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A REVIEW OF ADVANCEMENT IN MICROENCAPSULATION TECHNIQUES AND IT'S APPLICATIONS

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ABSTRACT

Microencapsulation is a rapidly expanding technology. It is one of the quality preservation techniques of sensitive substances and a method for production of materials with new valuable properties. There are different techniques available for the encapsulation of drug. The encapsulation efficiency of the microparticle or microsphere or microcapsule depends upon different factors like concentration of the polymer, solubility of polymer in solvent, rate of solvent removal, solubility of organic solvent in water, etc. Microencapsulation is described as a process of enclosing micron-sized particles of solids or droplets of liquids or gasses in an inert shell, which in turn isolates and protects them from the external environment. This review covers encapsulation materials, physics of release through the capsule wall, techniques of preparation, recent advancements, application of microcapsules and all evaluation parameters for microcapsules.

INTRODUCTION

These delivery system offers numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity and improved patient compliance and convenience. It is a new technology that has been used in the cosmetics industry as well as in the pharmaceutical, agrochemical and food industries, being used in flavours, acids, oils, vitamins, microorganisms and among others.[11] The first research leading to the development of microencapsulation procedures for the Pharmaceuticals was published by Bungen burg de Jong and Kan in 1931 and dealt with the preparation of gelatin spheres and the use of a gelatin Coacervation process.[21] Microencapsulation is a multidisciplinary field, which is regarded as the combination of many branches, such as colloid chemistry, polymer chemistry, physical chemistry and material science. It is a scientific fact that the more active the compound, the more reactive it becomes with the environment in which the compound is placed. This is especially true with respect to typical cosmetic formulations that can be considered harsh environments for active compounds. It is in this arena that the microencapsulation techniques can solve resulting stability issues and deliver the material in an active state to treat the problems. The term microencapsule is defined as spherical particle with the size varying between 50 nm to 2 mm containing a core substance. Microspheres are in strict sense, spherically empty particles. However, the terms microcapsules and microspheres are often used synonymously. Microspheres" specifically refers to spherical microparticles and the subcategory of "microcapsules" applies to microparticles which have a core surrounded by a material which is distinctly different from that of the core. The core may be solid, liquid or even gas. The microcapsules 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. Microcapsules continue to be of much interest in controlled release because of relative ease in design and formulation and partly on the advantages of microparticulate delivery systems. The latter include sustained release from each individual microcapsule and offer greater uniformity and reproducibility.

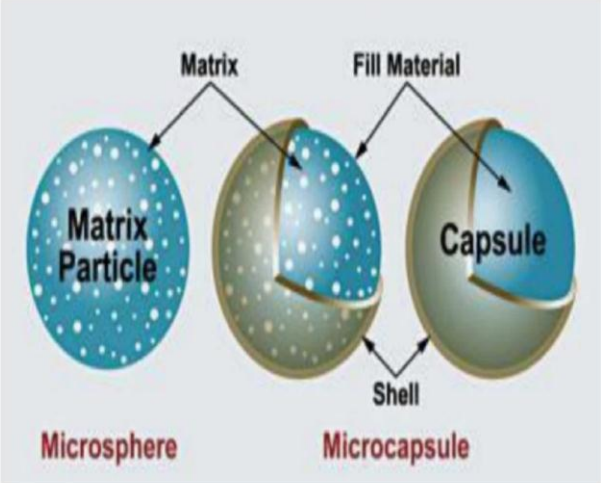

Figure.1 Microspheres and Microcapsules

➢ **Composition of Microcapsules**

A) Coating Material

A wide variety of coating materials are available for microencapsulation. Bioadhesive and mucoadhesive are two types of coating material. However, many traditional coating materials are satisfactory for the use in the gastrointestinal tract. Generally hydrophilic polymers, hydrophobic polymers or a combination of both are used for the microencapsulation process. They include inert polymers and pH sensitive ones as carboxylate and amino derivatives, which swell or dissolve according to the degree of cross-linking.[3] The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules or microspheres. While selecting a polymer the product requirements i.e. stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into consideration. 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.[18]

❖ **Different types of Coating Material use in Microencapsulations**

a) Water Soluble Resins- Gelatin, Carboxy Methyl Cellulose, Polyvinyl pyrrolidine, Hydroxyethyl Cellulose, Polyvinyl alcohol etc.
b) Water Insoluble Resins- Ethyl Cellulose, Polymethyl acrylate, Polyethylene vinyl acetate etc.
c) Waxes and Lipids- Paraffin, Stearyl alcohol, Stearic acid etc.
d) Enteric Resins- Shellac, Cellulose acetate pthalate etc.

- **Ideal Properties of Coating Material**

1) The polymer should be capable of forming a film that is cohesive with the core material.
2) 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.[14]
3) Soluble in an aqueous media or, on melting.
4) The coating can be flexible, brittle, hard, thin etc.
5) Coating material must be economical.

B) Core Material

The core material is the material over which coating has to be applied to serve the specific purpose. It can be solid or liquid in nature. The solid core can be mixture of active constituents, diluents, stabilizers, release rate retardant or accelerators. The ability to vary the core material composition provides definite flexibility to microcapsules.

- **Techniques of Microencapsulation**

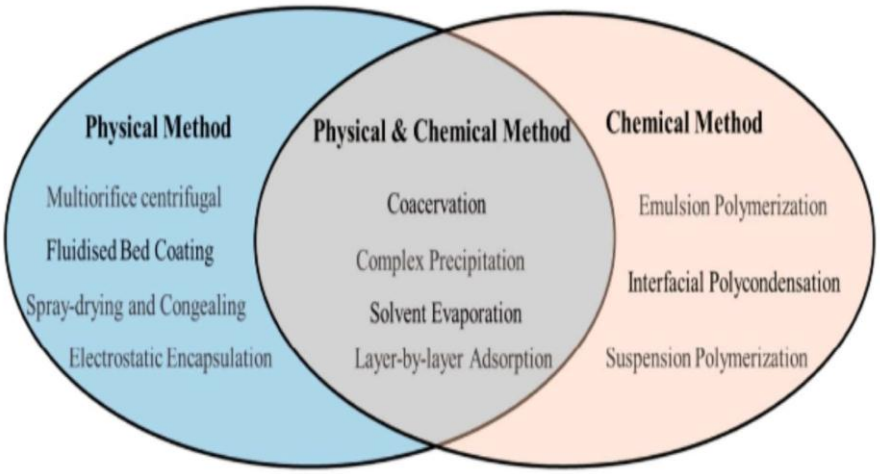

Figure.2 Techniques of Microencapsulation

The various microencapsulation processes can be divided into four classes i.e. chemical, physiochemical, electrostatic and mechanical processes.

1) Chemical processes
- Interfacial polymerization
- In situ polymerization

2) Physiochemical processes
- Coacervation phase separation
- Complex emulsion
- Meltable dispersion
- Powder bed methods

3) Mechanical processes
- Air suspension method
- Pan coating
- Spray drying
- Spray congealing
- Micro-orifice system
- Rotary fluidization bed granulator method.
- Spheronization is sometimes included under the mechanical process of microencapsulation.

- **Interfacial Polymerization (Ifp)**

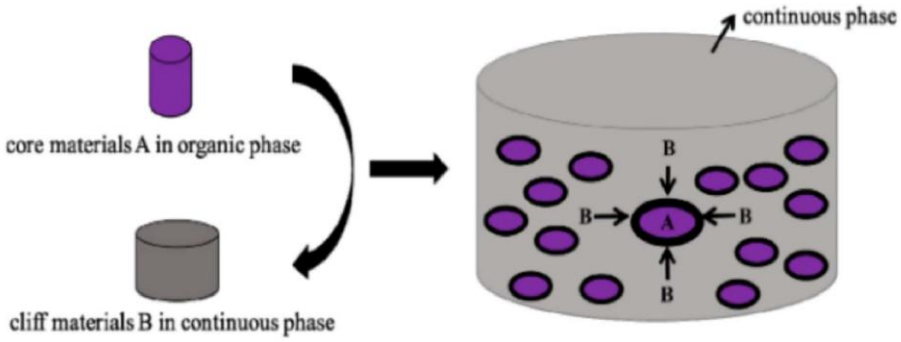

Figure.3 Microencapsulation with Interfacial Polymerization

Interfacial polymerization was mainly developed toward the end of the 1960s.[17] 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.[12] In interfacial polymerization, a monomer is made to be polymerized at the interface of two immiscible substances. If the internal phase is a liquid, it is possible to disperse or solublize the monomer in this phase and emulsify the mixture in the external phase until the desired particle size is reached. At this point a cross-linking agent may be added to the external phase.

- **In Situ Polymerization**

In situ polymerization is a chemical encapsulation technique very similar to IFP. The distinguishing characteristic of in situ polymerization is that no reactants are included in the core material. All polymerization occurs in the continuous phase, rather than on both sides of the interface between the continuous phase and the core material, as in IFP.

- **Coacervation Phase Separation**

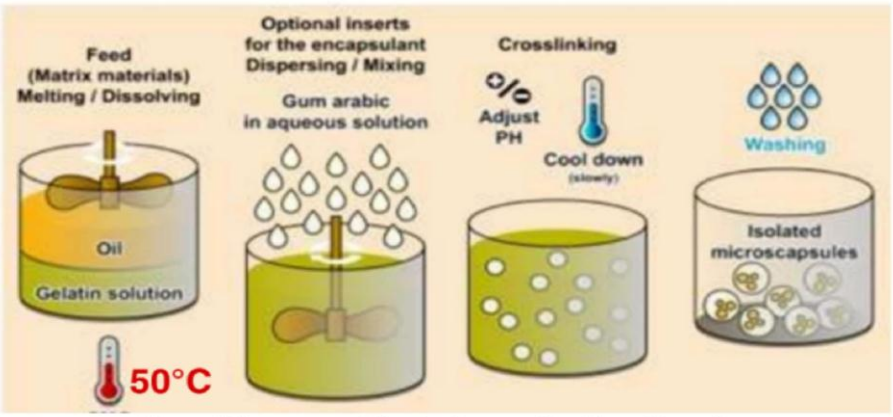

Figure.4 Microencapsulation by Coacervation Phase Separation

Microencapsulation by Coacervation phase separation is generally attributed to the National Cash Register (NCR) Corporation and the patent of B.K. Green et al. The microencapsulation by coacervation phase separation generally consists of three steps carried out under continuous agitation:
(a) Formation of three immiscible chemical phases
(b) Deposition of liquid polymer coating on the core material
(c) Rigidization of the coating usually by thermal, cross linking or dissolvation of techniques.

The coacervation-phase separation has been classified into two categories, simple coacervation and complex coacervation. Usually complex coacervation deals with the system containing more than one colloid.

- **Various Methods of Coacervation Phase Separation Method**

i) Salt Addition Method

Saturated salt solution having more affinity with water present in coating phase separates water. Coating phase starts coacervating over a core material.

ii) Temperature Change Method

In this Method the temperature of coating solution is decreased gradually. It deposits on core material while cooling.

iii) Incompatible Polymer Addition

Incompatible dissimilar polymer is added to solvent. Drug is first dispersed in a Polymer solution-x. Polymer solution-Y is added. Polymer-Y being Incompatible starts replacing polymer-x and gets deposited on core material. Solidified further by cross linking.

iv) Non-solvent Addition Method

A liquid that is a non-solvent for a given polymer is added to a solution of polymer to induce phase separation.

v) Polymer-Polymer Interaction

Oppositely charged polyelectrolytes are allowed to interact with each other, results in Complex with reduced solubility. Thus phase separation occurs.

- **Air Suspension Method**

Air suspension coating consist of the dispersing of solid, particulate core materials in a supporting air stream and the spray coating on the air suspended particles. Within the coating chamber, particles are suspended on an upward moving air stream. During each pass through the coating zone, the core material receives an increment of coating material. The cyclic process is repeated several hundred times. The supporting air stream also serves to dry the product while it is being encapsulated. The rate of drying is directly proportional to the temperature of the air stream which can be modified.

- **Pan Coating**

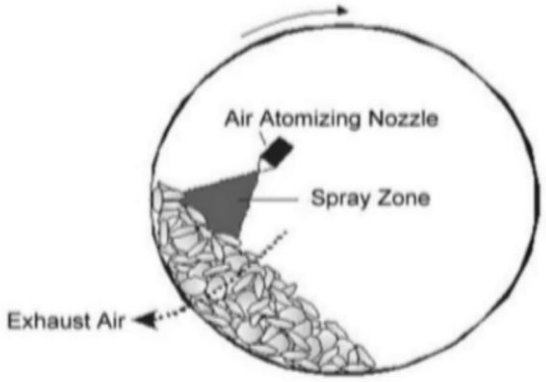

Figure.5 List of variables affecting pan coating

For the relatively large particles (Size-greater than 600 micron) pan coating method is widely used in pharmaceutical industry. In practice, the coating is applied as a solution or as an atomized spray to the desired solid core material in the coating pan. This method employs a rotating drum containing core materials (such as candies), onto which warm sucrose solution is ladled. The rotation distributes the syrup evenly as a thin coat on the cores and increases the surface area of the syrup that aids in evaporation of the water. As the water evaporates, the sugar hardens and coats the cores.

- **Spray Drying Method**

In this method core material is dispersed in a liquified coating substance. Core-coating mixture is atomized into an air stream. Warm air is required to remove the solvent of coating material. This process is suitable for particle size in between 5-600 micron. This method is applicable for liquid as well as solid core. Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected.

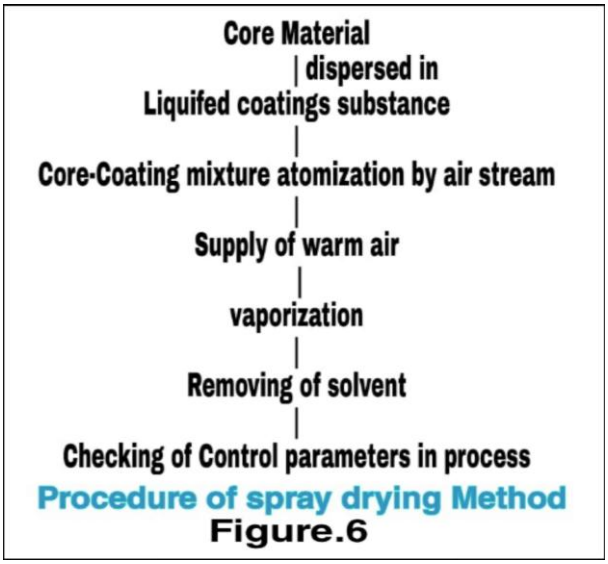

Figure.6

- **Spray Congealing**

Core material is dispersed in a melted coating material. Coating solidification is accomplished by spraying the hot mixture into a cool air stream.

- **Multiorifice Centrifugal System**

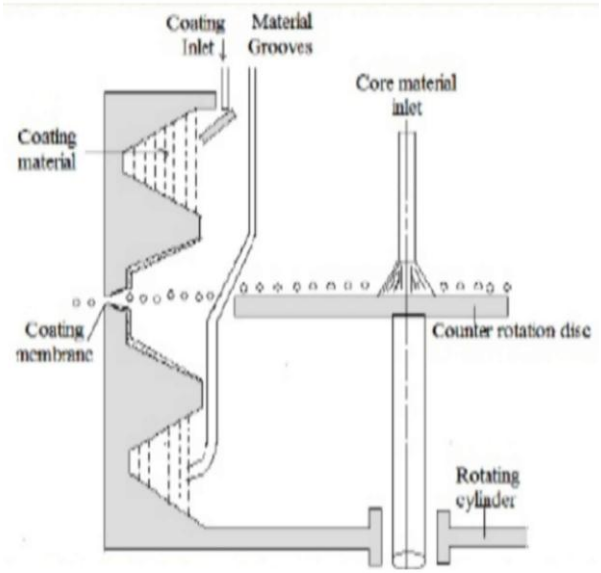

Figure.7 Microencapsulation by Multiorifice Centrifugal process

South West Research Institute has developed a mechanical process for producting microencapsules that utilizes centrifugal force. Multiorifice centrifugal process is capable for microencapsulating liquids as well as solids of varied size ranges with coating material. The encapsulated product can be supplied as slurry in hardening mediator for making dry powder. This method is better than others because rate of production is high. We can use diverse coating material also for this method. But it is costly process as well as wastage of coating material also takes place. In this process Coating material enters through coating material inlet. The coating material is pumped such that it should overflow through the grooves and edges of intermediate grooves. Coating material enters into counter sunk portion and form film across the orifice. Counter rotating disc disperse core material and move towards orifice. Core material reaches at orifice and encounters coating material membrane. Impact of centrifugal force makes the core material to encounter the coating material membrane results in formation of microencapsules.

❖ **Preparation of Microspheres Should Satisfy Certain Criteria**

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and Susceptibility to chemical modification.[19]

❖ **Factors Influencing Encapsulation Efficiency**

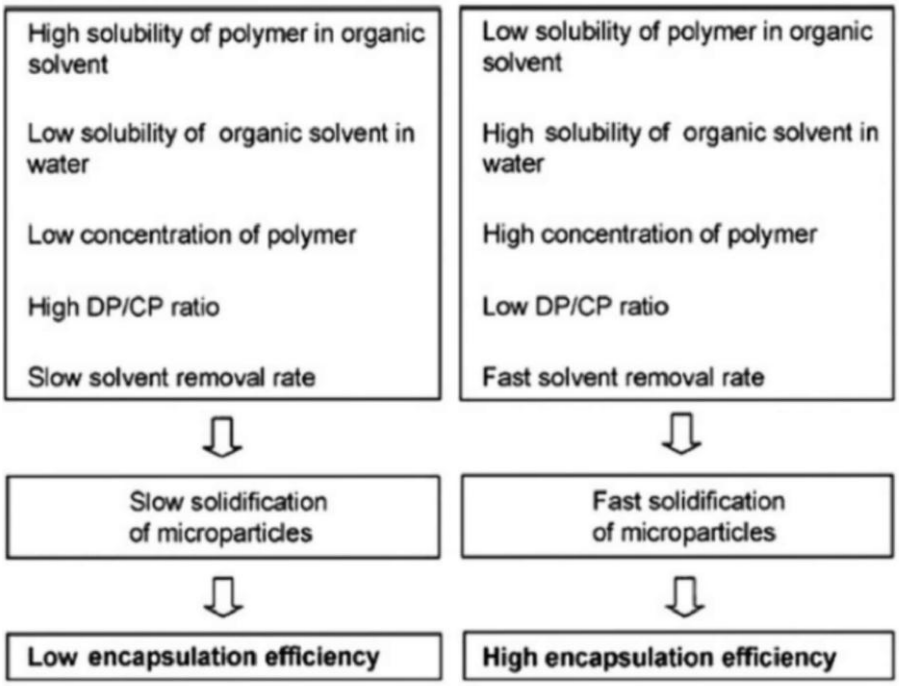

Figure.8 Factors influencing encapsulation efficiency

❖ **Mechanism And Kinetics of Drug Release**

1) Diffusion

Diffusion is the most commonly involved mechanism in drug release. In this dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels or pores. The utilization of the diffusion mechanism has fundamentally changed the pace of development in the pharmaceutical industry. As a quintessential example, Aspirin provides effective relief from fever, inflammation, and arthritis, but direct doses of aspirin can cause peptic ulcers and bleeding. To diffuse in a slow and sustained dose, aspirin is encapsulated in ethyl cellulose or hydroxypropylmethyl cellulose and starch, and these semipermeable celluloses make it possible for the drug to permeate at the beginning.[16] The diffusion of the drug is slow as compared with degradation of the matrix.

The kinetics of such drug release obeys Higuchi's equation.

$$Q = 1/2\ [D/J\ (2A - \varepsilon.Cs)\ Cs.t]$$

Q = Amount of drug released per unit area of exposed surface
t = Time
D = Diffusion coefficient of the solute in the solution
A = Total amount of drug per unit volume
C = Solubility of drug in permeating dissolution fluid
ε = Porosity of the wall of microcapsule
J = Tortuosity of the capillary system in the wall

2) Dissolution

Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid.

3) Osmosis

Because of the osmotic pressure drug solution drives out of the microencapsule through small pores present on semipermeable membrane. Polymer coat of microencapsule is act as semipermeable membrane.

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.[7]

❖ **Evaluation of Microcapsules**

- The size and shape of the prepared micro particles can be determined by light and scanning electron microscope.[22]

A) Microcapsule solvation can be predicted using following formula;

Microcapsule solvation (%) = $(M_1 / M_2) \times 100$
M_1 = Microcapsules weighed immediately
M_2 = After drying to a constant weight

B) Tapped Density

It is measured by employing the conventional tapping method using 10 ml measuring cylinder and the number of tapings will reduced to 100 as it is sufficient to bring about a plateau condition.

Taped density is calculated by following formula:

Tapped density = Weight of microcapsules /Volume of microcapsules after 100 tappings

C) Angle of Repose

It is measured by passing microcapsules through a funnel on the horizontal surface. The height (h) of the heap formed was measured and radius (r) of cone base is also

determined. The angle of repose (Ø) is calculated by following formula:
$Ø = \tan^{-1} h / r$
Where r = Radius of heap (calculate by using mean method) and
h = Height of heap

D) Bulk Density
It is determined by following formula:
Bulk Density = Sample weight / Sample volume

E) Compressibility Index (Ci)
It can be calculated using following formula:
Ci = {(Initial volume – Final volume) / Initial volume} × 100

F) Hausner's Ratio
Another index of flow ability of microcapsules, is calculated by following formula:
Hauser's ratio = Volume before tapping / Volume after tapping.
The Hausner ratio is a number that is correlated to the flowability of a powder. The Hausner ratio is not an absolute property of a material; its value can vary depending on the methodology used to determine it.

G) Determination of % Drug Entrapment
H) Sieve Analysis
Separation of the microspheres into various size fractions can be determined by using a mechanical sieve shaker. A series of five standard stainless steel sieves (20, 30, 45, 60 and 80 mesh) are arranged in the order of decreasing aperture size. Five grams of drug loaded microspheres are placed on the upper-most sieve. The sieves are shaken for a period of about 10 min, and then the particles on the screen are weighed.[23]

I) Atomic Force Microscopy (afm)
A Multimode Atomic Force Microscope from Digital Instrument is used to study the surface morphology of the microspheres. The samples are mounted on metal slabs using double-sided adhesive tapes and observed under microscope that is maintained in a constant-temperature and vibration-free environment.[24]

J) Density Determination
The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and density of the microsphere carrier is determined.[51]

❖ **Advantages**
1) Liquid can be converted into solids.
2) Increases the stability of core material.
3) It is use for taste masking of bitter drugs.
4) Microencapsulated product can be available in wide variety of dosage forms.
5) Colloidal and surface properties of particle can be modified to provide environmental protection and controlling release kinetics of product.
6) Reduce the gastric irritation by encapsulating the core material.
7) Hygroscopic property of core material can be reduce.
8) Low dose is required for encapsulation.
9) For potent drug Microencapsulation is suitable.
10) The unique advantage of Microencapsulation lies in that the core material is completely coated and isolated from external environment.
11) Microencapsulation would not affect the properties of core material.
12) Microencapsulation is very suitable for improving the stability of thermochromic mixture. After being encapsulated, the thermal stability and resistance to leaching would be significantly enhanced; this obviously extends their application fields.
13) Can combine two incompatible components for a multifunctional structure.[13]
14) Alteration in site of absorption can also be achieved by microencapsulation.
15) Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor.
16) A liquid can be converted to a pseudo-solid for easy handling and storage. eg. Eprazinone.

❖ **Limitations**
1) According to the need microencapsulation process is changing for each core material.
2) It is expensive.
3) Reproducibility of coating particles with same thickness is challenging.

❖ **Application**
1) The technology has been used widely in the design of controlled release and sustained release dosage forms.
2) To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin, Carbon tetrachloride etc.
3) Quality and safety in food, agricultural & environmental sectors.
4) Separation of incompatible substance has been achieved by encapsulation.
5) Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g. vitamin A palmitate.
6) Hygroscopic properties of core materials may be reduced by microencapsulation eg. Sodium chloride.
7) Carbon tetra chlorides and a number of other substances have been microencapsulated to reduce their odour and volatility.

❖ **Advancement In Microencapsulation Technology**
The microencapsulation technology, which started as a way of encapsulating dyes and flavors, has now become

one of the most intriguing fields in the area of controlled drug delivery systems. The encapsulation techniques have been advanced to such a level that not only small molecular weight drugs but also macromo-lecules, such as proteins and genes, can be delivered via microparticle carriers. Several methods and techniques are potentially useful for the preparation of polymeric microparticles in the broad field of microencapsulation. The preparation method determines the type and the size of microparticle and influence the ability of the interaction among the components used in microparticle formulations.

More recent development is fluidized bed coating using supercritical CO_2 as the fluidizing and drying medium. This is Well-established process use supercritical CO_2 in pharmaceutical applications include micronization by RESS (rapid expansion of supercritical solutions), SAS (supercritical antisolvent), or ScMM (supercritical melt micronization), microencapsulation via co-precipitation (in RESS, SAS, supercritical spray drying, etc.), active ingredient coating (spray coating, supercritical CO_2 fluid bed coating, etc.), sterilization (due to microbial inactivation properties of pressurized CO_2), biopolymeric microporous foam/sponges (supercritical foaming, supercritical impregnation, etc.). The selection of processing technique with supercritical CO_2 for biopolymers depends greatly on the interaction of the supercritical CO_2 with the active ingredient, coating material of interest, and suitable solvent. The favorable and tunable properties of supercritical CO_2 make it a very attractive option in processing products for pharmaceutical applications, particularly regarding the microencapsulation and nanoencapsulation of drugs or active ingredients for sustained or targeted release.[5] The versatility and compatibility of supercritical fluid processing techniques also allow smart coating materials such as cyclodextrins to be used as encapsulating agents, which is useful in microencapsulation.[8]

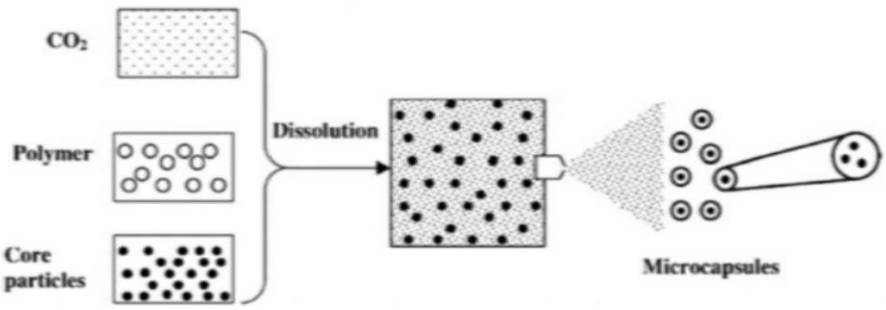

Figure.9 Microencapsulation by Rapid Expansion of Supercritical Solution (RESS)

❖ **Recent Advancement In Treatment Of Diabetes Mellitus With The Help of Microencapsulation Technology**

Type 1 diabetes mellitus (DMT1) contributes to 10% of the total of cases of diabetes mellitus worldwide. DMT1 is characterized by the self-immune destruction of the pancreatic cells that produce insulin (pancreatic islets), which leads to severe insulin deficiency and which is followed by the raising of blood glucose levels. The transplant of isolated pancreatic islets from donors provides a fresh source of insulin-producing cells capable of meeting insulin requirements in accordance with blood glucose levels in patients with DM1. One of the drawbacks of islet transplants is the long-term use of immunosuppressant drugs to prevent the immune rejection of the transplanted islets. To avoid this problem the 'pancreatic islets' can be isolated from the patient's immune system by means of 'Microencapsulation techniques' in which the islets are encapsulated in microcapsules made of biocompatible (non-toxic) materials. Among many materials used in cell microencapsulation, alginate is the most widely used one. This natural polymer has excellent properties for biomedical applications as it offers high compatibility and low toxicity. However, the microencapsulation technique has various technical obstacles that are hampering its clinical application.

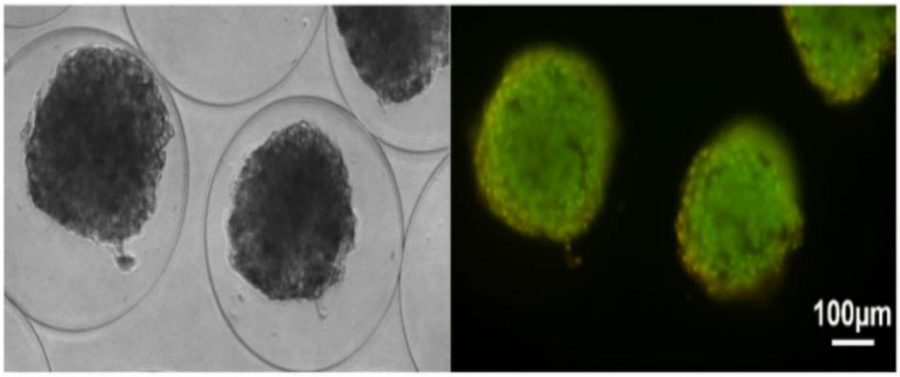

Figure.10 Microencapsulated Pancreatic Islets

A crucial problem is the high number of empty microcapsules generated during the process to microencapsulate the islets, which leads to a large increase in the volume of microcapsules to be implanted, and which in turn may increase the hosts immune reaction following implantation, said Espona-Noguera. In order to avoid the high number of empty microcapsules, we have come up with an innovative approach for purifying the microencapsulated islets in order to reduce the implant volume by separating the microencapsulated islets from the empty microcapsules, explained the researcher at the UPV/EHU-Ciber BNN which is part of the Nanbiosis ICTS (Singular Scientific and Technological Infrastructure). We have developed a system to magnetically separate the microcapsules and which combines different technologies. To separate the microcapsules, the pancreatic islets are put into contact with magnetic nanoparticles, thus providing them with magnetic properties. After that, the islets are microencapsulated, thus obtaining capsules containing magnetic islets and non-magnetic empty capsules. When the microcapsules are pumped through the chip's microchannels, the magnets move the magnetic capsules towards the exit microchannel, while the non-magnetic empty ones make their way through another exit microchannel. That way we are able to eliminate the empty capsules and, as a result, we reduce the volume of the therapeutic microcapsule implant.

The great purification efficiency of this magnetic separation system has enabled us to lower the implant volume by nearly 80%, thus reducing the complications arising out of the implanting of large volumes of microcapsules and providing us with an alternative DMT1 treatment.[28]

❖ CONCLUSION

Microencapsulation means packaging an active ingredient inside a capsule ranging in size from one micron to several millimeters. Microspheres and microcapsules are established as unique carrier systems for many pharmaceuticals and can be tailored to adhere to targeted tissue systems. Hence, micro-capsules and microspheres can be used not only for controlled release but also for targeted delivery of drugs to a specific site in the body. The microencapsules protects the active ingredient from its surrounding environment until an appropriate time. The microencapsulation technique offers a variety of opportunities such as protection, masking, reduced dissolution rate, facilitation of handling and spatial targeting of the active ingredient. On today's date microencapsulation is receiving considerable attention fundamentally, developmentally, commercially, etc. In coming few years by combining various other approaches, microencapsulation technique will find the vital place in novel drug delivery system.

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