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Microencapsulation: A Review

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ABSTRACT:
Microencapsulation is a technology that has shown significant promise in bio therapeutics ,and other applications. It has been proven useful in the immobile zation of drugs, live mammalian and bacterial cells and other cells, and other bio pharmaceutics molecules, as it can provide material structuration, protection of the enclosed product, and controlled release of the encapsulated contents, all of which can ensure efficient and safe therapeutic effects. Microparticulate drug delivery systems are an interesting and promising option when developing an oral controlled release system . This paper is a comprehensive review of microencapsulation and its latest developments in the field. It provides a comprehensive overview of the technology and primary goals of microencapsulation and discusses various processes and techniques involved in microencapsulation including physical, chemical, physicochemical, and other methods involved. It also summarizes the state-of-the-art successes of microencapsulation, specifically with regard to the encapsulation of microorganisms, mammalian cells, drugs, and other biopharmaceutics in various diseases. The limitations and future directions of microencapsulation technologies are also discussed.
Keywords: Microencapsulation, Matrix, Polymerisation

I. INTRODUCTION :

The science of microencapsulation is very old and was first used as gelatin coacervation process for coating in 1931. since then the large number of methods have been envisaged to prepare microencapsules.[1] Microencapsulation is defined as a process of enclosing or enveloping solids, liquids or even gases within second material with a continuous coating of polymeric materials yielding microscopic particle (ranging from less than 1 micron to several hundred microns in size). In this process, small discrete solid particles or small liquid droplets and dispersions are surrounded and enclosed by applying thin coating for the purposes of providing environmental protection and controlling the release characteristics or availability of coated active ingredients. Microencapsulation process is widely employed to modify and delayed drug release form different pharmaceutical dosage forms. The materials enclosed or enveloped within the microcapsules are known as core materials or pay-load materials ornucleus, and the enclosing materials are known as coating materials or wall material or shell or membrane . [2]

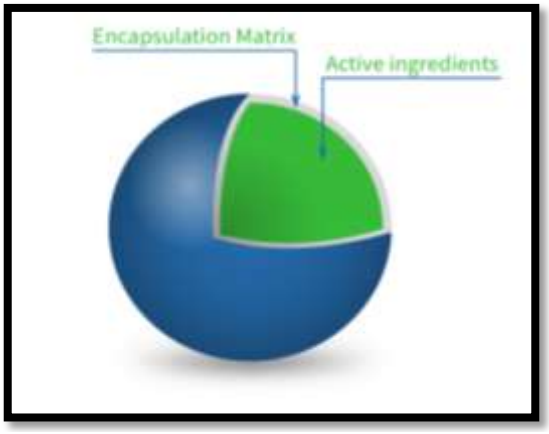

Fig: Microencapuslation

Microencapsulation is a promising technique, which provides core materials with protective barrier, good stability, controlled release, and targeting delivery[3] .Microencapsulation is a technology that uses microcapsules to serve as tiny containers of substances, liquid or solid, which are released to fulfill a specific on the characteristics of the capsule wall, including physical pressure, purpose. In a microcapsule, a coating acts as the wall, shell, or membrane to surround the material inside, which can be released in a variety of ways depending friction, diffusion, wall dissolution, and biodegradation.

REASON FOR MICROENCAPSULATION

- There are several reasons why substances may be encapsulated.

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- To control release of the active components for delayed (timed) release or long-acting (sustained) release.
- 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.[3]
- It is commonly used enhance the stability and provide release of product in a sustained/prolonged manner.
- Reactive substances are protected from the environment by microencapsulation
- Alteration in site absorption is also achieve by this technique
- Moisture, light and oxygen sensitive drugs can be protected by microencapsulation .[5]

FUNDAMENTAL CONSIDERATION

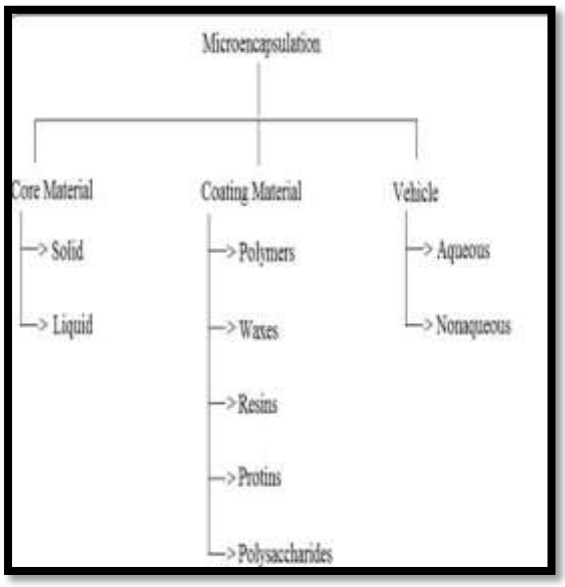

Fig : types of core materials, coating material and vehicles used in microencapsulation

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods . [5]

Core Material :

The core material, defined as the specific material to be coated, can be liquid or solid in nature. The composition of the core material can be varied as the liquid core can include dispersed and/or dissolved material. The solid core can be mixture of active constituents, stabilizers, diluents, excipients and release-rate retardants or accelerators. The ability to vary the core materials composition provides definite flexibility and utilization of this characteristic often allows effectual design and development of the desired microcapsules properties.[4]

Coating material :

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres. While selecting a polymer the product requirements ie. stabilization, reduced volatility, release characteristics, environmental 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 emaleic 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 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. [5]

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MICROENCAPSULATION TECHNIQUES

The technique of microencapsulation depends on the physical and chemical properties of the material to be **encapsulated.** Various techniques are available for the encapsulation of core materials. Broadly the methods are divided into three types.

Different types of microencapsulation techniques are-

- **Physical or physico-mechanical**
- **physico-chemical**
- **chemical**[6]

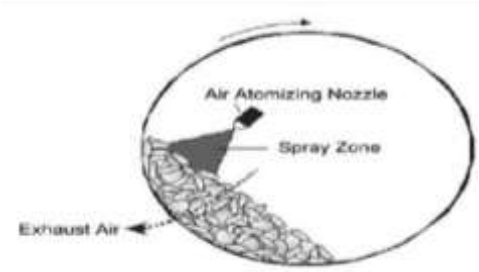
1. physical or physico-mechanical :

Air suspension:

Microencapsulation by air suspension method consists of the dispers -ing of solids, particulate core materials in a supporting air stream and the spray coating on the air suspended particles . Within the coating chamber, particulate core materials are suspended on an upward moving air stream. The chamber design and its operating parameters influence a recirculating flow of the particles through the coating-zone portion of the coating-chamber, where a coating material is sprayed to the moving particles. During each pass through the coating-zone, 3 the core material receives a coat and this cyclic process is repeated depending on the purpose of microencapsulation. The supporting air stream also serves to dry the product while it is being encapsulated. The drying rate is directly related to the temperature of the supporting air stream used.[2]

Pan coating:

For relatively large particles, which are greater than 600 µ in size, microencapsulation can be done by pan coating method, which is being widely used in pharmaceutical industry for the preparation of controlled release particulates. In this method, various spherical core materials, such as nonpareil sugar seeds are coated with a variety of polymers . In practice, the coating is applied as a solution o as an atomized spray to the desired solid core material in the coating pan. Generally, warm air is passed over the coated materials as the coatings are being applied in the coating pans to remove the coating solvent. In some cases, the process of final solvent removal is accomplished in the drying oven.[2]



Spray drying :

Spray drying and spray congealing methods of microencapsulation are almost similar in that both the methods entail the dispersion of core material in a liquefied coating agent and spraying or introducing the core coating mixture into some environmental condition, whereby relatively rapid solidification of the coating is influenced . The main difference in between these two microencapsulation methods are the means by which the coating solidification is carried out. In spray drying method, the coating solidification is influenced by the quick evaporation of a solvent, in which the coating material is dissolved. In spray congealing method, the coating solidification is accomplished by the thermal congealing of molten coating material or solidifying a dissolved coating by introducing the coating core material mixture into a non solvent. Removal of non-solvent or solvent from the coated product is often done by sorption extraction or evaporation.[2]

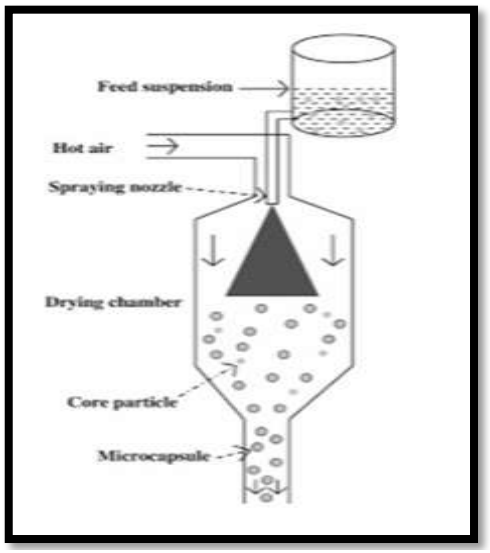


Fig :Spray Coating

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2. Physico-chemical :

Coacervation phase separation:

It is the method in which core material is dispersed in the solution of coating material. The core material cannot dissolve or react with coating The particle size rely upon dispersion parameters such as stirrer shape, viscosity, stirrer speed, surface tension. Range of particle size is in between 2 micrometer to 1200 micrometer.[9]

This technique comprises of three steps:-

- **Formation of three immiscible phases:-**

Three phases involves liquid manufacturing vehicle phase, core material phase, coating material phase. In this, the core material is disperse in solution of coating polymer, the vehicle phase used as solvent for polymer . The microcapsules are formed by one of the methods of phase separation-coacervation i.e by change the temperature of polymer solution or by addition of salt, non solvent, incompatible polymer addition or by polymer polymer attraction.

- **Deposition of the coating:-**

In second step depositing the liquid polymer on the core material by controlled mixing of coating material and core material in manufacturing vehicle. If the polymer absorbed at the interface formed between the core material and liquid phase then coating polymer is deposited on the core material. The deposition of coating material is promoted by deduction in total free energy of system.

- **Rigidization of coating:-**

It involves rigidiaztion of coating done by thermal, cross linking or dissolvation techniques, to form a self sustaining microcapsules .[7]

3. Chemical techniques:

Solvent Evaporation:

Solvent evaporation method is appropriate for liquid manufacturing vehicle (O/W emulsion), which is prepared by agitation of two immiscible liquids. The solvent evaporation method involves dissolving microcapsule coating (polymer) in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material (drug) to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core–coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate sized microcapsules. Agitation of system is continued until the solvent partitions into the aqueous phase and is removed by evapora -tion. This process results in hardened microcapsules. Several techniq -ues can be used to achieve dispersion of the oil phase in the continuous phase. The most common method is the use of a propeller style blade attached to a variable speed motor. Various process variables namely rate of solvent evaporation for the coating polymer(s), temperature cycles and agitation rates influence the methods of forming dispersion. The most important factors that should be considered for the preparation of microcapsules by solvent evaporation method include choice of vehicle phase and solvent for the polymer coating, and solvent recovery systems. The solvent evaporation method for microencapsulation is applicable to a wide variety of liquid and solid core materials. The core materials may be either water soluble or water insoluble materials. A variety of film forming polymers can be used as coatings.

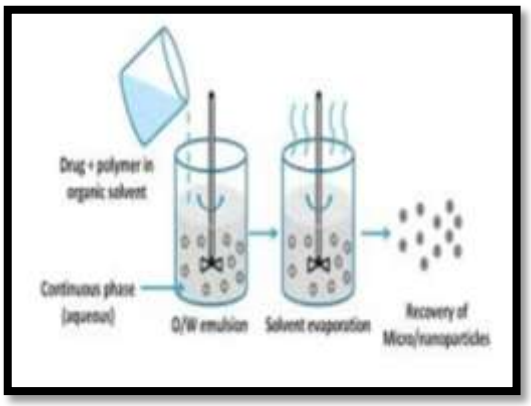

Fig: solvent Evaporation

Polymerization:

The polymerization method of microencapsulation is used to from protective microcapsule coatings, in situ.

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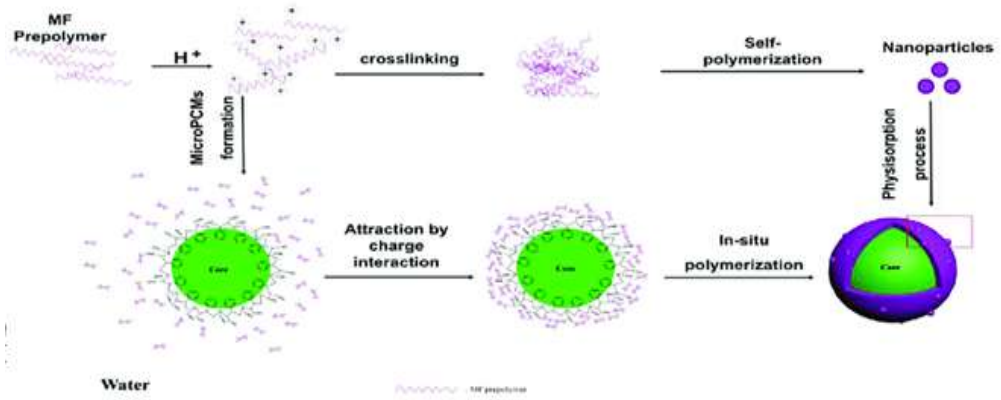


Fig: In-situ polymerization

The method involve the reaction of monomeric units positioned at the interface existing in between a core material and a continuous phase, wherein the core material is dispersed.
The continuous or core material supporting phase is usually a liquid or gas, and therefore, the polymerization reaction occurs at the interfaces ofliquid-liquid, liquid-gas, solid-liquid, or solid-gas.[7]

Interfacial polymer:-

In this, the two reactants in poly condensation meet at an interface and react rapidly. The basic of this method involves the classical schotten bauman reaction between compound containing acid hydrogen atom and acid chloride, such as amine, polyesters, alcohol, poly urea, polyurethane Under the desired conditions thin walls formed rapidly at interface. The solution of pesticide and di-acid chloride get emulsified in water and on aqueous solution containing amine as poly functional isocyanate is added. During the reaction the acid formation can be controlled by the base. Condensed polymer walls rapidly form at interface of the emulsion droplets. [7]

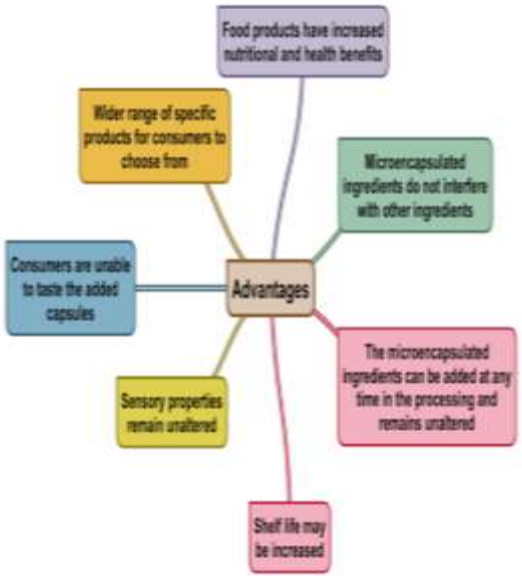
In-situ polymerization:-

Few microencapsulation processes involving the direct polymerization of a monomer can be carried out on the particle surface. In one process, e.g-cellulose fibers get encapsulated in polyethylene while immersed in dry toluene. Deposition rates are about 0.5 micrometer/minute. Coating thickness ranges upto0.2-75 micrometer. Over sharp projections coating is uniform.[7]

Interfacial cross-linking :

In interfacial cross-linking method of microencapsulation, the small bifunctional monomer containing active hydrogen atoms is replaced by a biosourced polymer, like a protein. When the reaction is performed at the interface of an emulsion, the acid chloride reacts with the various functional groups of the protein, leading to the formation of a membrane. The interfacial cross-linking method of microencapsulation is very versatile for pharmaceutical or cosmetic applications.[2]

ADVANTAGES OF MICROENCAPSULATION :



Flavor and odor masking of ingredients for foods and supplements:

One of the first benefits that most people think of when they think “microencapsulation” is flavor-masking. Masking the off-flavors associated with some nutrients is essential. The products we

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fortify, first and foremost, must taste good—otherwise, no one will eat them. By coating the vitamins and minerals that have objectionable flavors, we can minimize their impact on the flavor profile of the finished product, both for foods and chewable supplements.

Protection of nutrients for increased stability :

One of the most important benefits of microencapsulation is improving the stability of nutrients, preventing ingredient interactions and degradation. The coating matrix effectively separates particles and prevents them from contacting each other. It also protects them from moisture and oxygen, extending the product's shelf life.[8]

Precise nutrient amounts :

The improved nutrient stability achieved through microencapsulation also means that the nutrient levels in a product can be precisely controlled.

Reduced overages for cost savings : Microencapsulation can also reduce the overages required by minimizing losses. Overages can be expensive, and minimizing them will have a positive impact on gross margin**.**

Controlled release in the body and during processing :

Another benefit of microencapsulation is the control of release point or release parameters. Through controlled-release microencapsulation, we can specify exactly when the core (active material) is released. In this way, reactive materials can be released at the point in the process where the chemical reaction is desired.

Increased effectiveness :

For certain products, such as medical foods and nutraceuticals, product effectiveness is closely regulated. Microencapsulation is critical for these types of products to ensure optimal nutrient stability, delivery, and bioavailability.

Ease of handling in production :

Another valuable application of microencapsulation is to improve handling during production. Hygroscopic ingredients that tend to clump during processing can be encapsulated to improve their flowability. Microencapsulation can also be used to convert liquids into free-flowing powders.

Disadvantages Of Microencapsulation :

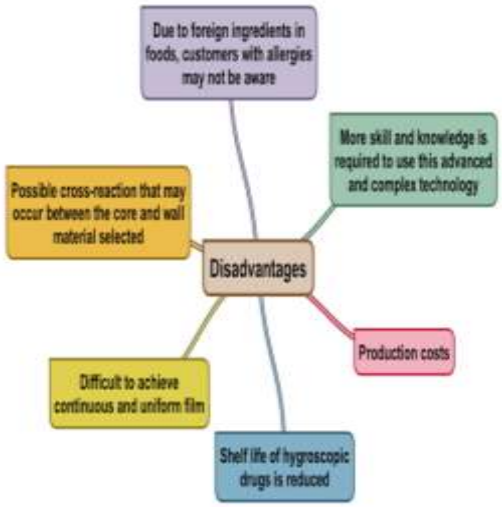

Fig. 11 Disadvantages of microencapsulation

- The cost of the materials used and the formulation process might be higher than standard formulations.
- Reproducibility is less.
- The effect of the polymer matrix, polymer additives, and their degradation products on the environment in response to heat, hydrolysis, or biological agents vary significantly.
- The core particle's stability is affected by the change in the process conditions like change in temperature, pH, solvent addition, or evaporation of the solvent.
- Coated products may have non reproducible and unstable release characters, may be too bulky.
- Because of the inadequate stability and shelf life, Sensitive pharmaceuticals cannot used .
- Sometimes coating may be uncompleted and discontinuous.
- The technique is not adaptable to all core materials.[3]
- There may be difficulties in scale up and large scale manufacturing the process.[8]

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Applications Of Microencapsulation :

Agriculture:

One of the most important applications of microencapsulated products is in the area of crop protection. Nowadays insect pheromones are becoming viable as a biorational alternative to conventional hard pesticides. Specifically, sexattractant pheromones can reduce insect populations by disrupting their mating process. Hence small amounts of species- specific pheromone are dispersed during the mating season, raising the background level of pheromone to the point where it hides the pheromone plume released by its female mate. Polymer microcapsules, polyurea, gelatin and gum arabic serve as efficient delivery vehicles to deliver the pheromone by spraying the capsule. dispersion. Further, encapsulation protects the pheromone from oxidation and light during storage and release.[9]

Pharmaceutics :

One of the major applications area of encapsulation technique is pharmaceutical/ biomedical for controlled/sustained drug delivery. Potential applications of this drug delivery system are replacement of therapeutic agents (not taken orally today like insulin), gene therapy and in use of vaccines for treating AIDS, tumors, cancer and diabetes. Protein such as insulin, growth hormone, and erythropoietin(used to treat anemia) are example of drugs that would benefit from this new form of oral delivery. The delivery of corrective gene sequences in the form of plasmid DNA could provide convenient therapy for a number of genetic diseases such as cystic fibrosis and hemophilia. The spheres are engineered to stick tightly to and even penetrate linings in the gastrointestinal track before transferring their contents over time into circulatory system.

Based on this novel drug delivery technique, Lupin has already launched in the market worlds first Cephalexin (Ceff-ER) and Cefadroxil (Odoxil OD) antibiotic tablets for treatment of bacterial infections. Aspirin controlled release version ZORprin CR tablets are used for relieving arthritis symptoms. Quinidine gluconate CR tablets are used for treating and preventing abnormal heart rhythms. Niaspan CR tablet is used for improving cholesterol levels and thus reducing the risk for a heart attack. Glucotrol (Glipizide SR) is an anti diabetic medicine used to control high blood pressure.[9]

Food industry :

Currently there is a trend towards a healthier way of living, which includes a growing awareness by consumers for what they eat and what benefits certain ingredients have in maintaining good health. Preventing illness by diet is a unique offering of innovative so called "functional foods", many of which are augmented with ingredients to promote health. However simply adding ingredients to food products to improve nutritional value can compromise their taste, colour, texture and aroma. Sometimes they slowly degrade and lose their activity, or become hazardous by oxidation reactions. Ingredients can also react with components present in the food system, which may limit bioavailability. Microencapsulation is used to overcome all these challenges by providing viable texture blending, appealing aroma release, and taste, odour and colour masking . The technology enables food companies to incorporate minerals, vitamins, flavours and essential oils. In addition, microencapsulation can simplify the food manufacturing process by converting liquids to solid powder, decreasing production costs by allowing batch processing using low cost, powder handling equipment. Microcapsules also help fragile and sensitive materials survive processing and packaging conditions and stabilize the shelf life of the active ingredient.[9]

Energy generation :

Hollow plastic microspheres loaded with gaseous deuterium (a fusion fuel) are used to harness nuclear fusion for producing electrical energy. The capsules are multilayered. The inner layer, which compresses the fuel, is a polystyrene shell about 3 mm thick. Next is a layer of poly(vinyl alcohol) about 3 mm thick, that retards diffusion of deuterium out of the capsule. The outer layer (the ablator) is about 50 mm thick and consists of a highly crosslinked polymer made from 2-butene. During the fusion experiments, energy from high powered laser beams is absorbed by the surface of the microcapsule shell. As the outside of the shell

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(called ablator) burns off, the reaction force accelerates the shell inward, compressing and heating the deuterium inside. This results in high densities and temperature in the centre of the capsule leading to the fusion of deuterium nuclei to give tritium, helium and other particles releasing an enormous amount of energy. This process has been named
as inertial confinement fusion (ICF). Such ICF targets made of organic microcapsules have been in use since 1980s.[4]

Cell immobilization :

In plant cell cultures microencapsulation, provides cell natural environment, improves efficiency in production of different metabolites used for medical, pharmacological and cosmetic purposes. Human tissue by microencapsulation are turned into bio-artificial organs in natural polymers and transplanted to control hormone-deficient diseases such as diabetes and severe cases of hepatic failure. In continuous fermentation processes immobilization is used to increase cell density, productivity and to avoid washout of the biological catalysts from the reactor and applied in ethanol and solvent production, sugar conversion or wastewater treatment.[8]

Drug delivery :

Microencapsulation has permitted controlled release delivery systems (allow controlling the rate, duration and distribution of the active drug.) after designing the right biodegradable polymers. One of the main advantages of such systems is to protect sensitive drug from drastic environment (pH,) and to reduce the number of drug administration's for patient and with these systems, micro particles sensitive to the biological environment are designed to deliver an active drug in a site specific way (stomach, colon, heart and specific organs).[8]

Green tea :

The food industry, represent a solution to the challenge of in corporating green tea poly phenols in food products. It enables to (i)overcome the solubility incompatibilities between ingredients, (ii)protect sensitive ingredients such as poly phenols from degradation e.g.by oxidation, (iii) increase their bioavailability including the controlled release of encapsulated compounds. The fortification of food products with microcapsules of green tea poly phenols is a novel approach. Therefore, the aim of the present review is to provide a comprehensive overview of the recent encapsulation techniques applied on green tea poly phenols, their application in the food industry and their effects on food systems properties.[11]

Catalysis :

Transition metal based catalytic processes are of vital importance to pharmaceutical, agrochemical and fine chemical industries. A vast proportion of such catalytic metal species are often expensive and toxic, thereby making operational handling potentially hazardous. Microencapsulation has recently been recognized as a useful alternative strategy to enable safe handling, easy recovery, reuse and disposal at an acceptable economic cost. Poly urea microcapsules due to their insolubility in aqueous and organic solvents, and resistance towards degradation have been used for encapsulation of different catalysts. Metal species such as palladium (II) acetate and osmium tetra oxide have been encapsulated in poly urea microcapsules and used successfully as recoverable and reusable catalysts without significant leaching and loss of activity. It is thought that the urea functionality, which forms the backbone of the polymer, ligates and retains the metal species with in the polymeric matrix. Futuristic trend is towards incorporation of other chelating and ligating functional groups within the polyurea framework to study rate enhancement in such reactions, and trying other polymers for encapsulation. [9]

Vitamins :

Microencapsulation of drugs is also done to those that are used to overcome deficiencies and as such must be administered for long periods of time in a relatively uniform dosage Vitamins are a large class of drugs in this group which has received much attention. Since most of this class are relatively water insoluble, they lend themselves nicely to microencapsulation, especially by simple or complex coacervation. Vitamins are also encapsulated because of their usually unpleasant taste. One of the earliest applications of microcapsules for pharmaceuticals was an article by Luzzi and Gerraughty, in which while en capsulating various oils, they mentioned that encapsulation could be employed to protect vitamin A and K from moisture and light.[10]

Aerosol Formulations:

While most applications of microcapsules are oral, topical, or parenteral, Feinstein and Sciarra microencapsulated dexta methasone for use in an

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aerosol formulation. After microencapsulation with ethyl cellulose and formulation of the aerosol using the traditional method with fluorinated hydrocarbons, the drug was administered to rabbits for bioavailability comparisons. Microcapsules have also been successfully used to produce a sustained release for ophthalmic drugs as an ocular insert using biodegradable polymers.[10]

Defence :

One of the important defence applications of microencapsulation technology is in self-healing polymers and composites. They possess microencapsulated healing agents embedded within the matrix and offer tremendous potential for providing long-lived structural materials. The microcapsules in self-healing polymers not only store the healing agent during quiescent states, but provide a mechanical trigger for the self-healing process when damage occurs in the host material and the capsules rupture. The microcapsules posses sufficient strength to remain intact during processing of the host polymer, yet rupture when the polymer is damaged. High bond strength to the host polymer combined with a moderate strength microcapsule shell are required.To provide long shelf life the capsules must be impervious to leakage and diffusion of the encapsulated healing agent for considerable time. These combined characteristics are achieved with a system based on the in situ polymerisation of urea-formaldehyde microcapsules encapsulating dicyclo pentadiene healing agent143. The addition of these microcapsules to an epoxy matrix also provides a unique toughening mechanism for the composite system. Such microcapsules have tremendous application in aerospace area for making self-repairable spacecrafts. Such self-healing spacecrafts open up the possibility of longer duration missions by increasing the lifetime of a spacecraft. Microencapsulation is also used for designing special fabrics for military personnel, for their enhanced chemical protection against chemical warfare11. For this purpose special reactive microcapsules have been developed which can be applied to fabrics or finished garments to provide reactive sites for neutralisation of chemical reagents. This involves microencapsulation of conventional decontamination chemicals that are currently effective for deactivation of toxic mustard blistering agents (H agents) and toxic nerve agents known conventiona -lly as G agents, for example isopropylmethyl phosphono fluoridate (GB, sarin) and the V agents, and formulation of the microcapsules in a resin finish that can be uniformly applied to fabric substrates. The preffered microcapsules containing a decontaminating agent were obtained by organic phase separation with ethyl cellulose microcapsules containing a solid decontamination agent consisting of sym-bis(N-chloro2,4,6- trichlorophenyl) urea and ZnO. The microcapsules were then bonded to the fabric with an acrylic binder emulsion. The very thin walls (1 to 10 microns) of microcapsules allow for rapid agent permeation for optimum decontamination and thus protect the wearer from toxic chemical agents.[9]

II. CONCLUSION :

The microencapsulation technique offers a variety of opportunities such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This approach facilitates accurate delivery of small quantities of potent drugs, reduced drug concentrations at sites other than the target organ or tissue and protection of labile compounds before and after administration and prior to appearance at the site of action.

Micro fabricated system offers potential advantages over conventional drug delivery systems. Microspheres and microcapsules are established as unique carrier systems for many pharmaceuticals and can be tailored to adhere to targeted tissue systems. Hence, microcapsules and microspheres can be used not only for controlled release but also for targeted delivery of drugs to a specific site in the body. Although significant advances have been made in the field of microencapsulation, there are still many challenges ahead in this field. Of particular importance are the development of cheaper biopolymers for the microencapsulation technology and the development of universally acceptable evaluation methods especially for bioadhesive microspheres. Therefore, the development of safe and efficient particular systems will require, in the future, in-depth investigations of both the biological and technological aspects of these systems.

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