MICROSPHERES AND MICRO CAPSULES: A CONCISED REVIEW

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ABSTRACT:

A thin covering material is generated using the micro encapsulation process, which surrounds the micro particles with a solid, liquid, or gas. A Controlled Release of the medication is provided using microencapsulation. The benefits of micro encapsulation over conventional drug delivery systems are numerous, and it may be more effective. The review of these microcapsules includes their structure, types, benefits, and drawbacks, as well as their uses.

Key words: "micro encapsulation," "micro particles," "controlled release," "conventional drug delivery system," "coating material," and "micro capsules."

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INTRODUCTION

Microencapsulation is the process of enclosing a substance inside a miniature called capsule. Microcapsules are a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core/ internal phase, whereas the wall is sometimes called a shell/coating. The microcapsule size range from 1 µ -7mm.

Microcapsule is a micro packaging technology that can wrap solids, liquids, and gases. The process of preparing microcapsules is called microencapsulation, which has the advantages of isolating the core material to reduce the influence of external environmental factors, enhancing the stability of the core material, concealing unpleasant odors, reducing the toxicity of the core material, increasing the utilization rate of the core material. With the continuous development of technology, the application prospects of microcapsules are gradually broad in the fields of food, cosmetics, medical engineering, production and construction, textiles and other fields. [1]

Microspheres can be characterized as solid, approximately spherical particles with a diameter having between 1–1000µm, including dispersed drugs in certain solution or microcrystalline shape. Both the terms microcapsules andmicrospheres are often used as synonyms. Medication That is simply transmitted in from gastrointestinal tract (GIT) and also has a short half-life is immediately destroyed from circulatory system in the blood. The oral sustained or controlled release (CR) have also been developed to avoid this problem, as that will Slowly discharge the substance into the GIT and retain a steady medication intensity in the plasma For a prolonged time period. A suitable dosage formulation is one that reaches the required plasma therapeutic Drug concentration and remains constant throughout the treatment period. This can be achieved by delivering a traditional dosage type in a fixed dose and at a specific frequency.[8]Microspheres are sometimes referred to as mi- croparticles. Microspheres can be manufactured fromvarious natural and synthetic materials. Microsphereplay an important role to improve bioavailability of conventional drugs and minimizing side effects.

ADVANTAGES OF MICROSPHERES OVER CONVENTIONAL DOSAGE FORMS

Microspheres provide prolonged and constant therapeutic effect. Particle size reduction for enhancing solubility of the poorly soluble drug. Microspheres reduce the dosing frequency and therefore improve the patient compliance. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein. Microspheres provide controlled, sustained and targeted delivery of the drug. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal. Microspheres produce more reproducible drug absorption. Drug discharge in stomach is hindered and that's why local unwanted effects are reduced. In case of microspheres, better therapeutic effect for short half-life of drugs can be achieved. Microspheres provide freedom from drug and recipients incompatibilities especially with buffer. Microspheres reduce dose dumping. Microspheres provide the protection of drugs against environment. Microspheres also mask the taste and odor. Microspheres avoids the first pass metabolism. Microspheres can be easily injected in body because of their small and spherical size. Microspheres enhance the biological half-life and also improve the bioavailability. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections. Microspheres also reduce the chances of G. I. irritation.[2]

LIMITATION

The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations. Controlled release rate of microspheres may vary due to certain factors like intrinsic or extrinsic factors may befood, rate of transit through gut, mucin turnover rate etc. The fate of polymer matrix and its effect on the environment. There are differences in release from one to another dosage form. Any loss of integrity in release pattern may cause potential toxicity. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and filers. Reproducibility is less. Low drug loading is done in case of parental microspheres. Process situations like change in temperature, pH, solvent addition, and evaporation/ agitation may influence the stability of core particles to be encapsulated. Parental delivery of microspheres may interact or form complex with blood components. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents[2]

REASONS FOR MICROENCAPSULATION

- The main reason for microencapsulation is for sustained or prolonged release of the drug
- This technique has been widely used for masking the organoleptic properties like taste and odor of many drugs and thus improves patient compliance e.g. Paracetamol, nitrofurantoine for masking the bitter taste.
- By using microencapsulation techniques the liquid drugs can be converted in a free flowing powder.
- The drugs sensitive to moisture, light and
- oxygen can be protected by microencapsulation. For example, nifedipine is protected from photo instability.Microencapsulation technique is also helpful to prevent the incompability between drugs.
- The drugs which are volatile in nature may vaporize at room temperature. Drugs like Aspirin and peppermint oil can be prevented by microencapsulation.
- Reduction in toxicity and GI irritation including with KCL and ferrous sulphate can be achieved by microencapsulation.
- Microencapsulation has also been employed to change the site of absorption. This application has been useful for those drugs which have the toxicity at lower pH.
- Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability, as prevent from oxidation.
- Microencapsulation method has also been employed to prepare intrauterine contraceptive device. [3]

MATERIALS USED IN THE DEVELOPMENT OF MICROSPHERE

Natural polymeric materials

Depending upon the source from which these materials are obtained these are further classified as:

- **Proteins:** Collagen, Albumin and Gelatin.
- **Carbohydrates:** Starch, Agarose, Chitosan and Carrageenan.

Chemically modified carbohydrates: Poly dextran, Poly Starch.***Synthetic polymers***

These polymeric materials are synthesized by using different chemical substances given below:

- Biodegradable polymers include Lactides, Glycolides & their copolymers, Poly anhydrides and Poly alkyl cyanoacrylates etc.
- Non–biodegradable polymers includes Poly methyl methacrylate (PMMA), Glycidyl methacrylate, Acrolein, Epoxy polymers.[4]

TYPES OF MICROSPHERES

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

i)Biodegradable polymeric microspheres ii)Synthetic polymeric microspheres[5]

1. BIOADHESIVE MICROSPHERES

The bioadhesion describes that the materials having the property to adhere at biosubstrate; such as mucosal membranes. Adhesions of bioadhesive drug delivery devices to mucosal tissue provide prolong contact of device with the site of administration. This prolonged contact time increase the absorption of drug from its device and controlled release of drug from device also maintained it improved patientcompliance by reducing the frequency of administration. Carrier system of drug delivery gives an approach pair the drug to a carrier system such as microspheres. Which mediate the release and absorption of the drug. Microspheres play an important role in these types of drug delivery systems due to their small size and efficient carrier capacity (Subbiah Ganesh et al. 2010).[6],[7]

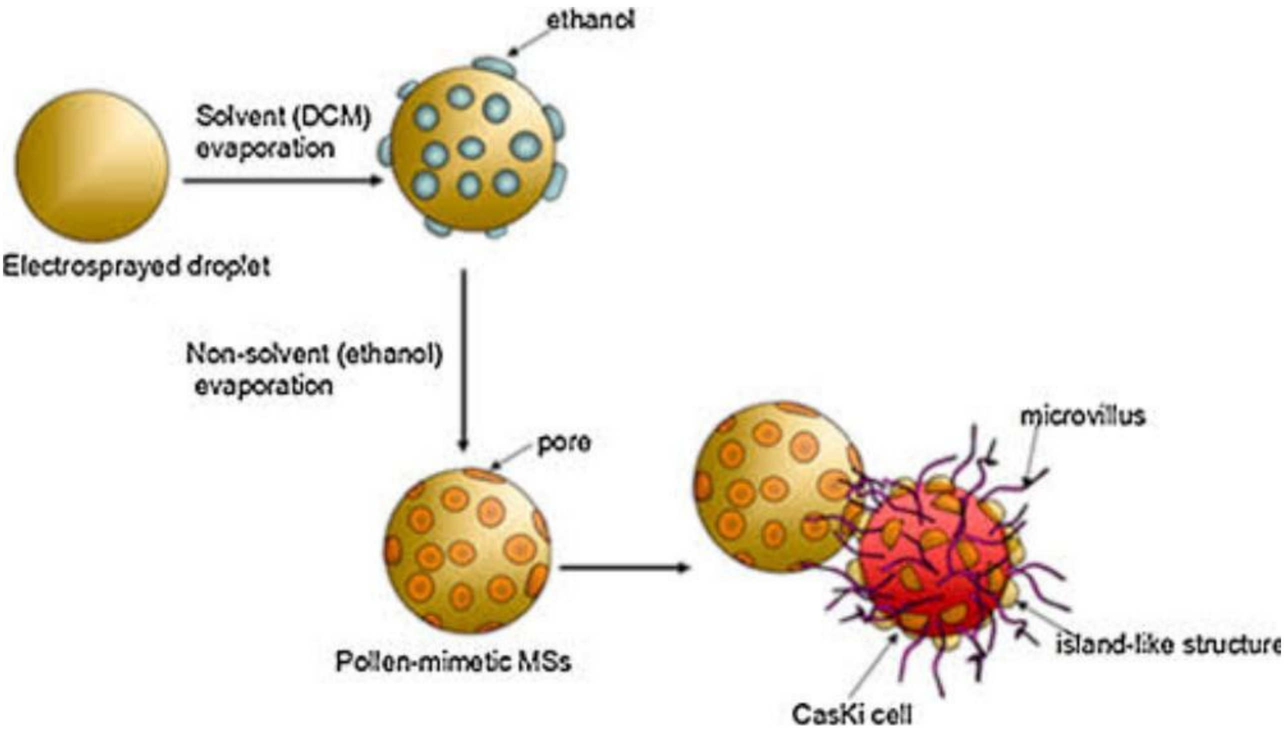

Figure1:-Bioadhesive microsphere

2. MAGNETIC MICROSPHERES

This type of microsphere has an important property to use as a conveyance system, that is, it restricts the drug to the disease site. The main focus of these kinds of microspheres is on replacement of high quantity of freely disseminating drug with a less quantity of the magnetically targeted drug. Magnetic microspheres are of size <4 μm, due to which it adequately circulates the blood capillaries without any vascular occlusion and are targeted to disease site through an external magnetic field of 0.5–0.8 tesla, for example, Removal of neuroblastoma cells from bone marrow with monoclonal antibodies conjugated to magnetic microspheres [5,6].

Magnetic microspheres are of two types:

Therapeutic magnetic microspheres:The main focus of this kind of microsphere is targeting liver tumors by transporting a chemotherapeutic agent to the disease site.These types of microspheres are mainly loaded with proteins or peptide drugs for targeting[9].

1) Diagnostic magnetic microspheres:

These types of microspheres mainly focused on liver metastases imaging. It can also be used for composing nano-sized particles like supramagnetic iron oxides which are used to differentiate bowel loops from other abdominal structures.[8]

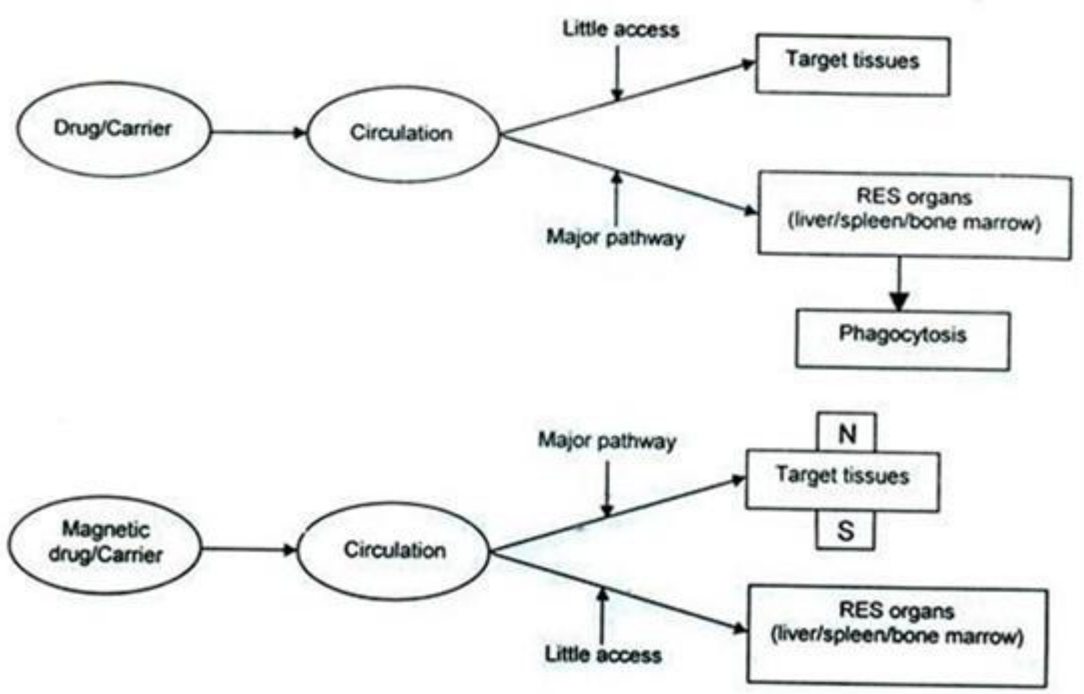

Figure2:-Principle of Magnetic Drug Targeting

3. Floating microspheres

In floating types, the bulk density is less than the gastric fluid and so remains buoyant in the stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate if the system is floating on gastric content, which increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces a prolonged therapeutic effect. Drug (ketoprofen) is given through this form.[10][11]

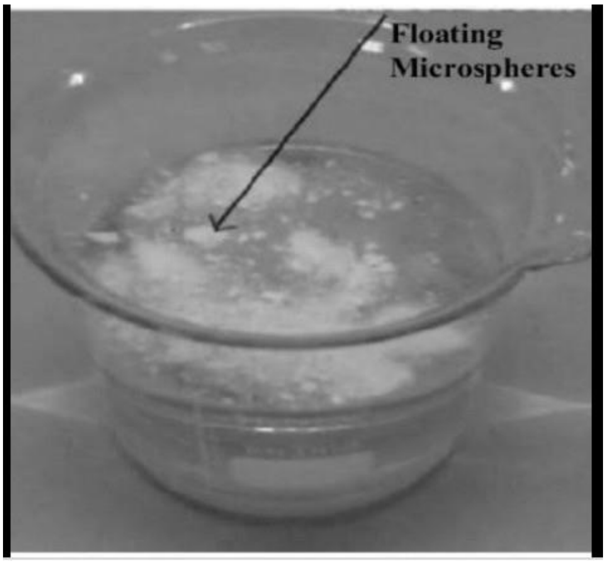

Figure3:- Floating microspheres

4. RADIOACTIVE MICROSPHERES

Radio demobilization therapy microspheres sized 10-30 nm are larger than capillaries and get tapped in the first capillary bed when they come across. They are injected into the arteries that lead to the tumor of interest. So these radioactive microspheres deliver a high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from the drug delivery system, as radioactivity is not released from microspheres but acts from within a radioisotope typical distance and the different So these radioactive microspheres deliver a high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from the drug delivery system, as radioactivity is not rulemakings of radioactive microspheres are α emitters, β emitters, γ emitters[12]

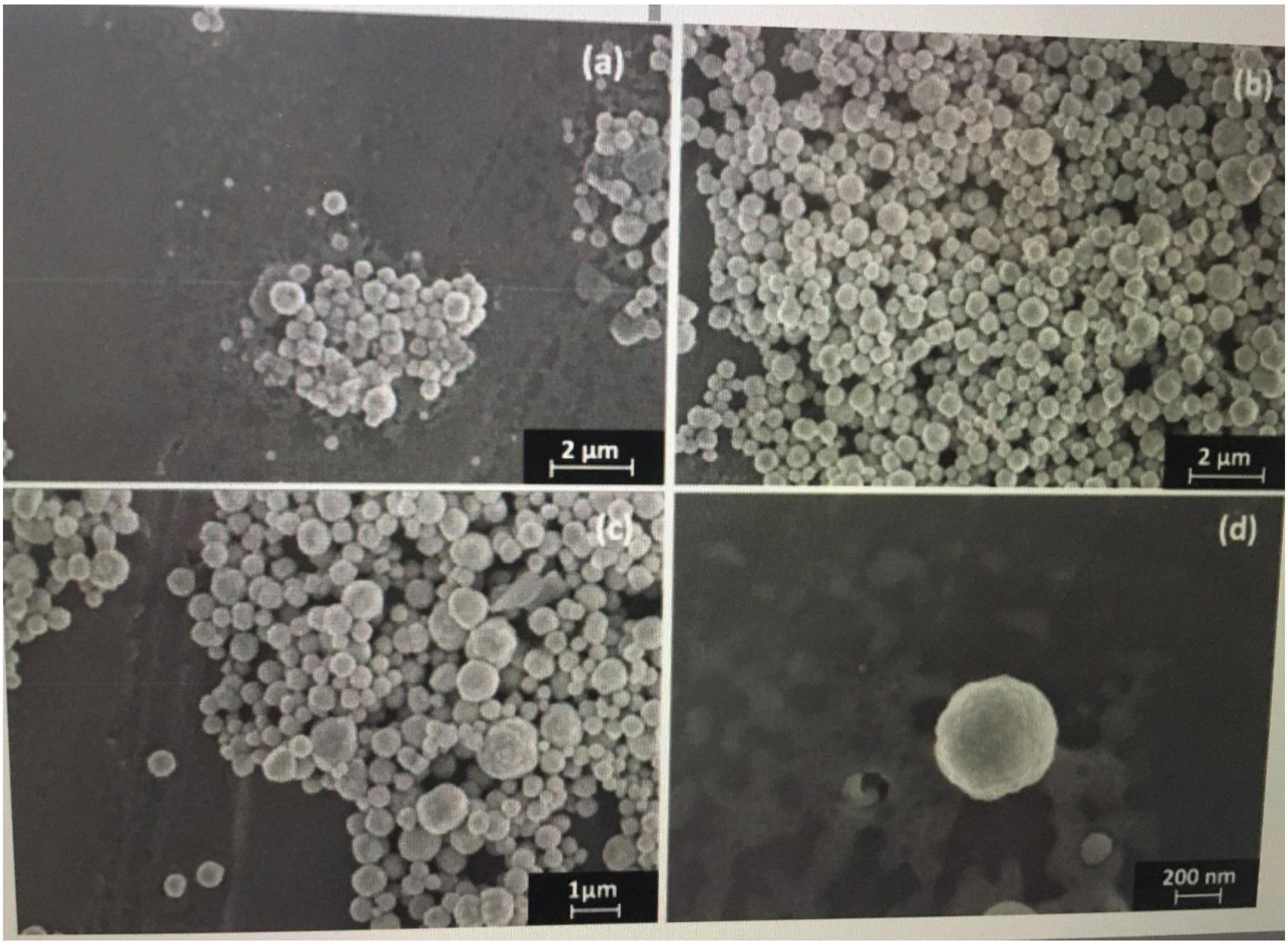

Figure4:- Radioactive microsphere

5. POLYMERIC MICROSPHERES

The different types of polymeric microspheres can be classified as follows. A. Biodegradable polymeric microspheres

B. Synthetic polymeric microspheres [13] Methods used in microsphere preparation

Choosing the method depends primarily on Character of a polymer been using, the drug, the factors equivocally determined by many formulations and technological factors as the size of the particles requirement, and the drug or protein should not be significantly impacted by the process, the reproducibility of the release profile and the method, there should be no stability Issue, in relation to the finished product.

Thevarious types of procedures used to prepare the microspheres using hydrophobic and hydrophilic polymers as matrix materials.

- The capacity to integrate medication doses which are relatively small.
- Stability of preparation after synthesis with a shelf spam which is clinically acceptable.
- Controlled particle size and dispersibility for injection in the aqueous vehicles.
- Effective reagent release with strong control over a large time-scale.
- Biocompatibility of controllable biodegradability and chemical alteration response.[14]

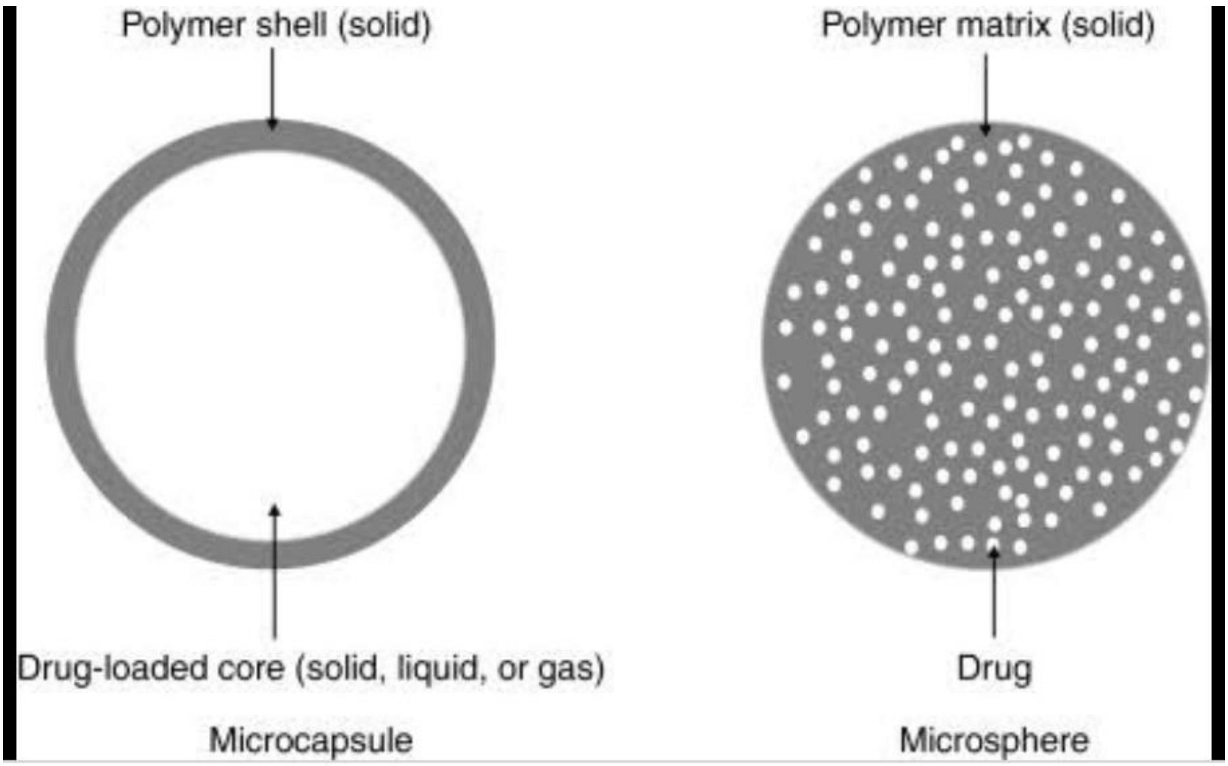

Figure 5:- Polymeric microspheres

GOALS OF MICROENCAPSULATION

Microencapsulation can be used to achieve a number of objectives. Some goals of microencapsulation include material structuration, protection of the enclosed product, and controlled release of the encapsulated contents, as shown in Figure 7. Microcapsules can provide structuration to compounds that are normally difficult to administer due to factors such as the material's insolubility, volatility, reactivity, hygroscopicity, and physical state . Microcapsules may also serve the role of protecting the encapsulated contents to prevent the degradation of the product due to external environmental factors such as oxygen, light, heat, and humidity which could destroy any labile compound. Protection by microcapsules may also be required when orally administering a therapeutic, due to exposure to the harsh conditions of the upper gastrointestinal tract (GIT). In addition, the host's immune system would quickly lead to the implanted cells' rejection and undesired side effects if the cells arerecognized as foreign. Immunoprotection and immunoisolation may be achieved by a microcapsule, important for the in vivo delivery and implantation of mammalian cells, such as stem cells, for tissue and cell engineering applications

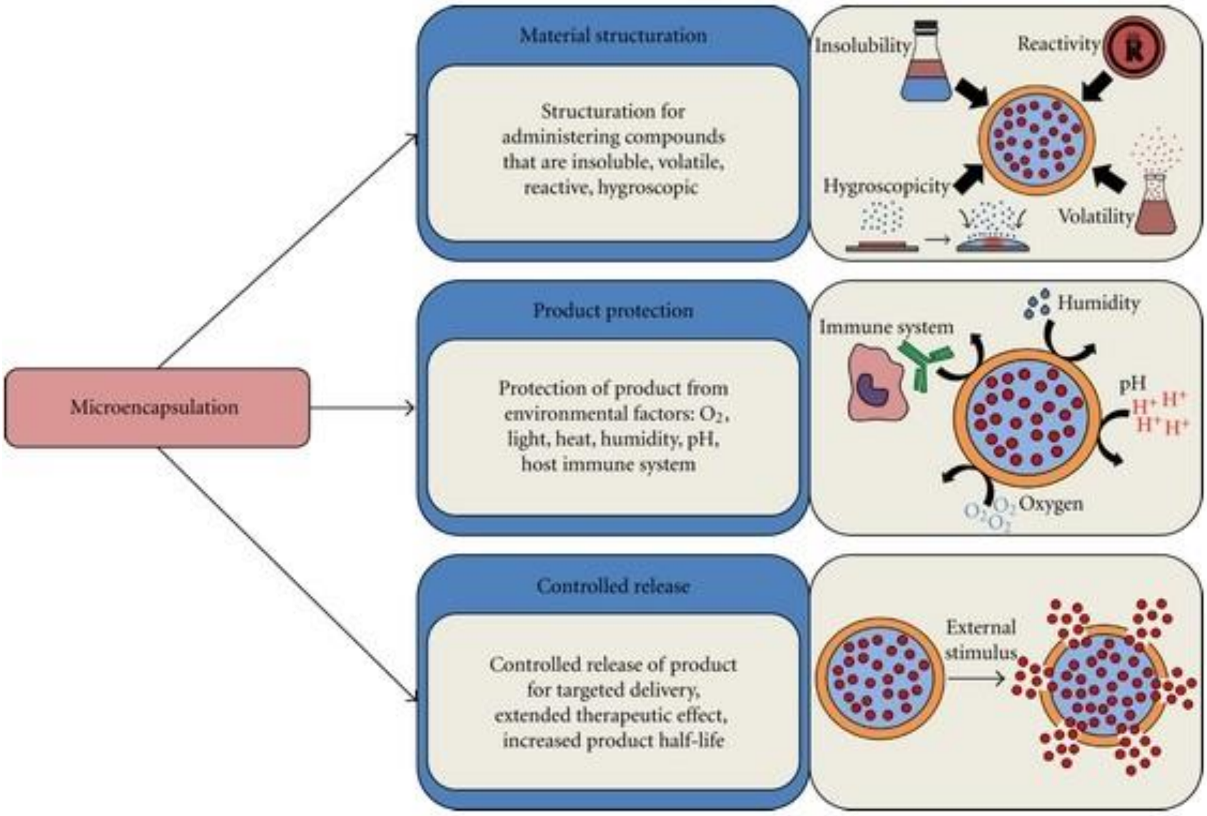

Figure6:- Goals of Microencapsulation

The capability of microcapsules to serve the purpose of immunoprotection has been well demonstrated in a number of disease contexts, including type 1 diabetes, Parkinson's disease, Alzheimer's disease, cancers, and other disorders . Microcapsules may also serve to permit the controlled release of the encapsulated contents, which can be regulated by chemical, physical, and mechanical factors. A controlled release can permit a longer and more efficient therapeutic effect of an enzymatic by-product, which, otherwise, may have a limited half-life in vivo. It may also regulate the release of the encapsulated product at the desired time, rate, dose, and site of action.[15]

MECHANISM AND KINETICS OF DRUG RELEASE

Major mechanisms of drug release from microcapsules include diffusion, dissolution, osmosis and erosion.

1. **Diffusion** is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels Thus, the overall release depends on, the rate at which dissolution fluid penetrates the wall of microcapsules, the rate at which drug dissolves in the dissolution fluid, and the rate at which the dissolved drug leak out and disperse from the surface.[9] The kinetics 1/2 of such drug release obeys **Higuchi's equation as below: Q=[D/J(2A–åC)C t] SS**
2. Where Q is the amount of drug released per unit area of exposed surface in time t; D is the

diffusion coefficient of the solute in the solution; A is the total amount of drug per unit volume; 'C' is the solubility of drug in permeating dissolution fluid ; a is the porosity of the wall of microcapsule; J is the tortuosity of the capillary system in the wall. The above equation can be simplified to Q = vt where **v** is the apparent release rate.**Dissolution**: Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid Thickness of coat and its solubility in the dissolution fluid influence the release rate.

3. Osmosis: The polymer coat of microcapsule acts as semi permeable membrane and

allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pores in the coat.

4. Erosion: Erosion of coat due to pH and/or enzymatic hydrolysis causes drug release with certain coat materials like glyceryl monostearate, bee's wax and stearyl alcohol. [3]

Coating materials:-

A wide variety of coating materials are available for microencapsulation. Some patent innovative coating polymers have also been developed for some special applications particularly among the bioadhesives and mucoadhesives. However, many traditional coating materials are satisfactory for the use in the gastrointestinal tract. They include inert polymers and pH sensitive ones as carboxylate and amino derivatives, which swell or dissolve according to the degree of cross-linkingThe selection of appropriate coating material from a long list of candidate materials needs consideration of the following general criteria by the research pharmacist:

1. What are the specific dosage forms or product requirements, such as stabilization, reduced volatility, release characteristics, and environmental conditions?
2. What coating material will satisfy the product objective and requirements?

What microencapsulation method is best suited to accomplish the coated product objectives?The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/ microspheres. While selecting a polymer the product requirements i.e. stabilization, reduced volatility, release characteristics, environmen-tal conditions, etc. should be taken into consideration. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability.

Generally hydrophilic polymers, hydrophobic polymers or a combination of both are used for the microencapsulation process. A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system. The micro-capsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms.[16]

Core materials :-

The core material is the material over which coating has to be applied to serve the specific purpose. Core material may be in form of solids or droplets of liquids and dispersions. The composition of core material can vary and thus furnish definite flexibility and allow effectual design and development of the desired microcapsule properties. A substance may be microencapsulated for a number of reasons. Examples may include protection of reactive material from their environment, safe and convenient handling of the materials which are otherwise toxic or noxious, taste masking, means for controlled or modified release properties means of handling liquids as solids, preparation of free flow powders and in modification of physical properties of the drug[17].

REASONS FOR MICROENCAPSULATION

The primary reason for microencapsulation is found to be either for sustained or prolonged drug release.

- This technique has been widely used for masking taste and odour of many drugs to improve patient compliance.
- This technique can be used for converting liquid drugs in a free flowing powder.
- The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.
- Incompatibility among the drugs can be prevented by microencapsulation.
- Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation.
- Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl.
- Alteration in site of absorption can also be achieved by microencapsulation.
- Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.[18]

DIFFICULTIES IN MICROENCAPSULATION TECHNIQUE

- Incomplete or discontinuous coating
- Inadequate stability or shelf life of sensitive pharmaceuticals
- Non reproducible and unstable release characteristics of coated products
- Economic limitations[19]

PHARMACEUTICAL APPLICATION OF MICROSPHERES

1) Oral drug delivery
2) Targeting drug delivery
3) Gastroretentive controlled delivery system
4) Bio-medical application Pharmaceutical application Vaccine delivery
5) Monoclonal antibodies
6) Imaging
7) Topical porous microsphere 10)Nasal drug delivery

1. ORAL DRUG DELIVERY

Shefi angel timmy49 et al. work on delivery of insulin by oral route by making microsphere with cyclodextrin making inclusion complex with drug molecule. In oral delivery of insulin for the treatment of diabetes mellitus. The main problem with insulin was degradation of drug due to enzyme in GI tract. Aliginate and enteric polymers, which protecting the insulin in acidic condition. Polk et al used chitosan alginate membranes for delayed release of protein.[20]

2. TARGETING DRUG DELIVERY

Microspheres exhibit a prolonged residence time at site of application and thus contribute to better therapeutic performance of drugs. Microspheres have been developed for oral, buccal, ocular, rectal, nasal and vaginal routes for either systemic or local effects. This article presents introduction and the advanced pharmaceutical applications of bioadhesive microspheres. There are number of drugs which are given by different route of administration and having good targeting effect

3. GASTRORETENTIVE CONTROLLED DELIVERY SYSTEM

In which Floating systems are low-density systems (fig 3) that have float over the gastric contents and remain in the stomach for a prolonged period than conventional dosage forms. Gastric emptying of dosage form is extremely variable process and ability to control the emptying time is valuable asset for dosage forms, there are several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability.56 While the system floats over thegastric contents, the drug is released slowly Several polymers are use for gastroretentive controlled delivery system such are Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene oxide etc,.

Some example of drug products in market are :

Tablets: Ampicillin, Atenolol, Amoxycillin, Acetyl salicylic acid, Acetaminophen, Chlorpheniramine maleate, Ciprofloxacin, Captopril, Cinnarazine, Diltiazem, Fluoruracil, Isosorbide di nitrate, Riboflavin, Prednisolone, Theophilline.

Capsules: Nicardepine, Propranolol, Verapamil. Microspheres/Floating

Ibuprofen, Ketoprofen, Amoxicillin,

Granules: Riboflavin, Meloxicam, Indomethacin, Diclofenac, Prednisolone3

4. IMPLANTABLE DEVICES:

Microencapsulation has also been used medically for the encapsulation of live cells and vaccines. Biocompatibility can be improved by the encapsulation of artificial cells and biomolecules such as peptides, proteins, and hormones,65, 66 which can prevent unwanted immunological reactions that would lead to inactivation or rejection. Microspheres are used for isolating materialsuntil their activity is needed. The biotechnology industry employs microspheres to contain organisms and their recombinant products to aid in the isolation of this products.[21]

5. PHARMACEUTICAL APPLICATIONS:

A number of pharmaceutical microencapsulated products are currently on the market, such as aspirin, theophylline and its derivatives, vitamins, pancrelipase, antihypertensives, potassium chloride, progesterone, and contraceptive hormone combinations.68 Microencapsulated KCL (Micro-K, R.H. Robins, Richmond, VA) is used to prevent gastrointestinal complications associated with potassium chloride. The dispersibility of the microcapsules and the controlled release of the ions minimize the possibility of local high salt concentrations,which could result in ulceration, hemorrhage, or perforation. Microspheres have also found potential applications as injection69, 70 or inhalation71-74 products. The number of commercially available products does not reflect the amount of research that has been carried out in this area, nor the benefits that can be achieved using this technology. Economic considerations have been a key factor in determining the number of pharmaceutical microencapsulated products. Most encapsulation processes are expensive and require significant capital investment for equipment. An exception is pan or sprays coating and spray drying, since the necessary equipment may already be available within the company. An additional expense is due to the fact that most microencapsulation processes are patent protected.

6. MICROSPHERES IN VACCINE DELIVERY:

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, Safety and convenience in application and cost. In 2000 limin et al. prepared poly- microparticle by using solvent evaporation method as a drug carrier for insulin.35 The aspect of safety and minimization of adverse reaction is a complex issue36. The aspect of safety degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.

Lamprecht et al. in 2000 prepared nanoparticle preparation of bovine serum albumin (BSA) by double emulsion method, found that on increase the protein concentration in the inner aqueous phase BSA encapsulation efficiency decreased while particle size was not influenced significantly. There is higher release rate with PLGA NP compared with PCL NP.

7. MONOCLONAL ANTIBODIES MEDIATED MICROSPHERES TARGETING

There are numbers of antibiotic drugs which are administrate in microsphere form, for improve the efficiency as well as compatibility with other salt. Such as amoxycilline, ampicillin, tetracilline, sulfadiazine, sulfathiazole, griseofulvine5. Monoclonal antibodiestargeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods

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

In 1999 Shan et al Prepared Amoxycillin and metronidazole loaded chitosan microspheres for stomach specific delivery were prepared for the treatment of Helicobacter pylori infection by crosslinking in addition to precipitation with sodium tripolyphosphate. In vitro studies in simulated gastric fluid showed that the total amount of drug was released in 2 h due to the high porosity of the drug-loaded microspheres. However, amoxicillin showed 40% degradation in 10 h in simulated gastric fluid while metronidazole was stable for 24 h. This study showed the usefulness of porous metronidazole containing chitosan microspheres for eradication of the above infection38. Ampicillin microparticles by spray- drying technique a new derivative of chitosan, methyl- pyrrolidinone chitosan was used. Giunchedi et al., in1998) used Scanning electron microscopy, particle size analysis, differential scanning calorimetery and in vitro drug release studies were carried out to characterize the microparticles and microbiological assays were also performed usingdifferent bacterial strains. Results of the assay showed that ampicillin microspheres were able to maintain the antibacterial activity of the drug[21].

8. IMAGING

The particle size plays an important role in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labeled human serum albumin microspheres9 Hejazi and Amiji (2003) Prepared microsphere by ionic crosslinking and precipitation method Studied the gastric residence time of tetracycline loaded chitosan microspheres. Following their oral administration in gerbils chitosan microsphere suspension in the nonacid-suppressed and acid-suppressed states. Animals were sacrificed at different time points, and the radioactivity in tissues and fluids was measured with a gamma counter.

9. TOPICAL POROUS MICROSPHERES

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 μm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner.

10. NASAL DRUG DELIVERY

Intranasal (IN) administration has many theoretical and practical advantages for the local and systemic delivery of a diverse therapeutic compound. IN delivery is needle- free, non-invasive, and essentially painless, does not require sterile preparation, and can be self-administered. The large surface area of the nasal mucosa originated from the presence of a large number of microvilli, a porous endothelial membrane, and ahighly vascularized epithelium serves a rapid onset of therapeutic effect.It is describes various systems, devices, formulations, and methods of delivery of drugs to the nose or nasal cavity (table 2). Depending on the therapeutic intent, intranasal drugs may be targeted for local treatment or systemic action. For treatment and prevention of nasal symptoms E.g. Rhinitis, Allergy, Decongestion and Local inflammation etc. Martinac and at el in 2004 prepared Loratadine-loaded microspheres by spray-drying of dispersions, emulsions and suspensions differing in polymeric composition and solvents used. And he delivered loratadine (lipophilic) drug through nasal drug delivery by making bioadhesive microsphere48. In nasal drug delivery, coupling of bioadhesive properties to microspheres is of great importance because of additional advantages: efficient absorption and enhanced bioavailability of the drug, a much more intimate contact with the mucus layer and reduction in frequency of drug administration due to the reduction in mucociliary clearance of drug delivery system adhering to nasal mucosa[15]

OTHER APPLICATIONS

Applications of microencapsulation in other industries are numerous. The best known microencapsulated products are carbonless copying paper, photosensitive paper, microencapsulated fragrances, such as ''scent-strips'' (also known as ''snap-n-burst''), and microencapsulated aromas (''scratch-n-sniff''). All of these products are usually prepared by gelatin–acacia complex coacervation. Scratch-n-sniff has been used in children's books and food and cosmetic aroma advertising. Microcapsules are also extensively used as diagnostics, for example, temperature-sensitive microcapsules for thermo graphic detection of tumors. In the biotechnology industry microencapsulated microbial cells are being used for the production of recombinant proteins and peptides73. The retention of the product within the microcapsule can be beneficial in the collection and isolation of the product. Encapsulation of microbial cells can also increase the cell- loading capacity and the rate of production in bioreactors. Smaller microcapsules are better for these purposes; they have a larger surface area that is important for the exchange of gases across the microcapsule membrane.[22]

METHOD OF PREPERATION

The various methods of preparations are:

1.Emulsion Solvent Evaporation Technique 2.Emulsion Cross Linking Method 3.Coacervation Method

1. Spray Drying Technique
2. Emulsion-Solvent Diffusion Technique
3. Multiple Emulsion Method
4. Ionic Gelation Method
5. Hap method(hydroxyl appetite microspheres)
6. Novel quasi-emulsion solvent diffusion method

1. EMULSION SOLVENT EVAPORATION TECHNIQUE

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with1963.demineralised water and desiccated at room temperature for 24 hrs28.[23]

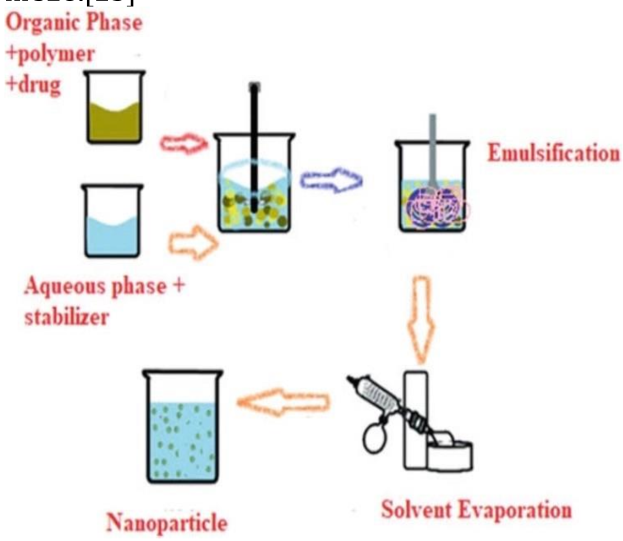

Figure7:-Emulsion Solvent Evaporation Technique

2. EMULSION CROSS LINKING METHOD

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40 0C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 oC, results in w/o emulsion then further stirring is done for 10 min at 150C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution

at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 370 C for 10 min to block unreacted glutaraldehyde.18 Examples for this technique is Gelatin A microspheres. [24]

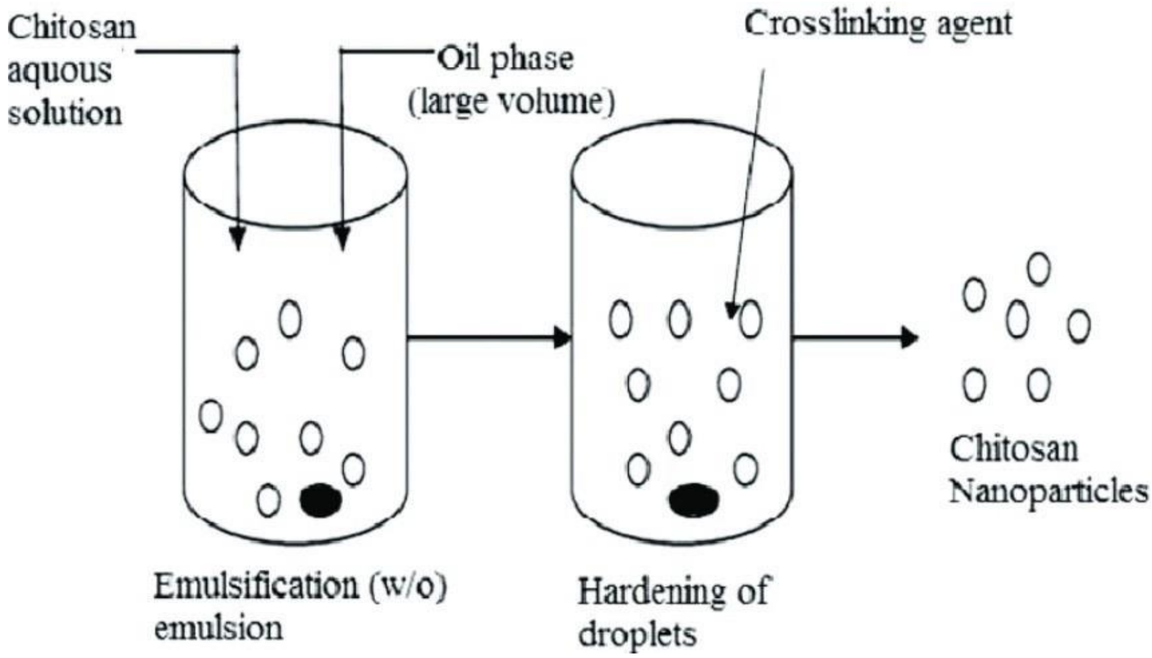

Figure8-Emulsion Cross linking method

3. COACERVATION METHOD

Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 800C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twicely with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule25. Co- acervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for 6 hr at 500rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin 5 times with continuous stirring.1After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50oC for 4 hr25.[25]

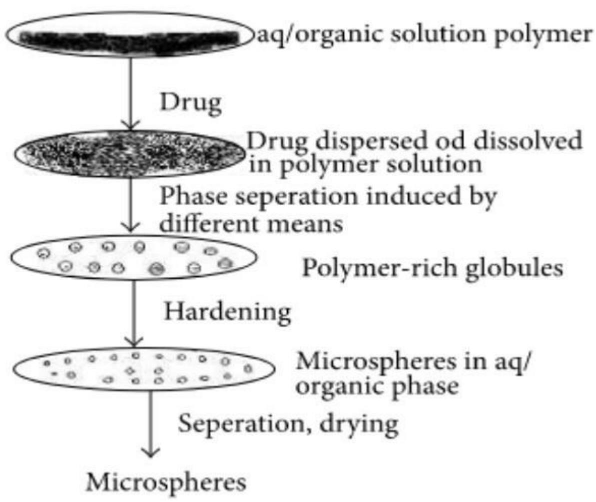

Figure9:-Coacervation Method

4. SPRAY DRYING TECHNIQUE

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent29. Organic solution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may loose crystalinity due to fast drying process.[26]

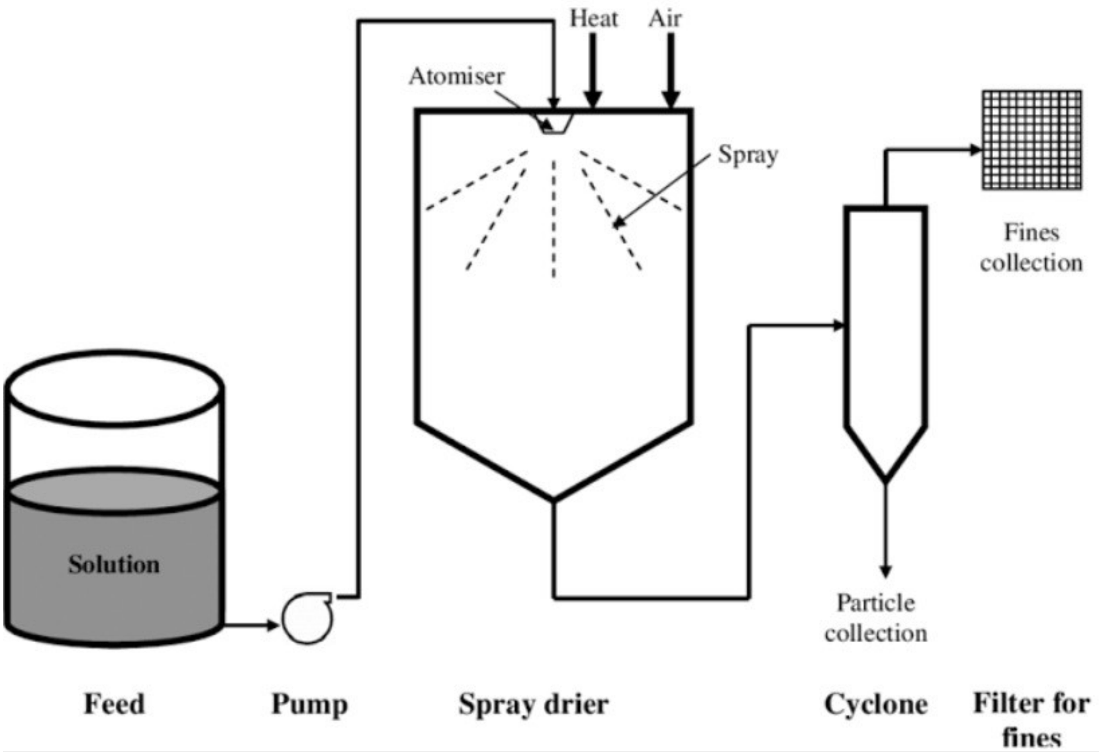

Figure10:-Spray Drying Technique

5. EMULSION-SOLVENT DIFFUSION TECHNIQUE

In order to improve the residence time in colon floating microperticles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added dropwise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a dessicator at room temperature. The following microparticles were sieved and collected29.[27]

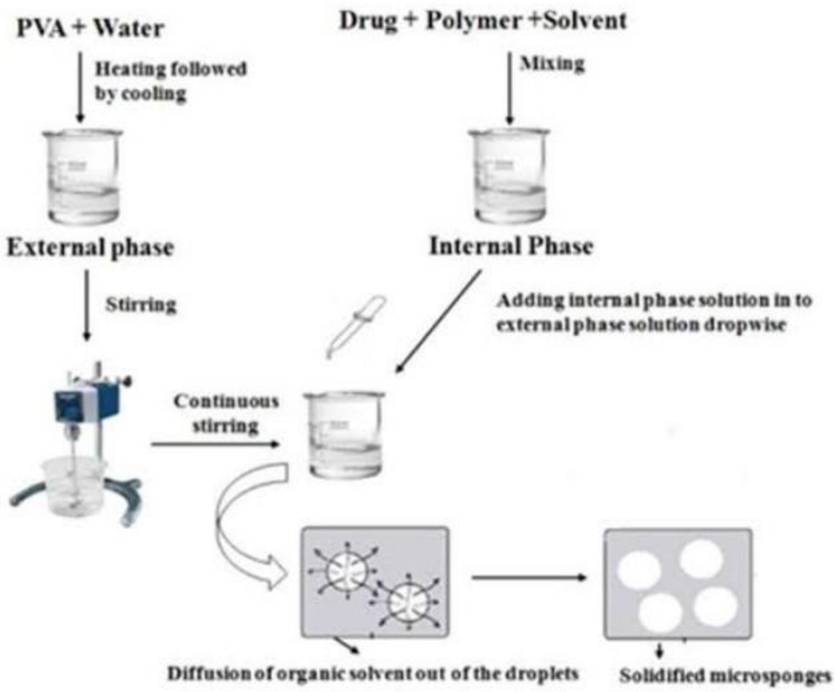

Figure11:-Emulsion-Solvent Diffusion Technique

6. MULTIPLE EMULSION METHOD

Oral controlled release drug delivery of various drugs was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The the primary emulsion was then re-emulsified in aqueous medium. Under optimised condition discrete microspheres were formed during this phase29.[28]

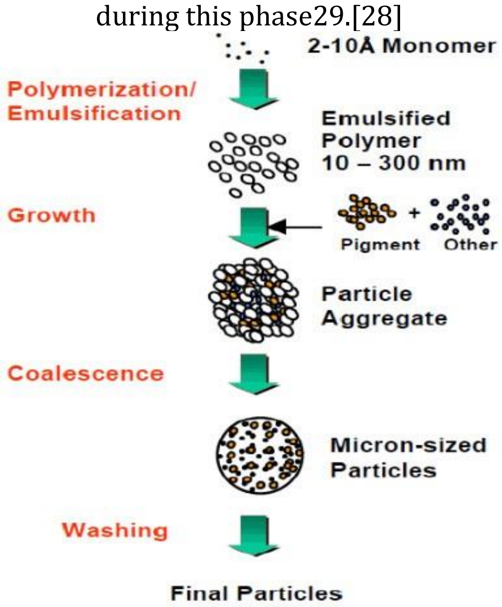

Figure12:-Multiple Emulsion Method

7. IONIC GELATION METHOD

Alginate/chitosan particulate system for Nateglinide release was prepared using this technique Different % (w/v) of Nateglinide was added to 2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 6 hrs & 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 7.4 but the drug did not release in acidic pH29. [29]

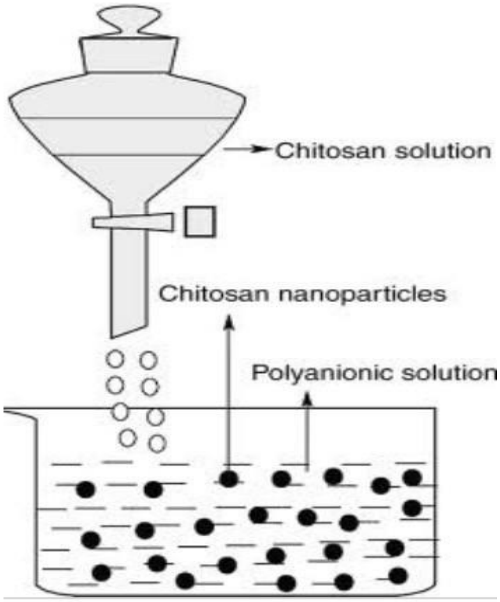

Figure13:-Ionic Gelation Method

8. HAP METHOD(HYDROXYL APPETITE MICROSPHERES)

This was used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation. Atfirst o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres[30.]

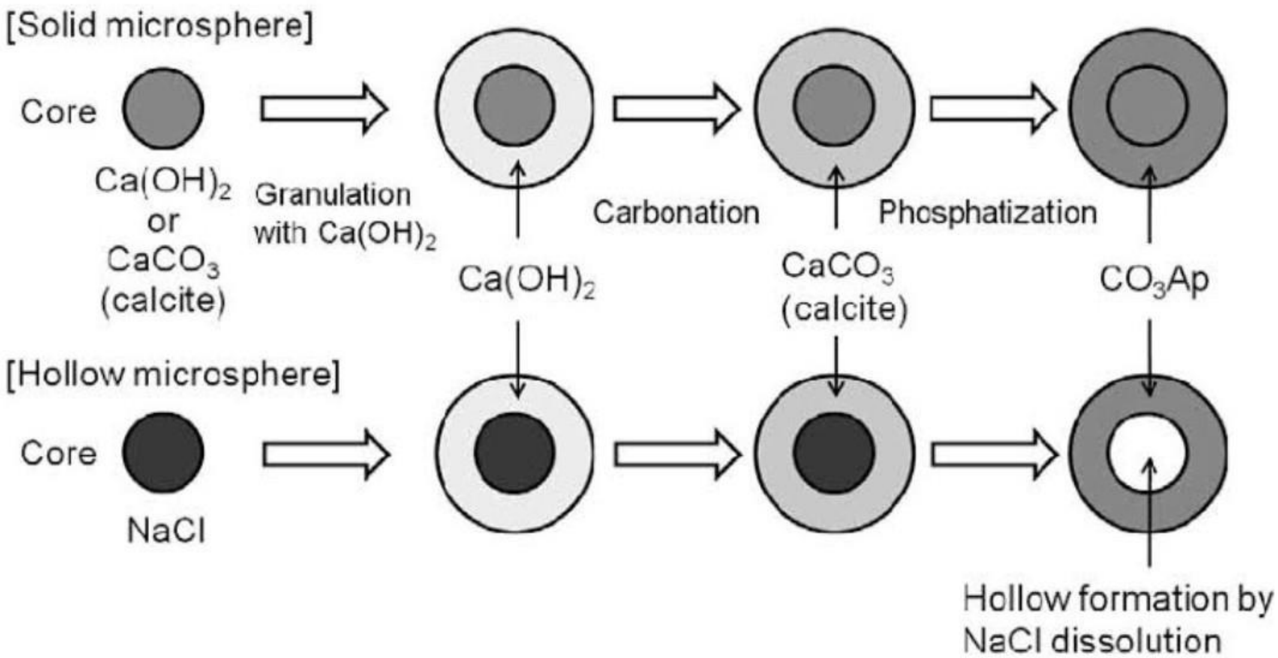

Figure14:- Hap method

9. NOVEL QUASI-EMULSION SOLVENT DIFFUSION METHOD

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in theliterature. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60oC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40oC for a day.[28]

1.IN VITRO RELEASE RATE STUDIES

These studies were carried out through dialysis bag using dissolution apparatus USP

1. The treated dialysis membrane was soaked in diffusion medium (Phosphate buffer pH = 7.4) up to 48 hr and refrigerated till use. The membrane was washed with distilled water before use. The formulations A and B each equivalent to 20 mg of silymarin, were filled in different dialysis bags and placed in basket of dissolution apparatus USP 1. The study was run at 50 rpm, and the dissolution vessel was maintained at 37 ± 0.5°C. An aliquot of 5 ml of samples was withdrawn at suitable time intervals till 36 hr and replaced with same amount of medium to maintain the volume of dissolution medium as 900 ml. The samples were quantitated by UV spectrophotometer at 287 nm [31]

2. DRUG LOADING AND ENCAPSULATION EFFICIENCY OF ABMS

The microspheres (10 mg) were added to the mixture of acetonitrile and methanol (1:1) and fully shaken to dissolve completely, and then filtered with a 0.22 μm microporous membrane (organic membrane) to obtain the test solution. The peak areawas determined by HPLC, and the external reference method was used to calculate the drug loading (*DL*) according to the following equation:

$$DL(\%) = \frac{A_{(sample)} \times C_{(reference)} \times D}{A_{(reference)} \times W} \times 100\% \quad (1)$$

where $A_{(sample)}$ is the peak area of the sample, $A_{(reference)}$ is the peak area of the reference, $C_{(reference)}$ is the concentration (mg/mL) of the reference, D is the dilution times, and W is the weight (mg) of the sample.

Based on the *DL* of ABMs, the encapsulation efficiency (*EE*) is calculated according

to the following equation:

$$EE(\%) = \frac{W_{(sample)} \times DL}{W_0} \times 100\% \quad (2)$$

where $W_{(sample)}$ is the total weight (mg) of ABMs, DL (%) is the drug loading of ABMs, and W_0 is the weight (mg) of AB used to prepare ABMs.

The detection adopts Agilent 1260 type HPLC, and the detector is Agilent G1314F 1260 VWD detector. The data processing system is an Agilent open LAB chromatography work- station. The chromatographic column is Thermo Syncronis C18 (150 mm × 4.6 mm, 5 μm), the column temperature is 35 °C, the flow rate is 1.0

mL/min; the detection wavelength is 210 nm, the injection volume is 10 μL, and the mobile phase is acetonitrile: water (55:45). [32]

3. PREPARATION OF 4% (W/V) RAT CECAL CONTENTS

Male albino rats weighing 115–150 g were maintained on a normal diet and used for the study. The rats were asphyxiated using carbon dioxide and the abdomens were opened and cecum was traced. The cecal bags were opened and the contents were individually weighed, pooled and then suspended in PBS to provide a 4% (w/v) dilution. As the cecum is naturally anaerobic, all these operations were carried out under CO_2The rats were cared in accordance with institutional guidelines for animal studies.[33]

4. DRUG RELEASE KINETICS

In vitro drug release data of the optimized starch microspheres were fitted to the common drug release kinetic models. From the respective models, the Higuchi square root model was found to be the best-fitted model (). As per the Korsmeyer-Peppas release kinetic model analysis, the value of the exponent “” was 0.526, which revealed that the drug release mechanism of the optimized enset starch microspheres was non- Fickian anomalous transport mechanism [29].

5. PERCENTAGE YIELD

The prepared microspheres were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = Actual weight of microspheres x 100
Total weight of drug and polymer

PARTICLE SIZE DETERMINATION

Optical microscope was used to determine the size of the microspheres. This method involves the calibration of eye piece micrometer for which the stage micrometer is used. In stage micrometer one mm is divided into 100 equal divisions and hence, each division is equal to 10 mm and the particles are measured chosen fixed line across the center of the particle. The average diameter of was calculated using following formula. Average diameter = Σnd/n×C.F.

Where n = number of microspheres, d =diameter of microspheres, C.F =calibration factor[36]

SHAPE AND SURFACE MORPHOLOGYMorphology of microspheres was investigated by using optical Leica microscopy. The photographs of the optimized formulations taken by Leica microscope are shown in the figure-6 and figure-7. The results of Leica microscope revealed that the microspheres of Rabeprazole sodium using HPMC15000cps combination with carbopol934p as a polymer (F5) were spherical and their surface was smooth and devoid of cracks giving them a good appearance.

CARR'S INDEX

The compressibility index and the hausner rati are determined by measuring both bulk volume and tapped volumeof microspheres. The percentage compressibility of microspheres was calculated according to equation given below.

% Compressibility Index (Vf V0) 100 Vf Where V0 is bulk density and Vf is Tapped density.

HAUSNER RATIO

Hausner ratio of microspheres was calculated according to equation given below (USP NF 2007).

Hausner ratio: = Vf V

where Where V0 is bulk density and Vf is Tapped density

SWELLING INDEX

Preweighed rabeprazole sodium microspheres (W0) formulated with HPMC and Carbopol by employing different coat:core ratios were placed in pH 7.4 phosphate buffer which was maintained at 37oC±0.5oC. After 6th hour, the microcapsules were collected and blotted to remove excess water and weighed (Wt). The swelling index was calculated with the following formula.

Swelling index Wt W0 100 W0

Where Wt = weight of microspheres observed at 6th hour; W0 = initial weight of microspheres.

MUCOADHESION TEST

The mucoadhesive property of microspheres was evaluated by an in-vitro adhesion testing method known as wash- off method,Freshly excised pieces of goat intestinal mucosa (2 × 2cm2) were mounted on to glass slides with cotton thread. About 50 microbeads were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP tablet disintegration test apparatus, When the test apparatus was operated, the sample is subjected to slow up and down movement in the test fluid at 370C±0.50C contained in a 1-liter vessel of the apparatus. At an interval of 1 hours up to 6 hours the machine is stopped and number of microspheres still adhering to mucosal surface was counted. The test was performed at intestinal (Phosphate buffer pH 7.4) condition.

% Mucoadhesion = Total no. of microspheres remains x 100 Total no. of applied microspheres

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The physical state of drug, Drug polymer mixture, and formulation was analyzed by DSC. The thermograms of Rabeprazole sodium, Rabeprazole sodium microspheres with different polymers were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25–350oC, respectively.[31]

Avantages

1. Controlled release for longer period of time (like 1-3 months).

2. Frequency is reduced and hence patient compliance is increased.

3. Constant release and hence no peaks and troughs in concentration of drug.

4. Low dose and hence toxic effect is less.[35]

Disadvantages

1. Intended mainly for parenteral route which causes pain.Forms a depot in tissue or muscle for long period and hence may produce pain when muscle activities are done
2. Once administered, it is difficult to take back the dose.[34]

CONCLUSION:-

One micrometre to several millimetres of an active component can be found inside a capsule by a process known as micro encapsulation. The development of a managed drug delivery system is the result. Solid, liquid, and gaseous phases of three different types of matter are all contained within it. Micro encapsulation lessens toxicity, GI discomfort, and other adverse effects. The application of micro encapsulation in the pharmaceutical industry has been well established. In this work, many micro encapsulation techniques, including physical, chemical, and physicochemical techniques, have been discussed.

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