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A Review of Microencapsulation with their Utilization

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Abstract: *The formulation of natural substances together with a biocompatible or biodegradable carrier material to form composites or encapsulates has great relevance for the pharmaceutical, cosmetic, and food industries. The main objective of this article is to take a look at microencapsulation as a novel drug delivery system. Its scope extends beyond conventional microcapsules to all other small particulate systems such as self-assembling structures that involve preparative manipulation. The review covers encapsulation materials, techniques of preparation, physics of release through the capsule wall, characterization of microcapsules, and the many uses to which microcapsules are put. The review of State of Art of Microencapsulation of Microcapsule Preparation Process Technology is a well-established dedicated to the preparation, properties, and uses of individually encapsulated novel small particles, as well as significant improvements to tried-and- tested techniques relevant to microcapsules and their use in a wide variety of industrial, engineering, pharmaceutical, biotechnology, and research applications.*

Keywords: Microencapsulation, Materials, Classification, Mechanism, Utilization EvaluationParameter

I. INTRODUCTION

The method of microencapsulation involves the binding of solids, liquids, or even gases in minute particles to produce thin wall material coverings throughout the substances. The technique was first developed in the late 1930s as a refined replacement for carbon paper and carbon ribbons, which the business machines sector was searching for. A variety of microencapsulated products, including medications, advanced as a result of the breakthrough invention of replication paper and ribbons in the1950s that contained dyes in microscopic gelatin capsules that were released upon being hit by a typewriter key or the pressure of a pen or pencil [1]. Bungen burg de Jong and Kan published the first study in 1931 that led to the creation of microencapsulation techniques for pharmaceuticals. This studyfocused on the utilization of a gelatin Coacervation method and the composition of gelatin spheres. A well-thought-out controlled drug delivery system can improve a given medicine's therapeutic efficacy and mitigate some of the complications associated with conventional therapy. Delivering the substanceto the target tissue in the ideal amount and at the ideal time will result in short toxicity and negligible side effects, which is important to achieve optimum therapeutic efficacy [2].

A medicinal ingredient can be delivered to the target place in several ways using prolonged controlled release techniques. Using microspheres as drug carriers is one such method. Typically, microspheres are free-flowing powders made of proteins or artificial polymers that are biodegradable and preferablyhave a particle size of less than 200 µm. [3].

II. THE REASONS FOR MICROENCAPSULATION

There are numerous justifications for microencapsulation. Sometimes it is necessary to separate the core from its surrounding material. Examples of these situations include protecting vitamins from oxygen's damaging effects, delaying the evaporation of a volatile core, improving the handling characteristics ofa sticky substance, and shielding a reactive core from chemical attack. In other situations, such as the controlled release of medications or insecticides, the goal is to regulate the rate at which the core exits the microcapsule rather than completely isolate it. The problem could

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be as straightforward as hiding the core's flavor or aroma, or it could be more intricate like improving the extraction or adsorption process' selectivity.

III. FUNDAMENTAL CONSIDERATIONS

A fundamental understanding of the general characteristics of microcapsules, such as the makeup of the core and coating materials, the stability and release properties of the coated materials, and the microencapsulation technique, is necessary to fully realize the potential thatmicroencapsulation offers[4].

IV. MATERIALS FOR MICROENCAPSULATION

CORE MATERIAL

The particular material to be coated, known as the core material, might have a liquid or solid composition. Since elements can be dissolved or dispersed in the liquid core, the composition of the core material might vary. Active ingredients, stabilizers, diluents, excipients, and accelerators or retardants of release rates make up the solid core. The desired microcapsule qualities can be effectively designed and developed thanks to the usage of the distinct flexibility offered by the variation in the composition of the core material.15

LIQUID CORE MATERIAL EXAMPLES

16 fragrances, lubricants, oils from vegetables, insecticides, fertilizers, dyes, catalysts, bleaches, sugars, salts, acids, pigments, fungicides, and nutrients

SOLID CORE MATERIAL EXAMPLES

Minerals, Dextrin's, Bases, Herbicides, and Pharmaceuticals

COATING MATERIAL

For microencapsulation, a large range of coating materials are available. Innovative coating polymers with patents have also been used for specific purposes, namely in the fields of mucoadhesives and bioadhesives. Nonetheless, a lot of conventional coating materials work well in the digestive system. These comprise pH-sensitive polymers like carboxylate and amino derivatives, which expand or dissolve depending on the degree of cross-linking, as well as inert polymers.

Table 1: Example of coating materials [18]

Water Soluble resins	Water insoluble resins	Waxes and resins	Enteric resins
Gellatin	Ethyl Cellulose	Paraffin	Shellac
Starch	Polyethylene	Beeswax	Cellulose Acetate Pthalate
Polyvinylpyrrolidine	Polyamide	Stearic acid	Zein
Hydroxyethylcellulose	Polymethacrylate	Steryl Alcohol	

CLASSIFICATION OF MICROENCAPSULATIONS

Table 2: Microencapsulation methods [15]

Physical Method	Chemical Method
• Air suspension • Coacervation phase separation • Multiorifice-centrifugal process • Pan coating • Spray drying and congealing	• Solvent evaporation techniques • Polymerization

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PAN COATING 19

One of the first industrial processes for creating tiny, coated particles or tablets is the pan-coating method, which is extensively employed in the pharmaceutical and chemical sectors. The coating material is applied gently while the particles are tumbling in a pan or equivalent apparatus. One of the first methods used in industry to make small, coated particles or tablets is the pan-coating technique, which is mostly utilized in the pharmaceutical sector. The particles are flung about in a pan or another device. Solid particles larger than 600 microns are generally regarded as needed for effective coating, even when the coating material is applied slowly in terms of microencapsulation. The procedure has been heavily utilized for the preparation of controlled-release beads.

AIR SUSPENSION

The air suspension coating process was invented by Professor Dale E. Wurster while at the Department of Pharmacy, University of Wisconsin. Air suspension apparatus consists of disparate sections such as a control panel, coating chamber, air distribution plate, and nozzle for applying film coatings.

Within the coating chamber of the air suspension apparatus particles are suspended on an upward- moving air stream. In the coating zone, the coating material is applied by spraying the moving core particles. The design and operating parameters of the chamber assume the recirculating flow of the coreparticles through the coating zone. The core material receives an increment of coating material, usually polymer solution during each pass through the coating zone. The cyclic process is repeated until the desired coating thickness is achieved. The supporting air stream helps to dry the product during encapsulation.20 Air suspension techniques are generally applicable only to encapsulate the solid core materials. The rate of drug release from the microcapsules was highly dependent on the encapsulating materials. 21

COACERVATION-PHASE SEPARATION

The general outline of the coacervation phase separation procedure consists of three steps carried outunder incessant agitation: A liquid manufacturing vehicle phase, a core material phase, and a coatingmaterial phase. To form the three phases, the core material is dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase. 22

MULTI ORIFICE-CENTRIFUGAL PROCESS

In this process, a jet of core liquid is surrounded by a covering of wall solution or melt. As the jet movesthrough the air it breaks, owing to Rayleigh instability, into droplets of core, each coated with the wallsolution. While the droplets are in flight, a molten wall may be hardened or a solvent may be evaporatedfrom the wall solution. Since most of the droplets are within ± 10% of the mean diameter, they land ina narrow ring around the spray nozzle.

The South-West Research Institute (SWRI) has developed a mechanical procedure for producing microcapsules that utilizes centrifugal forces to hurl, a core material particle through an enveloping microencapsulation membrane therapy effecting mechanical microencapsulation. The device has a rotating barrel shape which has three circumferential grooves. Processing variables include the rotational speed of the barrel shape, the flow rate of the core and coating materials, the concentration and viscosity of the coating material, and the viscosity and surface tension of the core material. This technique is capable of microencapsulating liquids and solids of varied size ranges, with diverse coatingmaterials.23,24

SPRAY DRYING AND SPRAY CONGEALING

Spray drying and spray congealing methods have been used as microencapsulation methods for multipleyears. The main difference between the two techniques is by which coating solidification is completed.In the case of spray drying, the coating solidification is affected by the rapid evaporation of a solvent in which the coating material is dissolved. In the spray congealing technique the coating solidification is completed thermally or by solidifying the dissolved coating by reacquaint the core material mixture into a nonsolvent. Removal of the nonsolvent from the coated product is then accomplished by sorption,evaporation, or extraction methods.24

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SOLVENT EVAPORATION

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dissolved in a volatile solvent, which is incompatible with the liquid manufacturing vehicle phase. A core material 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 proper size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent for the polymer. In the case in which the core material is dispersed in the polymer solution, the polymer shrinks around the core. In the case in which core material is dissolved in the coating polymer solution, a matrix-type microcapsule is formed. Once all the solvent for the polymer is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with constant agitation. At this stage, the microcapsules can be used in suspension form, coated onto substrates, or isolated as powders. 25

POLYMERIZATION-

Polymerization is a new method of microencapsulation to form protective microcapsule coatings in situ. Microencapsulation by polymerization involves a reaction between a core material substance and an incessant phase in which the core material is dispersed. In polymerization, a liquid or gaseous phase is used as continuous or core material and as a result, the polymerization reaction occurs at a liquid-liquid, solid-liquid, liquid-gas, or solid-gas interface. 15, 26

V. FACTORS INFLUENCING PROPERTIES OF MICROENCAPSULATION

Properties of material

- Dispersed phase
- Continuous phase

THE POLYMER PLAYS AN IMPORTANT ROLE IN ENCAPSULATING THE DRUG WHICH DEPENDS ON THE:-

- The solubility of the polymer.
- The concentration of polymer.
- The organic solvent used.
- Rate of solvent removal.
- Dispersed and continuous phase ratio.
- Nature of the drug –hydrophilic /hydrophobic

If the polymer concentration is increased the encapsulation efficiency of the drug also increases and if the dispersed phase is highly viscous it reduces the porosity of the microcapsules thus sustaining the drug release. Dispersed and continuous phase ratios affect the rate of solidification of microcapsules. If the volume of the continuous phase is large it causes a high concentration gradient of the organic solvent across the phase boundary by diluting the solvent, leading to fast solidification of the microcapsules. This rate of solidification in turn affects the particle size of the microcapsules; an increase in the volume of the continuous phase increases the particle size. The rate of solvent removal is temperature dependent, a rapid increase in temperature results in the formation of a thin wall and a large hollow core resulting in burst release of the drug whereas step step-wise increase in temperature reduces the core size leading to control drug release. The solubility of the polymer depends on the cloud point (Cs) of the organic solvent used, the higher the cloud point of the organic solvent higher the solubility of the polymer and hence requires more amount of organic solvent to precipitate out from the polymeric solution.

Parameters to Be Considered for the Formulation:-

♣ Viscosity of dispersed phase.
♣ Volume fraction of dispersed phase to continuous phase.
♣ Quantity of drug in the dispersed phase.
♣ Concentration of surfactant.
♣ Operating parameters:
♣ Agitation rate

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♣ Temperature
♣ Pressure
♣ Geometry of reactor and agitator27

VI. MECHANISM OF RELEASE METHOD OF MICROENCAPSULATION

Even when the aim of microencapsulation application is the isolation of the core from its surroundings,the wall must be ruptured at the time of use. Many walls are ruptured easily by the pressure of shear stress, as in the case of breaking dye particles during writing to form a copy. Capsule contents may be released by melting the wall, or dissolving it under particular conditions, as in the case of an enteric drug coating. In another system, the wall is broken by solvent action, enzyme attack, chemical reaction,hydrolysis, or slow disintegration. Microencapsulation can be used to slow the release of a drug into the body. This may permit one controlled release dose to be alternately for several doses of non-encapsulated drugs and also may decrease side effects for some drugs by preventing high initial concentrations in the blood. There is usually a certain desired release pattern. In some cases, it is zero-order, i.e. the release rate is constant. In this case, the microcapsules deliver a fixed amount of drug perminute or hour during the period of their effectiveness. This can occur as long as a solid reservoir or dissolving drug is preserved in the microcapsule. A more typical release pattern is first-order in which the rate decreases exponentially with time until the drug source is exhausted. In this situation, a fixed amount of drug is in solution inside the microcapsule. The concentration difference between the inside and the outside of the capsule decreases continually as the drug diffuses. Nevertheless, some other mechanisms may take place in the liberation of the encapsulated material. These include biodegradation, osmotic pressure, diffusion, etc. Each one will depend on the composition of the capsule made and theenvironment it is in. Therefore, the liberation of the material may be affected by various mechanisms that take place simultaneously.7

Utilization

AGRICULTURE

One of the most important applications of microencapsulated products is in the area of crop protection87-93. Nowadays, insect pheromones are becoming viable as a rational alternative to conventional hard pesticides. Specifically, sex-attractant pheromones can reduce insect populations bydisrupting their mating process. Hence small amounts of species-specific pheromone are dispersed during the mating season, raising the background level of the pheromone to the point where it hides the pheromone plume released by its female mate91,93. 3. Polymer microcapsules, polyurea92, gelatin, and gum arabic93 serve as efficient delivery vehicles to deliver the pheromone by spraying the capsuledispersion. Further, encapsulation protects the pheromone from oxidation and light during storage andrelease.

PHARMACEUTICS

One of the major application areas of the encapsulation technique is pharmaceutical/ biomedical for controlled/sustained drug delivery94-103. Potential applications of this drug delivery system are replacement of therapeutic agents (not taken orally today like insulin)104,105gene therapy106,109 andin use of vaccines for treating AIDS110-112, tumors113,114 cancer115 and diabetes116-118. Proteinssuch as insulin, growth hormone119,120, and erythropoietin121,122 (used to treat anemia) are examples of drugs that would benefit from this new form of oral delivery. The delivery of corrective gene sequences in the form of plasmid DNA123 could provide convenient therapy for several genetic diseases such as cystic fibrosis124,125 and hemophilia126. The spheres are engineered to stick tightly to and even penetrate linings in the gastrointestinal tract before transferring their contents over time into the circulatory system127

Based on this novel drug delivery technique, Lupin has already launched in the market the world's first Cephalexin (Ceff-ER) and Cefadroxil (Odoxil OD) antibiotic tablets for the 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 of a heart attack. Glucotrol (Glipizide SR) is an anti-diabetic medicine used to control high blood pressure.

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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, color, 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, odor, and color masking 128-133. The technology enables food companies to incorporate minerals, vitamins, flavors, 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 activeingredient134.

ENERGY GENERATION

Hollow plastic microspheres loaded with gaseous deuterium (a fusion fuel) are used to harness nuclear fusion for producing electrical energy135 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 (called the ablator) burns off, the reaction force accelerates the rest of the shell inward, compressing and heating the deuterium inside. This results in high densities and temperatures in the center 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 inertial confinement fusion (ICF). Such ICF targets made of organic microcapsules have been in use since the 1980s.

CATALYSIS

Transition metal-based catalytic processes are of vital importance to the 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. Polyurea 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 tetroxide have been encapsulated in polyurea microcapsules and used successfully as recoverable and reusable catalysts without significant leaching and loss of activity39,40.

DEFENCE

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 possess sufficient strength to remain intact during the 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 is 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 polymerization of urea-formaldehyde microcapsules encapsulating dicyclopentadiene healing agent143

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VII. EVALUATION OF MICROENCAPSULATIONS

Particle size and shape:-

The most widely used procedure to visualize microcapsule is conventional Light microscopy, and scanning electron microscopy (SEM). Both techniques can be used to determine the shape and outer structure of microcapsules. SEM provides higher resolution in contrast to light microscopy. It allows investigation of the microsphere surfaces and after particles are cross- sectioned, it can also be used to investigate double-walled systems. Confocal laser scanning microscopy (CLSM) is applied as a non-destructive visualization technique, which allows the characterization of structures not only on the surface but also inside the particles.

Fourier transform–infrared spectroscopy:- (FTIR)

FTIR is used to determine the degradation of the polymeric matrix of the carrier system, and also the interaction between the drug and polymer system if present.

Density determination:-

The density of the microcapsule can be measured by using a multi volume\ pychnometer. An accurately weighed sample in a cup is placed in a pycnometer, and helium is introduced at a constant pressure in the chamber and allowed to expand. The expansion results in a decrease inpressure within the chamber. From two pressure readings, the volume and hence density of themicrocapsule can be determined.

Isoelectric point:-

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of the microsphere from which the isoelectric point can be determined. The electrophoretic mobility can be related to surface contained charge, ionizable behavior, or ion absorption nature of the microsphere.

Capture efficiency:-

The capture efficiency of the microcapsule or the percent drug entrapment can be determinedby allowing the washed microcapsule to lyse. The lysate is then subjected to the determinationof active constituents as per the monograph. The percent encapsulation efficiency is calculatedusing the following equation:-

%Entrapment=Actual content/Theoretical content x 100

Contact angle:-

The angle of contact is measured to determine the wetting property of the microcapsule. It determines the nature of the microsphere in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water surface by placing a droplet in a circular cell mounted above the objective of the inverted microscope. The contact angle is measured at 200Cwithin a minute of the decomposition of the microsphere.

Hausner's ratio:-

It is the ratio of tapped to bulk density and was calculated by using the eq: Hausner'sratio=TD/BD

In-vitro release studies:-

Release studies for microcapsules can be carried out in different pH conditions like pH 1.2 andpH 7.4 using a USP rotating basket or paddle apparatus. The samples are taken at specific timeintervals and are replaced by the same amount of fresh medium. The samples withdrawn are analyzed as per the monograph requirement and the release profile is determined using the plotof the amount released as a function of time.

Advantages of Microencapsulation:-

Reliable means to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest without untoward effects.

- Solid biodegradable microspheres have the potential throughout the particle matrix for thecontrolled release of drugs.
- Microspheres received much attention not only for prolonged release but also for targetinganticancer drugs to the tumor.

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- The size, surface charge, and surface hydrophilicity of microspheres are important indetermining the fate of particles in vivo.
- Microencapsulated ingredients do not interfere with other ingredients
- Shelf life may be increased
- The microencapsulated ingredients can be added at any time in the processing and remainunaltered
- Consumers are unable to taste the added capsules.[3][4]

Disadvantages of Microencapsulation:-

- Due to foreign ingredients in foods, customers with allergies may not be aware.
- More skill and knowledge are required to use this advanced and complex technology.
- Production cost.
- The shelf life of hygroscopic drugs is reduced.
- Difficult to achieve continuous and uniform film.
- Possible cross-reaction that may occur between the core and wall material selected.

IX. CONCLUSION

As the concept of a controlled drug delivery system was introduced in the year 1970 much more progress and promising results were made in microencapsulation. In this process, three phases of matter can be encapsulated such as solids, liquids, and gases. It converts the liquid drugs into free-flowing powder. It reduces toxicity GI irritation and side effects. Microcapsules proved to be a better delivery system for sustaining the drug release and targeting the specific site thereby reducing the toxicity and adverse effects of the drugs.

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 the 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 before appearance at the site of action. In the future by combining various other approaches, the microencapsulation technique will find a vital place in novel drug delivery systems.

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