

Review article

Microencapsulation: A potential and promising approach in drug delivery system

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Abstract

Novel drug delivery system is a method by which drug delivered can have significant effect on its efficacy. There are several advantages of novel drug delivery system over conventional multi dose therapy, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Many efforts have been made in developing novel drug delivery system, which emphasizes on controlled and sustained release dosage forms to obtain optimum benefits. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres or microcapsules. Microencapsulation is a process by which solids, liquids or gases can be enclosed in microscopic particles by forming a thin coating of wall material around substances, which protects it from external environment and control the drug release yielding capsules ranging for one micron to several hundred microns in size (1μ - 800μ). There are different microencapsulation techniques, which are used to obtain microcapsules for controlled release of drug. The morphology of microcapsules depends on the core material and deposition of coating material. Substances may be microencapsulated for the purpose of confining core material within capsule wall for specific period of time. Core materials are also encapsulated so that the core material can be gradually released (controlled release or diffusion) or when external conditions trigger the capsule walls to rupture, melt, or dissolve. Microencapsulation has found many applications in science and technology.

Introduction

Microencapsulation is a process by which solids, liquids or even gases may be enclosed in a microscopic particle forming a thin layer of coating of wall material around it. This process has been first developed in late 1930s as a substitute for carbon paper and carbon ribbons used for cleaning used by business machine industry [1,2]. This coating involves coating of particles ranging from one to several hundred microns. This technology enables elimination of incompatibilities, masking of taste, stabilization of drug substance and protection of drug from environment. Hence, playing an important role in increased bioavailability of drugs, reduced toxicity and minimizing the side effects [3].

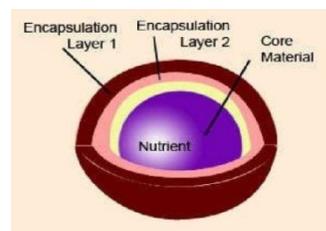


Figure 1. Microencapsulation



Figure 2. Microcapsule

Microencapsulation is helpful in converting liquids to solids having different colloidal and surface properties and controlling the release characteristics of coated materials. The uniqueness of this technology is the smallness of coated particles and their subsequent use in wide variety of dosage form [4]. In a simple form, a microcapsule is said to be a small sphere with a consistent wall around it. The material inside the microcapsule is known as core or fill and the wall is known as coating or membrane. Microencapsulation depends on physical and chemical properties of substances to be encapsulated [5].

Reasons of microencapsulation

1. The predominant reason for microencapsulation is sustained and prolonged drug release.
2. The sensitive to oxygen or moisture can be stabilized by microencapsulation.
3. For masking the taste or odor of drugs to improve patient compliance.
4. Incompatibility between the drugs can be hindered by microencapsulation. [6]
5. Microencapsulation is used to prevent the vaporization of volatile drugs like peppermint oil.
6. To reduce the toxicity and GI irritation.
7. By this technique, free flowing powders are obtained from liquid drugs. [7]

Benefits of microencapsulation [5]

1. Enzymes have been microencapsulated in food products to accelerate ripening and flavor development.
2. The stability of starter cultures has been improved by encapsulation of microorganism.
3. Microencapsulation is done to protect the compounds against UV, heat, oxidation. (E.g. vitamin A).
4. Shelf life of drugs is improved by preventing degradative reaction.
5. Microencapsulation is done to mask the taste or odor of drugs.
6. One of the benefits of microencapsulation is handling of liquids as solids.
7. Microencapsulation delivers vitamins and minerals in children in tasty way.

Limitations of microencapsulation [4]

1. No single microencapsulation process is adaptable to all core material candidates or product applications.
2. Incomplete or discontinuous coating.
3. Inadequate stability or shelf life of sensitive pharmaceuticals.
4. Unstable release characteristics of coated products.
5. Economic limitations often are encountered in the attempt to apply a particular microencapsulation method to a specific task.

Fundamental consideration

Core material

The core material is said to be a specific material to be coated which can be solid or liquid in nature. The composition of core material can vary, liquid core can include dispersed or dissolved material or both. The solid core consists of active constituents, diluents, excipients and accelerators. The ability to vary the composition of core material provides flexibility, which allows hike in desired microcapsule properties [8].

Example of core material

Liquid Core Material Examples:

Perfumes, Solvents, Vegetable Oils, Pesticides, Dyes, Catalysts, Bleaches, Cosmetics, Insecticides, Sugars, Salts, Acids, Pigments, Fungicides, Nutrients.

Solid Core Material Examples:

Dextrins, Bases, Herbicides, Pharmaceuticals, Biocides, Minerals [9].

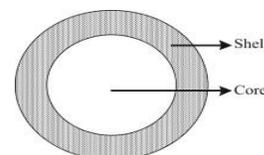


Figure 3. Microcapsule with core and coat

Coating Material

Inert substances, which coat on core material with desired thickness are called as coating material. The physical and chemical properties of resulting microcapsule depend on selected core material. Stability, reduced volatility, environmental conditions should be taken into consideration while selecting polymer. The polymer should form a film, which is cohesive with core material. It should be non reactive, chemically compatible with core material to provide coating properties like flexibility, stability, strength. [2]

The selection of a given coating often can be aided by the review of existing literature and by the study of free or cast films, although practical use of free-film information often is impeded for the following reasons:

1. Cast or free films prepared by the usual casting techniques yield films that are considerably thicker than those produced by the microencapsulation of small particles; hence, the results obtained from the cast films may not be extrapolate to the thin microcapsule coatings.
2. The particular microencapsulation method employed for the deposition of a given coating produces specific and inherent properties that are difficult to simulate with existing film-casting methods.

- The coating substrate of core material may have a decisive effect on coating properties. Hence, the selection of a particular coating material involves consideration of both classic free-film data and applied results [4].

Coating material properties

- Compatible with the core material.
- Stabilization of core material.
- Inert toward active ingredients.
- Controlled release under specific conditions.
- The coating can be flexible, brittle, hard, thin etc.
- Film-forming, pliable, tasteless, stable.

Examples of coating materials:

- Water soluble resins** – Gelatin, Gum Arabic, Starch, Polyvinylpyrrolidone, Carboxymethylcellulose, Hydroxy ethylcellulose, Methylcellulose, Polyvinyl alcohol, Polyacrylic acid.
- Water insoluble resins** – Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (Ethylene Vinyl acetate), and cellulose nitrate, Silicones, Poly lactideco glycolide.
- Waxes and lipids** – Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates.
- Enteric resins** – Shellac, Cellulose acetate phthalate, Zein. [10]

Morphology of microcapsule [5]

- The morphology of microcapsule depends on core material and deposition of coating material (shell).
- Mononuclear- in this microcapsules contain shell around core.
- Polynuclear- in this microcapsule have core enclosed within the shell.
- Matrix encapsulation- in this core material is distributed homogenously into shell material.

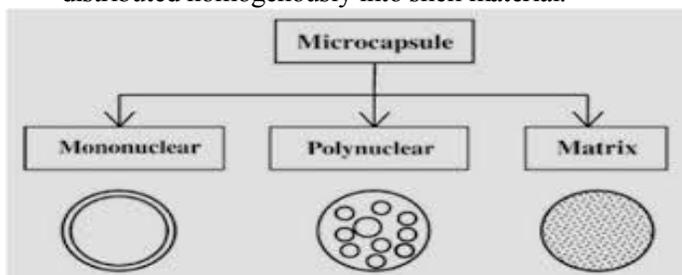


Figure 4. Morphology of microcapsule

Release Mechanism [5, 6]

Different mechanisms by which drug releases from microsphere are as follows:

Degradation controlled monolithic system

The drug disperses in the matrix and distributes evenly. The drug firmly attached to the matrix is released on degradation of matrix. The release of drug is slow compared to degradation of matrix.

Diffusion controlled monolithic system

The active agent is released by diffusion earlier or simultaneously with the degradation of matrix. Rate of drug release depends where the polymer degradation takes place either by homogeneous or heterogeneous mechanism.

Diffusion controlled reservoir system

The rate controlling membrane through which the drug diffuses encapsulates the active agent and after the complete delivery of the agent membrane erodes. Rate of release is unaffected by degradation of matrix.

Erosion

Drug releases through the erosion of coat due to pH or enzymatic hydrolysis with coating materials like beeswax, steryl alcohol, glyceryl mono sterate etc.

Techniques of Microencapsulation

Preparation of microspheres should satisfy following criteria

- The ability to incorporate high concentrations of the drug.
- Stability of the preparation & clinically acceptable shelf life.
- Controlled particle size. [11]

Various techniques are available for the encapsulation of core materials. Broadly the methods are divided into two types.

- Physical method
- Chemical method

Table 1. Methods of microencapsulation

Physical method	Chemical method
Air Suspension	Solvent evaporation
Pan Coating	Polymerization
Coacervation Phase Separation	
Spray Drying & Spray Congealing	

Physical Method:

Air Suspension:

Microencapsulation by air suspension technique is the invention of Prof. Dale E. Wurster. The wurster process consists of dispersing of solid particulate core material in a supporting air stream and the spray coating of the air-suspended particles.

The figure 5 depicts a type of wurster air suspension encapsulation unit.

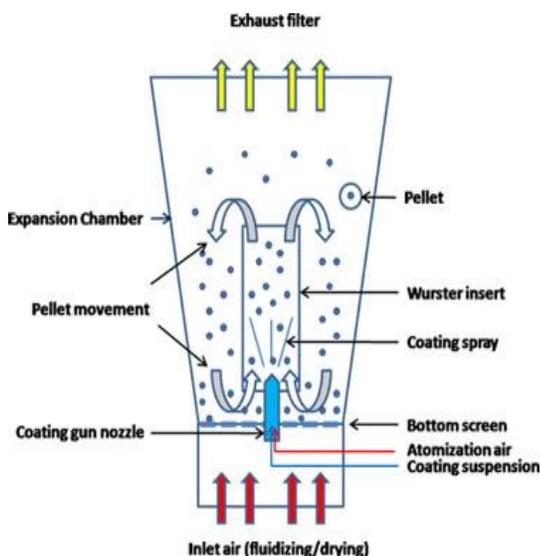


Figure 5. Wurster air suspension encapsulation unit

It consists of a coating chamber, in which the particles are suspended on an upward moving stream. The design of the chamber and its operating parameters effects recirculating flow of the particles through the coating zone of the chamber, where a coating material generally a polymer solution is spray-applied to the active particles. During each pass, through the coating zone, the core material collects an increment of coating material. The cyclic process is repeated, perhaps several times during processing, depending on the reason of microencapsulation, the coating material thickness desired, or whether the core material particles are thoroughly encapsulated. The supporting stream also completely dries the product while it is being encapsulated. Drying rates are parallel to the volume temperature of the supporting air stream. Processing variables that collect consideration for efficient, effective encapsulation by air suspension techniques involve the following density, surface area, melting point, solubility, friability, volatility, crystallinity and flow ability of the core material.

Coating Material Concentrations:

- Coating material application rate.
- Volume of air necessary to support and fluidize the core material.
- Amount of coating material necessary.
- Inlet and outlet temperature.

The air suspension offers a broad variety of coating material candidates for microencapsulation. The process has the capability of applying coating in the form of solvent solution, aqueous solution, emulsion and dispersion. The practical particle size range for microencapsulation is

considered to be in excess of 74 microns. Under ideal conditions, Particles, as small as 37 microns can be effectively encapsulated as single entities. [4]

Pan coating:

The pan coating method is broadly used in pharmaceutical industry for formulating small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly with respect to microencapsulation, solid particles greater than 600 microns in size are generally considered necessary for successful coating and the process has been extensively used for the preparation of controlled - release beads. Medicaments are generally coated into various spherical substrates such as nonpareil sugar seeds and then coated with protective layers of various polymers. In practice, the coating is applied as a solution, or as an atomized spray, to get the desired solid core material in the coating pans. Normally to remove the coating solvent, warm air is passed over the coated materials as the coatings are applied in the coating pans. In some cases, final solvent removal is occurred in drying oven [12].

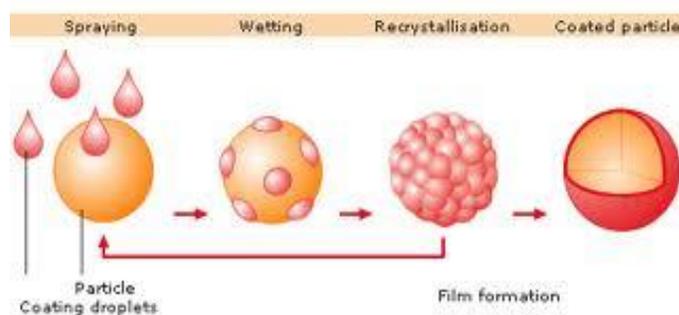


Figure 6. Pan coating

Coacervation phase separation:

Coacervation generally refers to the phase separation of a liquid precipitate or phase, when solutions of two hydrophilic colloids are mixed under suitable conditions. [13] The general outline of the processes for coacervation consists of three steps carried under continuous agitation.

- Step 1: Formation of three immiscible chemical phases.
- Step 2: Depositing the liquid polymer coating upon the core material
- Step 3: Rigidizing the coating.

Step 1: Formation of three immiscible chemical phases

The immiscible chemical phases are

- (i) A liquid manufacturing vehicle phase
- (ii) A core material phase and
- (iii) A coating material phase.

To form this three phases, the core material is dissolved in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase. The coating material phase, an immiscible polymer in a liquid state, is

formed by using one of the methods of phase separation coacervation, that is:

- By modifying the temperature of the polymer solution
- By adding a salt
- By adding a non-solvent
- By adding incompatible polymer to the polymer solution
- By involving a polymer-polymer interaction. [4]

Step 2: Depositing the liquid polymer coating upon the core material

This is occurred by controlled, physical mixing of the coating material (while liquid) and the core material in the manufacturing vehicle. Deposition of the liquid polymer coating around the core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to effective coating. The continued deposition of the coating material is promoted by a reduction in the total free interfacial energy of the system, brought about by the decrease of the coating material surface area during coalescence of the liquid polymer droplets. [5]

Step 3: Rigidizing the coating

This is normally done by thermal cross linking or desolvation techniques, to form a self sustaining microcapsule.

Coacervation can also occur with the neutralization of two oppositely charged polymers. The core material such as an oily phase is dissolved in an aqueous solution of the two polymers. A change is made in the aqueous solution to involve the formation of a polymer rich phase. The Coacervates are normally stabilized by thermal treatment, crosslinking or desolvation techniques. They found that the product of gelatin-acacia microcapsules reduces at surfactant concentrations above or below the optimum. In the coacervation process, the pH value of a continuous gelatin phase will be adjusted above its isoelectric point to form negatively charged gelatin, which are capable to create monodispersed droplets. The positively charged gelatin is attracted to the negatively charged acacia to form coacervate droplets when the pH value is adjusted to its isoelectric point. Therefore, the particle size distributions of emulsion droplets are accomplished by the factors of pH adjustment. [8]

Methods for phase separation coacervation

Temperature Change - Alteration of temperature induces phase separation. With the decrease in temperature, one phase becomes polymer rich (coating material phase) and another polymer poor (microencapsulation vehicle phase). Phase separation of dissolved polymer occurs in the form of immiscible droplets. Under ideal concentration of the polymer, temperature and agitation condition, liquid polymer droplets blend with dispersed core material particles which results in the formation of embryonic microcapsule.

Incompatible Polymer Addition: Liquid phase separation of the polymeric coating material and microencapsulation can be accomplished by utilizing an incompatibility of dissimilar polymer existing in the common solvent.

Non- Solvent Addition – By addition of a liquid that is a non solvent for given polymer to a solution of polymer, phase separation induces.

Salt Addition – Addition of soluble inorganic salts to aqueous solution of certain water soluble polymers causes the phase separation process.

Polymer - Polymer Interaction- Interaction of oppositely charged polyelectrolytes, results in the formation of a complex having reduced solubility that causes the phase separation. [4]

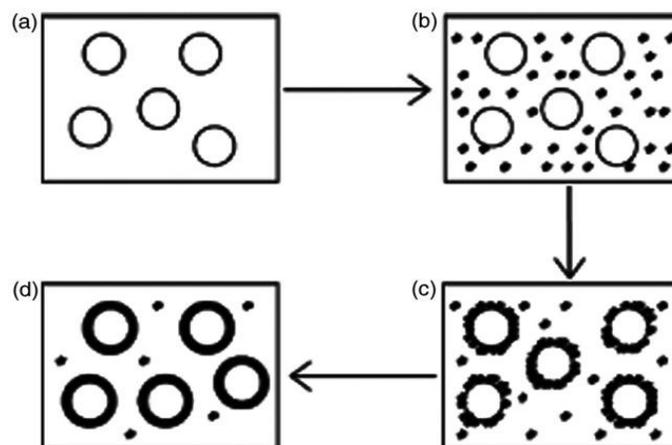


Figure 7. Schematic representation of the coacervation process.

(a) Core material dispersion in solution of shell polymer; (b) separation of coacervate from solution; (c) coating of core material by microdroplets of coacervate; (d) coalescence of coacervate to form continuous shell around core particles

Spray Drying and Congealing:

Spray drying as a microencapsulation technique. When an active material is dispersed or suspended in a polymer solution and becomes dried particle. Core particles are dispersed in a polymer solution and sprayed into a hot chamber. The shell material solidifies into the core particles as the solvent evaporates and microcapsules obtained are of polynuclear or matrix type. An emulsion is made by dispersing the core material, normally in oil or active ingredient which are immiscible with water a concentrated solution of wall material until the desired size of oil droplets are obtained. The resultant emulsion is reduced into a spray of droplets by pumping the slurry through a revolving disc

into the heated compartment of a spray drier. There the water portion of the emulsion is evaporated and they yield dried capsules of variable shape containing scattered drops of core material. The capsules are collected through continuous discharge from the spray drying chamber [14].

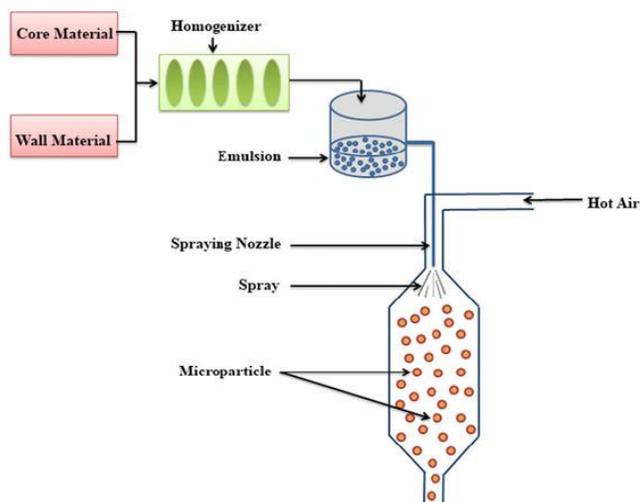


Figure 8. Microencapsulation by spray drying

Spray congealing can be performed by spray drying equipment where protective coating will be applied as melt. The core material is dispersed in a coating material melt instead of melting in a coating solution. Coating solidification is accomplished by spraying the hot mixture into cool air stream. Waxes, fatty acids and alcohols, polymers which are solids at room temperature but melt able at reasonable temperature and are applicable to spray congealing [15].

Spray drying and spray congealing processes are similar both involve dispersing the core material in a liquefied coating substance and spraying the core coating mixture into some environmental condition whereby relatively rapid solidification (and formation) of the coating is affected. The principal difference between the two methods is coating solidification. Coating solidification in the process of spray drying is effected by instant evaporation of a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods however is accomplished by thermally congealing a molten coating material or by introducing the coating - core material mixture into a non-solvent. Removal of the non-solvent or solvent from coated product is then obtained by sorption, extraction, or evaporation techniques [16].

Chemical Methods

Solvent Evaporation:

Solvent evaporation method includes three phases. They are core, coat material, liquid manufacturing vehicle (LMV). Initially coat material is dissolved in a volatile solvent, which is not soluble in LMV phase. A core material to be encapsulated is dissolved in the coating polymer solution.

Then this mixture is added to the liquid manufacturing vehicle phase with continuous agitation, the mixture is heated to volatilize the solvent for polymer. Here the coat material shrinks around the core material and encapsulates the core. Microspheres of 5-fluorouracil have been prepared by using three grades of ethyl cellulose as wall forming materials normally a solvent evaporation technique under ambient conditions [17].

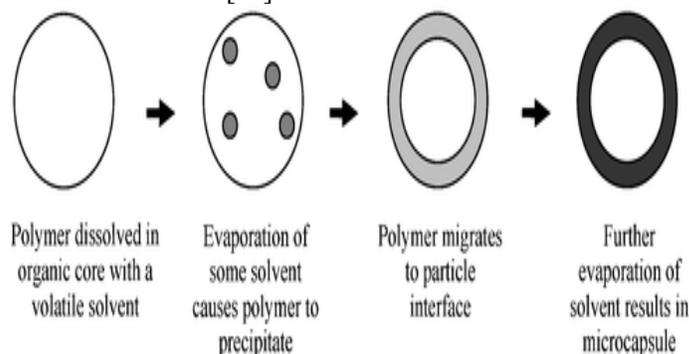


Figure 9. Steps involved in solvent evaporation

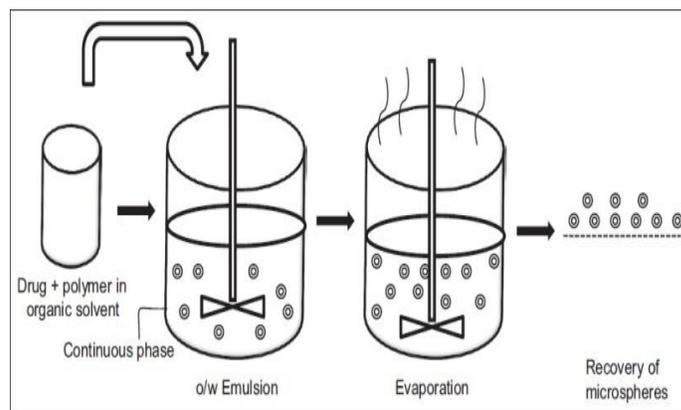


Figure 10. Schematic representation of solvent evaporation

Polymerization:

In this technique the capsule shell will be developed on the surface of the droplet or particle by polymerization of the reactive monomers. The substances utilized are multifunctional monomers. Generally monomers involve multifunctional isocyanates and multifunctional acid chlorides. These will be utilized either individually or in combination. The multifunctional monomer dispersed in liquid core material and it will be dispersed in aqueous phase containing dispersing agent. A co-reactant multifunctional amine is added to the mixture. This results in speedy polymerization at interface and generation of capsule shell takes place. A polyurea shell is formed when isocyanate reacts with amine, polynylon or polyamide shell is formed when acid chloride reacts with amine. When isocyanate reacts with hydroxyl containing monomer it produces a polyurethane shell [18, 19].

Applications:

Microencapsulate drug delivery system offers several applications for drugs having poor bioavailability. Many pharmaceutical encapsulated products are currently on the market, Such as aspirin, theophylline and its derivatives, vitamins, antihypertensive, potassium chloride, progesterone and contraceptive hormone combinations etc. [20].

Sustained Drug Delivery:

By encapsulating a drug in a polymer matrix, which shows the biological fluid into the drug until the time microparticles prolong the blood level of the drug within a therapeutic window for a prolonged period. Toxic side effects can be enhanced by reducing the frequency of administration.

Controlled Drug Delivery:

The drug is delivered at a pre decided rate, by any route locally or systemically for a designated period of time. The depot formulation of short acting peptide has been successfully developed by using microparticle technology e.g. leuprorelin acetate and triptoreline, both are luteinizing hormone releasing hormone agonists.

Local Drug Delivery:

This delivery system is subcutaneously or intramuscularly applied microparticles can prolong a therapeutically effective concentration at the site of action for a desirable duration of the drug. The local delivery system removes the systemic drug administration for local therapeutic affects and can be reduced in related systemic side effects. It is beneficially proven for delivery of local anesthetics.

Targeted Drug Delivery:

Drugs can be targeted in many different ways. Drug is delivery to a tissue:

- Antitumor microparticles are given intra-arterially and targeted an organ
- Therapeutic drug delivery of Anti cancer drugs. E.g. doxorubicin and 5-fluorouracil [21].

Cell immobilization:

In plant cell cultures microencapsulation by copying cell natural environment, enhance efficiency in production of different metabolites which are used for medical, pharmacological and cosmetic purposes. Human tissue are converted into bioartificial organs by encapsulation in natural polymers and transplanted to control hormone deficient diseases such as diabetes and severe cases of hepatic failure. Immobilization increase cell density by continuous fermentation processes. The product is to avoid washout the biological catalysts from the reactor. This has already applied in ethanol and solvent production, sugar conversion or wastewater treatment [22].

Quality & Safety in Different sectors:

Development of “biosensors” has been improved by encapsulated bio-systems used to control environmental pollution, food cold chain (abnormal temperature change).

Soil Inoculation:

Rhizobium is a very interesting bacterium which enhances the nitrate adsorption and conversion. But inoculation is often unsuccessful because the cells are washed out by rain by cell encapsulation processes, it is practicable to maintain continuous inoculation and higher cell concentration. This list is not fully complete, the nutraceuticals’ world could be mentioned last because of the rapid growing interest & increasing demand we have to select the ingredients with health benefits which are often require the enhancement of their efficiency and stability (e.g. probiotics, vitamins.) by protecting and offering targeting release of the active materials.

Construction

In an analysis of scientific articles they shows numerous possibilities of adding microencapsulated active ingredients into construction materials, such as cement, lime, concrete, mortar, artificial marble, sealants, paints and other coatings, and functionalized textiles [23].

Table 2. Microencapsulation process and their applicabilities

Microencapsulation process	Applicable core material	Approximate particle size(μm)
Air suspension	Solids	35-5000
Pan coating	Solids	500-5000
Coacervation phase separation	Solids & liquids	2-5000
Spray drying and congealing	Solids Solids & liquids	5-5000 600
Solvent evaporation	Solids & liquids	5-5000
Polymerization	Liquids	0.5-1100

Examples of Microencapsulated Drugs [21]

Table 3. Some of the examples of microencapsulated drugs are as follows

Active moiety	Characteristic	Property Purpose of encapsulation	Final product form
Aspirin	Slightly soluble in water	Taste masking, sustained release, reduced in gastric irritation	Tablet or capsule
Paracetamol	Slightly soluble in water	Taste masking	Tablet
Islet of Langerhans	Viable cells	Sustained normalization of diabetic condition	Injection
Isosorbide dinitrate	Water soluble	Sustained release	Capsule
Progesterone	Slightly soluble in water	Sustained release	Varied
Menthol	Volatile solution	Reduction in volatility, Sustained release	Lotion
Potassium chloride	Highly soluble in water	Reduction in gastric irritation	Capsule
Urease	Water soluble enzyme	Selectivity of enzyme, substrate and reaction	Dispersion
Vitamin A Palmitate	Nonvolatile liquid	Stabilization to oxidation	Dry powder
Nifedipine	Practically insoluble in water	Prevention from photo instability	Dry powder

Conclusion

Microencapsulation means packaging an active ingredient inside a capsule ranging in size from one micron to several millimeters. The capsule protects the active ingredient from its surrounding environment until an appropriate time. Microencapsulation is both an art and a science. These delivery systems offer numerous advantages compared to conventional dosage forms, which include efficacy, reduced toxicity and improved patient compliance and convenience. Such system often uses macromolecules as carriers for drug. This approach facilitates accurate delivery of small quantities of potent drug; reduced drug concentration at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at site of action. In future by combining various other approaches, microencapsulation technique will find vital place in novel drug delivery system.

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