispersed droplets. On the other hand, when the continuous phase was 80 mL or more, the microspheres hardened quickly and formed irregular precipitates. This is because the large volume of continuous phase provided nearly a sink condition for ethyl acetate and extracted the solvent instantly. Due to the fast solidification of the polymer, particle size increased with increasing volume of the continuous phase. Microparticles generated from a low DP/CP ratio had a lower bulk density (0.561 g/cc at 1/50 vs. 0.357 g/cc at 1/ 300), which the authors interpret as an indication of higher porosity of the polymer matrix. On the other hand, a different example shows that a higher DP/ CP ratio resulted in increased porosity, providing a large specific surface area (measured by the BET method) and the scanning electron microscope (SEM) pictures as evidence. This apparent discrepancy can be explained by the fact that low bulk density is not a true reflection of porosity but a result of large particle size. In fact, porosity increases with increasing DP/CP ratio, i.e., decreasing rate of the polymer precipitation.

Rate of solvent removal

The method and rate of solvent removal influence the solidification rate of the dispersed phase as well as morphology of the resulting microparticles. In the emulsion-solvent evaporation/extraction method, the solvent can be removed by (i) evaporation, in which the solvent is evaporated around its boiling point or (ii) extraction into the continuous phase. The rate of solvent removal can be controlled by the temperature ramp or the evaporation temperature in the former and by the volume of the dilution medium in the latter. PLGA microparticles containing salmon calcitonin (sCT) were prepared by emulsification, followed by different solvent removal processes. In the temperature dependent solvent removal process, the solvent (methylene chloride) was removed by increasing the temperature from 15 to 40°C at different rates. The microparticles that resulted from this process had a hollow core and a porous wall. The core size and wall thickness were dependent on the temperature ramp. A rapid rise in temperature resulted in a thin wall and a large hollow core, whereas a stepwise temperature rise (15 to 25, then to 40°C) resulted in a reduced core size. It is believed that the hollow core was due to the rapid expansion of methylene chloride entrapped within the solidified microparticles. In controlled extraction of the solvent, the solvent was removed gradually and slowly by dilution of the continuous phase, which left the microparticles in the soft state for a longer period of time. The resulting microparticles showed a highly porous honeycomb- like internal structure without a hollow core. In the later study, it was noted that the porosity was a function of the amount of water diffused into the dispersed phase from the continuous phase, which could only be allowed before the dispersed phase solidified completely. In other words, the high porosity of the microparticles was due to the slow solidification of the microparticles. Even though it is generally assumed that fast polymer solidification results in high encapsulation efficiency, this does not apply to the observation of Yang et al. Here, the encapsulation efficiency was not affected by the solvent evaporation temperature. It may be due to the different processing temperatures influenced not only the rate of polymer solidification but also the diffusivity of the protein and its solubility in water. While the high temperature facilitated solidification of the dispersed phase, it enhanced diffusion

of the protein into the continuous phase, compromising the positive effect from the fast solidification.

Interaction between drug and polymer

Interaction between protein and polymer contributes to increasing encapsulation efficiency. Generally, proteins are capable of ionic interactions and are better encapsulated within polymers that carry free carboxylic end groups than the end-capped polymers. On the other hand, if hydrophobic interaction is a dominant force between the protein and the polymer, relatively hydrophobic end-capped polymers are more advantageous in increasing encapsulation efficiency. For example, encapsulation efficiencies of more than 60% were achieved for salmon calcitonin (sCT) microparticles despite the high solubility of sCT in the continuous phase. This is attributed to the strong affinity of sCT to hydrophobic polymers such as PLGA. On the other hand, such interactions between protein and polymer can limit protein release from the microparticles. In certain cases, a co-encapsulated excipient can mediate the interaction between protein and polymer. Encapsulation efficiency increased when gammahydroxypropylcyclodextrin (g-HPCD) were co-encapsulated with tetanus toxoid in PLGA microparticles. It is supposed that the g-HPCD increased the interaction by accommodating amino acid side groups of the toxoid into its cavity and simultaneously interacting with PLGA through van der Waals and hydrogen bonding forces.

Solubility of drug in continuous phase

Drug loss into the continuous phase occurs while the dispersed phase stays in a transitional, semi-solid state. If the solubility of the drug in the continuous phase is higher than in the dispersed phase, the drug will easily diffuse into the continuous phase during this stage. For example, the encapsulation efficiency of quinidine sulfate was 40 times higher in the alkaline continuous phase (pH 12, in which quinidine sulfate is insoluble) than in the neutral continuous phase (pH 7, in which quinidine sulfate is very soluble).

Molecular weight of the polymer

X. Fu et al., studied the effect of molecular weight of the polymer on encapsulation efficiency, developed a long-acting injectable huperzine A-PLGA microsphere for the chronic therapy of Alzheimer's disease, the

microsphere was prepared by using o/w emulsion solvent extraction evaporation method. The morphology of the microspheres was observed by scanning electron microscopy. The distribution of the drug within microspheres was observed by a confocal laser scanning microscope. The results indicated that the PLGA 15 000 microspheres possessed a smooth and round appearance with average particle size of 50 µm or so. The encapsulation percentages of microspheres prepared from PLGA 15 000, 20 000 and 30 000 were 62.75, 27.52 and 16.63%, respectively. The drug release percentage during the first day decreased from 22.52% of PLGA 30 000 microspheres to 3.97% of PLGA 15 000 microspheres, the complete release could be prolonged to 3 weeks. The initial burst release of microspheres with higher molecular weight PLGA could be explained by the inhomogeneous distribution of drug within microspheres. The encapsulation efficiency of the microspheres improved as the polymer concentration increase in oil phase and PVA concentration decreased in aqueous phase. The burst release could be controlled by reducing the polymer concentration. Evaporation temperature had a large effect on the drug release profiles. It had better be controlled under 30°C. Within a certain range of particle size, encapsulation efficiency decreased and drug release rate increased with the reducing of the particle size.

EVALUATION OF MICROPARTICLES:

The parameters and methods used to evaluate microspheres are:

1. Microsphere recovery/yield:

These studies involve determination of the amount of microsphere obtained at the end of preparation and polymer and drug that are consumed in its preparation [22]. It can be calculated as follow:

$$\text{Percentage Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

$$\text{Practical yield of microspheres} = \frac{\text{Amount of encapsulated drug}}{\text{Amount of added drug}}$$

2. Drug Entrapment Efficiency:

It is determined by calculating the amount of drug that is entrapped in the microsphere and the drug which is adsorbed on the surface or interior of the polymer. The amount of free, adsorbed and entrapped drug should be capable of being determined separately and this determination indicated the efficacy of the microsphere produced in terms of its active ingredients.

Determination of free drug in microspheres (unentrapped drug):

Accurately weighed microsphere is taken in a beaker. Saline is added to the mixture and shaken well to liberate the free drug present in the polymeric matrix.

The free drug is quantified by suitable analytical method. It is calculated by:

Percentage loading of microsphere =

$$\frac{\text{Quantity of free drug present}}{\text{Weight of microsphere}}$$

The amount of drug present at the surface is measured by digesting the microsphere with saline (0.9%w/v) at room temperature, sonicating the solution in an ultrasonic bath for 5 min and centrifuging it at 3000vpm for 2 min. The supernatant is filtered through 0.45µm filter and the drug is quantified by a suitable analytical method.

Percentage loading of microsphere =

$$\frac{\text{Quantity of drug present}}{\text{Weight of the microsphere}}$$

Entrapped drug in micro sphere:

The residue left over from the extraction of the free and adsorbed drug is mixed with 5ml of 0.1m glacial acetic acid. The sample is centrifuged at 5000rpm for 10 minutes. The supernatant is filtered through 0.45µm filter and the amount of drug entrapped is quantified by suitable analytical method [22].

Percentage of the encapsulated drug =

$$\frac{\text{Quantity of drug encapsulated (g)}}{\text{Quantity of drug added for encapsulation}}$$

3. Surface Morphology:

It provides vital information about the porosity and microstructure of these drug delivery systems. The most common technique used is scanning electron microscopy (SEM).

The sample prepared for this method should be dehydrated as vacuum field is necessary for image generation in SEM (shown in figure:16). Prior to loading the samples are coated with electron dense coating materials such as gold, palladium or a combination of both to take photomicrograph. The coating can be done by sputter coating or thermal vacuum evaporation.
Franklin et.al attached microsphere samples to aluminium stages and coated with 10µm of gold/palladium using a Hummer sputter coater and captured the images electronically.

4. Particle Size Analysis:

Particle size characterization is an important study of ensure that the particle size of the formulation lies in the optimal range. A wide variety of methods which employ different physical principles for the determination of size include:
(A) Manual:
a) Optical Microscopy
b) Electron Microscopy –
(i) Transmission electron microscopy (figure: 17).
(ii) Scanning electron microscopy
c) Sieving
d) Sedimentation (Andreason Pipette Method)

(B) Automated:
a) Particle counters – (i) Optical particle counting
(ii) The counter principle
(iii) Permeability
(iv) Impaction & inertial techniques
b) Light Scattering – (i) Dynamic light scattering
(ii) Enhance laser diffraction
c) Flow cytometry
d) Field flow fractionation
S.C.Lee et.al & H.Takahata et.al sized micro particles by laser diffractometry [22-27].

5. In vitro Release Studies:

These studies aid in understanding the behavior of these system in terms of drug release and their efficacy.

Since microsphere is heterogeneous system, the drug release form the polymer taken place through a diffusion process, in an in vitro environment. As a result, the drug and polymer matrix are phase separated and form a biphasic system. The release of the drug is determined by the extent of degradation of polymeric microsphere.

The in vitro release experiment can be performed using the dialysis method. In this method, a weighed quantity of the microsphere is placed in a dialysis bag, which is immersed in a larger volume of continuous phase acceptor fluid. The compartment is stirred and the drug which different uses out of the microspheres into the continuous phase is periodically sampled and assayed.
H.Takahata et.al performed invitro studies by incubating microparticles in PBS alone and PBS in a dialysis tube, in internal and gastric media [22,28].

6. Differential Scanning Calorimetry (DSC) Analysis:

The DSC technique can provide qualitative and quantitative information about the physicochemical status of the drug in the microsphere. This involves an endothermic or exothermic process and the related thermal transitions include melting, recrystallisation, decomposition, out gassing or a change in the heat capacity of the listed material. DSC is used to monitor different samples of the same materials to assess their similarities/differences, or the effects of additives on the thermal properties of the material [22].

7. Invivo Tissue Distribution Studies:

In vivo studies are a key component of any study since they provide tangible evidence of the efficacy of microspheres, and because the properties exhibited by microsphere are crucial for understanding the functional characteristics of formulation in a biological system.

To examine the appropriate properties of the formulation in vivo, adult albino mice/wirstar rats/ Rabbits, etc of certain specified weight can be used. A calculated dose of the drug is administered to each animal as dispersion in saline with 1% of tween 80. At predetermined time intervals, the animals are injected with the microsphere through the tail route vein and sacrificed by cervical dislocation. The organs like lungs, liver, kidneys, heart and spleen are extracted and studied for target action. The tissue samples are stored for 24 hrs at -200c. Then the concentration of drug localized in each organ is determined quantitatively using the HPLC method.

In vivo tissue distribution studies in animal models are carried out to prove the hypothesis of targeting of microsphere/formulation to the organs and compare them with conventional dosage forms of the drug [22,29,30].

Examples of some microencapsulated drugs:

Examples of some microencapsulated drugs are shown in table:4.

FIGURE: 1. MICROPARTICLES.

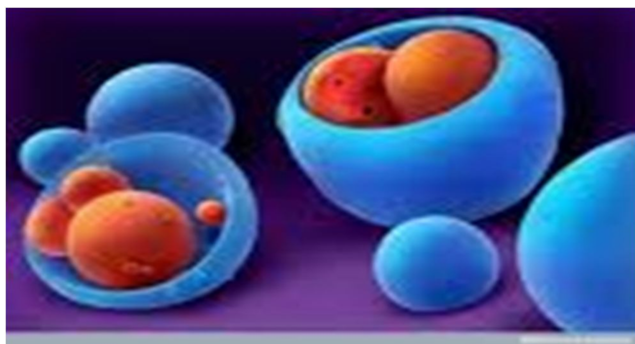

FIGURE: 2. MICROCAPSULE

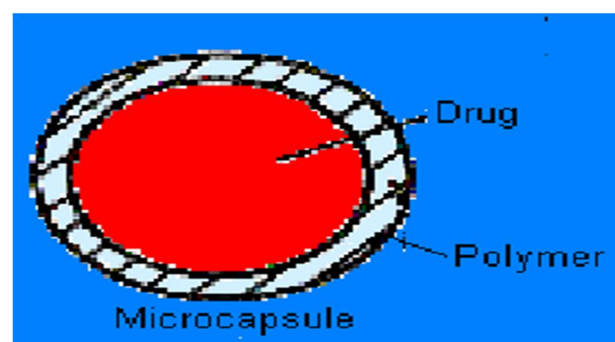

TABLE-1 : BIODEGRADABLE POLYMERS USED IN DRUG DELIVERY SYSTEMS

	I. Internal Protein	II. Animal polysaccharide	III. Plant Polysaccharide
Natural Polymers	Albumin Collagen Gelatin Fibrinogen Casein Fibrin Polylactic acid	Chitin Chitosan Hyaluronic acid	Starch Dextrose Dextran Alginic acid
Synthetic Polymers	Polylactic/glycolic acid	Poly (β-hydroxybutyric acid) Poly caprolactone Polyanhydrides	Poly (ortho ester) Poly alkylcyanoacrylate

FIGURE: 3. DIFFERENT TYPES OF MICROCAPSULES

FIGURE: 4. MICROSPHERE

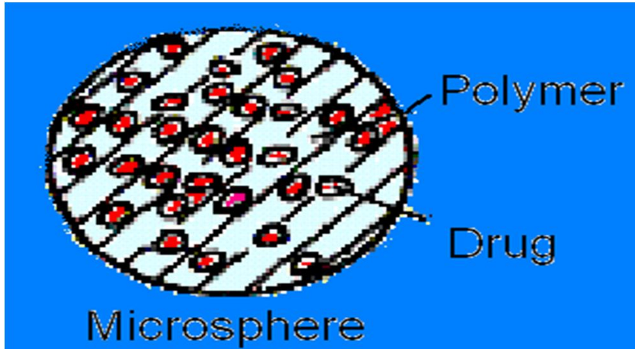

FIGURE: 5. RESEALED ERYTHROCYTES

FIGURE: 6. DIAGRAM REPRESENTING A PROTEIN MICROSPHERE

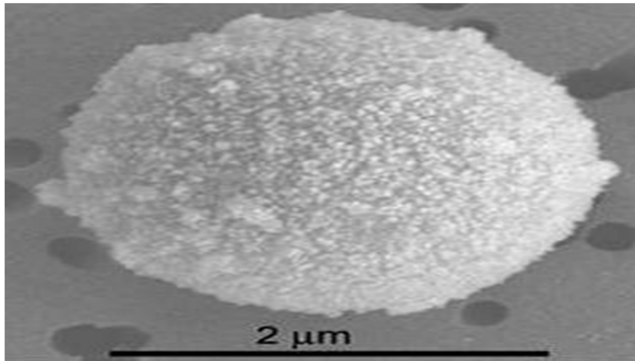

FIGURE: 7. RELEASE MECHANISM OF MICROPARTICLES

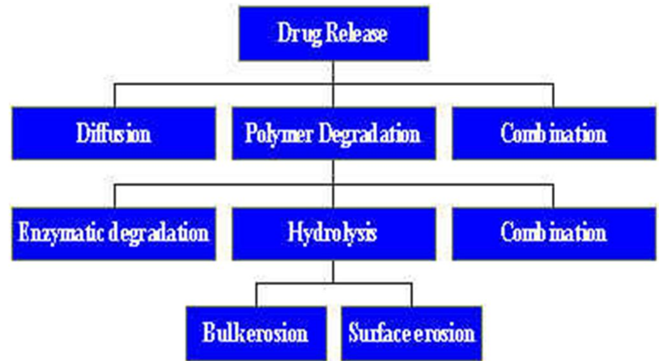

FIGURE: 8. DRUG RELEASE THROUGH DIFFUSION

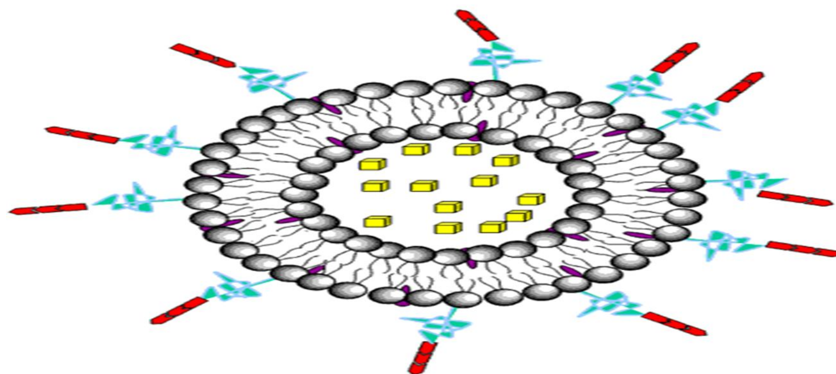

FIGURE :9. EMULSION POLYMERIZATION

FIGURE: 10. SOLVENT EVAPORATION

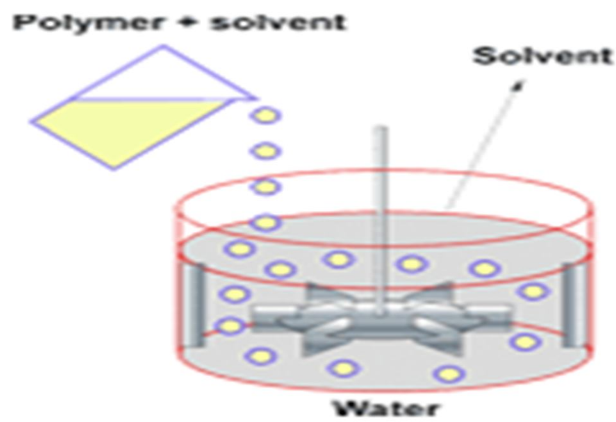

Figure: 11. schematic representation of the coacervation process. (a) core material dispersion in solution of shell polymer; (b) separation of coacervate from solution; (c) coating of core material by microdroplets of coacervate; (d) coalescence of coacervate to form continuous shell around core particles.

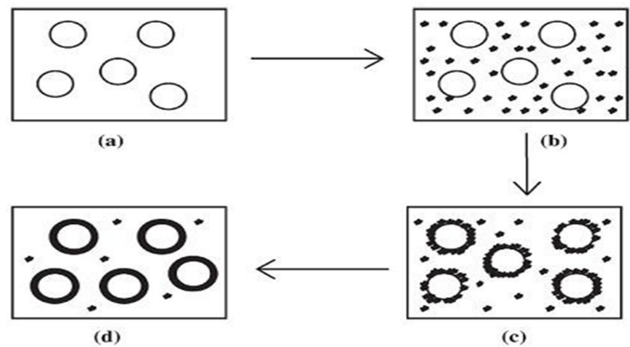

FIGURE: 12. SPRAY DRYING

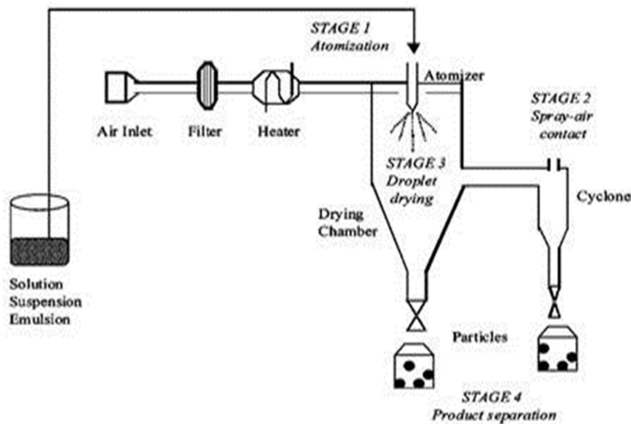

FIGURE: 13. FLUIDIZED BED COATING

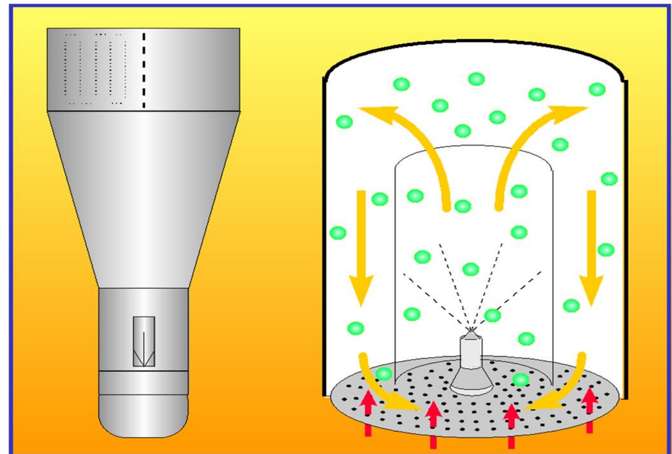

FIGURE: 14. MICROENCAPSULATION BY RAPID EXPANSION OF SUPERCRITICAL SOLUTIONS (RESS).

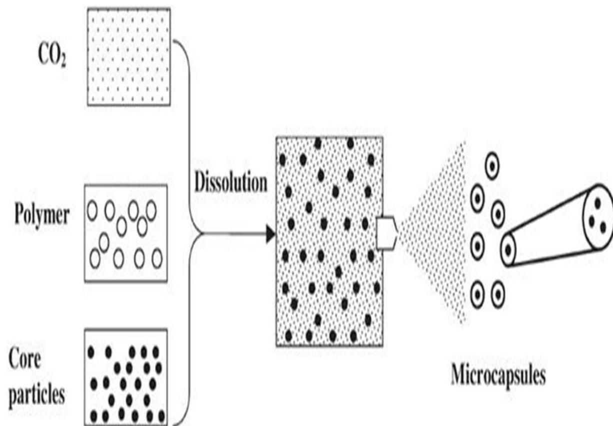

FIGURE: 15. FACTORS INFLUENCING ENCAPSULATION EFFICIENCY

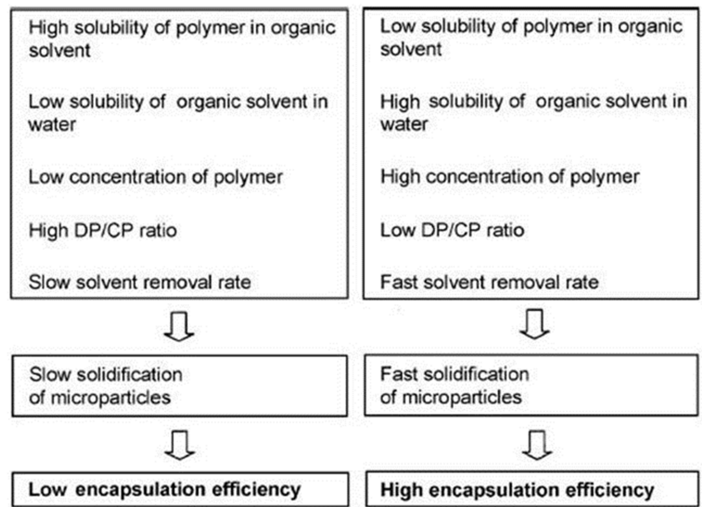

FIGURE: 16. SCANNING ELECTRON MICROSCOPE

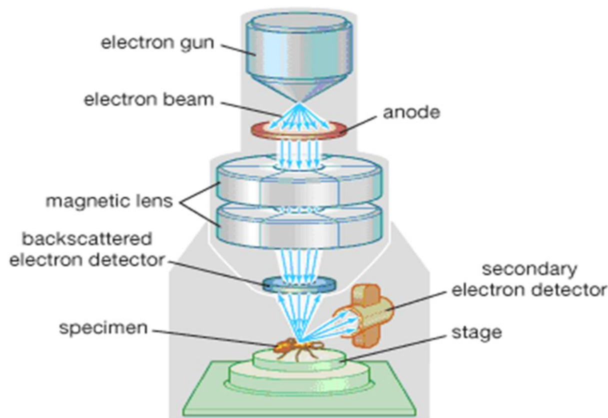

FIGURE: 17. TRANSMISSION ELECTRON MICROSCOPE

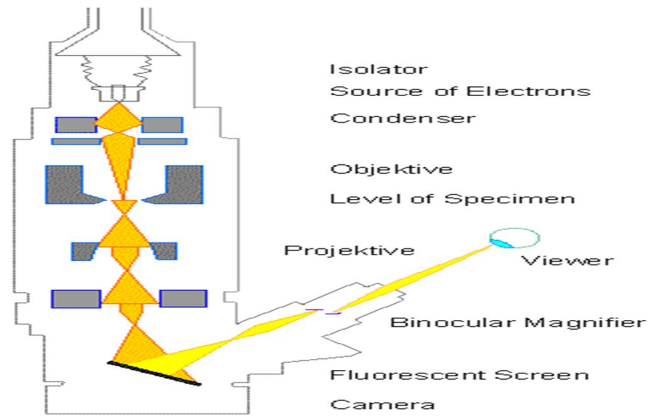

TABLE 2. TECHNIQUES EMPLOYED IN MICROENCAPSULATION

Microencapsulation methods	**Materials Investigated Shell(core)**	**Applications**
Chemical methods		
Suspension Polymerization	Poly(styrene)[PCM]	Textile
Emulsion Polymerization	Poly(acrylate)s[Insulin]	Drug delivery
Dispersion	Poly(2-hydroxyethyl-co-glycidyl methacrylate)[ferrofluid],Poly(N-vinylα-phenylalanine)[fluorescein isothiocyanate]	Biosciences
Interfacial	Polyurea[insecticides, catalysts], Polyamide[oils], Polyurethane[insecticides], Polyester[protein]	Crop protection, Catalysis, drug delivery.
Physical/Mechanical methods.		
Suspension crosslinking	Protein, Albumin[doxorubicin, magnetite],Polysaccharides.	Drug delivery
Solvent evaporation/extraction	Poly(lactide), Poly(lactide-co-glycolide) [drugs]	Drug delivery
Coacervation/Phase separation	PLGA[Triptorelin],PLGA[Octreotide].	Drug delivery
Spray drying	PLGA[Bromocriptine],Polymers[Food ingredients]	Drug delivery, Food Technology
Fluidized bed coating	Gelatin, carbohydrates, lipids.	Food Technology
Melt solidification	Polyanhydride[Insulin]	Food Technology
Precipitation	Phenolic polymers[enzymes]	Biocatalysis
Co-extrusion	Polyacrylonitrile[hepatocytes]	Biomedical
Layer by layer deposition	Polyelectrolytes[organic compounds]	Biosensor
Supercritical fluid expansion	Poly(ethylene glycol)[felodipine]	Drug delivery
Spinning disk	Paraffin	Food Engineering
Impregnation	Amberlite[Benzoic acid]	Drug delivery

TABLE 3. SELECTION OF MICROENCAPSULATING METHODS FOR DRUGS WITH DIFFERENT PROPERTIES

	Water-soluble drugs	Water-insoluble drugs
Liquid drugs	w/o/w double emulsion w/o/o double emulsion w/o emulsion Ionic gelatin Spray drying	o/w (or) o/o emulsion coacervation spray drying
Solid drugs	Cryogenic solvent extraction method s/o/w (or) s/o/o emulsion Fluid-bed coating Supercritical fluid	Coacervation Fluid bed coating

TABLE 4. EXAMPLES OF SOME MICROENCAPSULATED DRUGS

Active moiety	**Characteristic**	**Property Purpose of encapsulation**	**Final product form**
Aspirin	Slightly soluble in water	Taste masking , sustained release, reduced in gastric irritation	Tablet or capsule
Paracetamol	Slightly soluble in water	Taste masking	Tablet
Islet of Langerhans	Viable cells	Sustained normalization of diabetic condition	Injection
Isosorbide dinitrate	Water soluble	Sustained release	Capsule
Progesterone	Slightly soluble in water	Sustained release	Varied
Menthol	Volatile solution	Reduction in volatility, Sustained release	Lotion
Potassium chloride	Highly soluble in water	Reduction in gastric irritation	Capsule

Active moiety	Characteristic	Property Purpose of encapsulation	Final product form
Urease	Water soluble enzyme	Perm selectivity of enzyme, substrate and reaction	Dispersion
Vit.A Palmitate	Nonvolatile liquid	Stabilization to oxidation	Dry powder
Nifedipine	Practically insoluble in water	Prevention from photoinstability	Dry powder

CONCLUSION

Controlled drug delivery technology represents one of the frontier areas of science, which involves multidisciplinary scientific approach, contributing to human health care. These delivery systems offer numerous advantages compared to conventional dosage forms, which include efficacy, reduced toxicity, and improved patient compliance and convenience. Such systems often use macromolecules as carriers for drugs. Microparticles for their attractive properties occupy unique position in drug delivery technology. We are now in the process of conducting pre clinical tests to evaluate the potential of different microparticles as drug delivery systems for administration via different routes. Although toxicity problems may exist, they will be resolved by modifying the factors that influence these systems.

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