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A Review: Recent Advances in Microencapsulation Technology for Controlled Drug Delivery Systems

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Abstract: *Controlled drug delivery technology is a rapidly advancing field, integrating knowledge from various disciplines to improve therapeutic outcomes. Microencapsulation plays a vital role in this technology by converting liquids into solids, modifying colloidal and surface-active properties, offering environmental protection, enhancing bioavailability, and controlling drug release. Microcapsules, typically spherical particles ranging from 50 nm to 2 mm, enclose a core material within a polymer coating, protecting the active substance and allowing precise release control. The morphology of microcapsules is primarily influenced by the core material and the method of shell deposition. The primary drug release mechanisms from microcapsules include diffusion, dissolution, osmosis, and erosion. Microencapsulation techniques can be broadly classified into chemical and mechanical (or physical) processes, each tailored to optimize drug release profiles. This review discusses the latest advancements in microencapsulation technologies and their applications in controlled drug delivery systems.*

Keywords: Controlled drug delivery, Microencapsulation, Drug release mechanisms, Bioavailability, Polymer coating, Core material, Diffusion, Dissolution, Osmosis, Erosion, Chemical processes, Mechanical processes

I. INTRODUCTION

One of the most advanced disciplines in science is controlled drug delivery which incorporates more than one science that helps improve healthcare delivery in society. Such systems depict that drugs are carried by macromolecules. Microencapsulation is a technique in relation to drugs whereby isolated droplets or particles whether that be liquid or solid or even gas are completely enclosed or coated by a polymer. It comprises also of bioencapsulation which is quite much limiting to usage of a biologically active substance such as DNA or a whole cell, or group of them with an aim of making it more useful or prolonging its shelf life. [4]

Bungen burgh de Jon and Kan (1931) noted the introduction of the technique while Vyas and Khar (2002) localized the microencapsulation procedures to include the production of particles of less than 200 μm in size.

Minicapsulation works toward resolving useful substances so dispersed in a liquid as to be unrecoverable into discrete solids changing surface and colloidal interfaces imparting shield from the surroundings increasing absorption and controlling the release drug rate of various coated materials.

Microencapsulated products are minute objects which encapsulate an active ingredient called the core material within a coating material or a matrix structure.

As Microparticle shells are made of synthetic polymers, waxes and lipids are also common. The size of microencapsulated products well lies in the range of 1 to 1000 μm in diameter. The core in commercially available microparticles constituted 10-90% w/w.

There is a wide range of core material that comprise of live cells, polymeric adhesives, essence, agrochemicals, biologicians such as enzymes, and medicinal bioparticles Among others. Scanning electron micrography provides information on various structural cross-sectional details of the microcapsules as these are purposefully made different and elaborate. The walled prototype can be either unibodied or there can exist core structure of plurality and also there can be double or more than double concentric coating. Though, there are filled microcapsules that contain an extra external or secondary wall and hence are different in size and shape. Although indeed microstructure of membrane and

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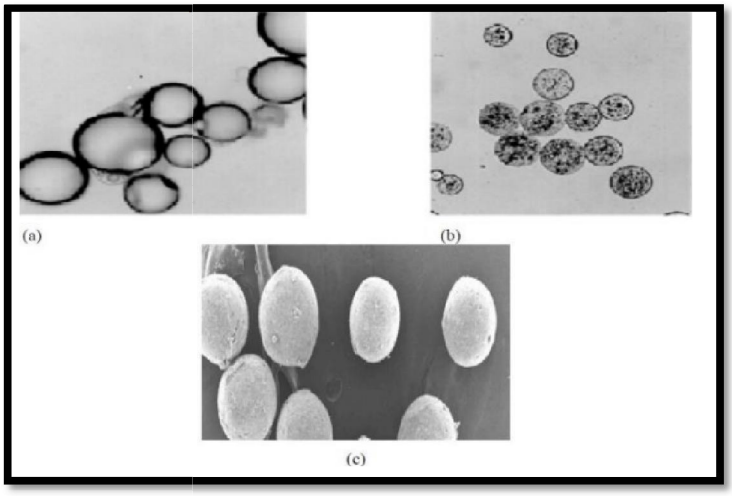
the interior of microcapsule surface can be identified by epithelialized surfaces of microcapsules from semiconductor microscopy it is still difficult to comprehensively define their mechanical integrity quantitatively. Porosity and permeability are computable using releasing data within bulk densities, geometrical dimension, and core to wall ratios.

II. MICROCAPSULE

A microcapsule is a tiny, spherical particle measuring between 50 nanometers and 2 millimeters. It has a core material inside. Microspheres, on the other hand, are hollow spherical particles. As shown, they have a simple spherical structure with an empty center. Microcapsules used in various forms like hard or soft gelatin capsules, enteric-coated capsules, or liquid suspensions. These forms allow the individual microcapsules to be released.



a) Mononuclear microcapsules b) Aggregated microcapsules c) Surface of microcapsule

III. MATERIAL INVOLVED IN THE MICROCAPSULESULATION

It can be defined as the process of encapsulation in which small particles or droplets of liquid or solid material known as core is enveloped or coated with polymeric material known as shell to form structures in the range of micrometers to millimeters are called as microcapsules.

Core Material

The material which is intended to be coated by applying this method.
It may be in the form of liquid or solid(temporarily).

- Liquid core is a material which is dissolved or dispersed in a fluid.

Composition of coating material

- Drug / active ingredient
- Additive like diluents
- Stabilizers
- Release rate enhancers

Coating Material

Material that is placed on to core material to give it the thickness that is required.

- Some humanities are compatible with the core material of the paper.
- Stabilization of the medium; Increase in thickness of the material.
- Non reactivity with the active ingredients.
- Permission to release under certain circumstances.
- It can be flexible, brittle, hard, thin or have any other property which it is desirable to produce by coating.

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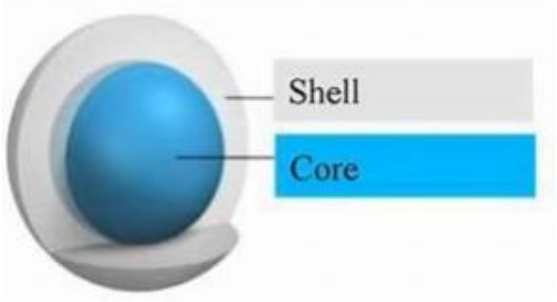
• Readily available and at a very low cost
• Composition of coating
Inert polymer
Plasticizer
Colouring age



MORPHOLOGY OF MICROCAPSULES

It also has to be noted that size and shape of the microcapsules depend to a considerable extent on the characteristics of the core substance and the method used to form the shell.

1. The structure of mononuclear (core-shell) microcapsules is covered on side of the shell is on the side of the core.
2. Polynuclear capsules has many cores imbedded within the shell layer.
3. Matrix encapsulation in which, the matrix of one phase is uniform at the cross-sectional area of the shell with the matrix of the other phase.

MECHANISM OF RELEASE

Mechanism	Information
Diffusion	Most commonly used. Mechanism involved dissolution fluid penetrates the shell, dissolves the core and leak out through interstitial channel or pores. Overall release depends on Rate at which dissolution fluid penetrates from the walls of microcapsule The rate at which drug dissolve in dissolution fluid. The rate at which the dissolve drug leak out and disperse from the surface.
Dissolution	Thickness of coat and its solubility in the dissolution fluid influence the release rate.
Osmosis	Polymer coat of microcapsule acts as permeable membrane. It allows the creation of an osmotic pressure difference between inside and outside of the microcapsule
Erosion	Erosion of coat due to pH and/or enzymatic hydrolysis causes drug release with certain coat materials like glyceryl monostearate, bee's wax and stearyl alcohol.

MICROENCAPSULATION TECHNOLOGIES

PHYSICO - CHEMICAL PROCESSES	PHYSICO – MECHANICAL PROCESSES
Coacervation (2 – 1200 um)	Spray-drying (5 – 5000 um)
Polymer-polymer incompatibility (0.5 – 1000 um)	Fluidized- bed technology (20 – 1500 um)
Solvent evaporation (0.5 – 1000 um)	Pan coating (600 – 5000 um)
Encapsulation by supercritical Fluid	Spinning disc (5 – 1500 um)
Hot Melt (1—1000 um)	Co-extrusion (250 – 2500 um)

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Encapsulation by Polyelectrolyte multilayer (0.02 – 20 um)	Interfacial polymerization (0.5 – 1000 um)
Phase Inversion (0.5—5.0 um)	In situ polymerization (0.5 – 1100 um)

1} Coacervation Phase Separation

• Main components, namely core material, are well distributed in the solution of coating material.

• A coacervate is a very small spherical mass of various biopolymers which is emulsified in water and is bonded by hydrophobic forces.

• The diameter of coacervates ranges between 1 and 100 micrometers in size.

• It is also important that the core material does not react or dissolve in the solvent of coating material.

Microencapsulation By Coacervation Phase Separation Process

2. Polymer-Polymer Incompatibility: (Phase Separation)

This employs two polymers which are soluble in a single solvent but are insoluble in each other and therefore do not dissolve with each other.

The polymers type two distinct regions, where one region is having the desired polymer for the creation of the capsule walls while the other is having an incompatible polymer that will cause.

separation of the two phases. The second polymer is not intended to be part of the finished microcapsule wall.

3. Solvent Evaporation

It facilitates a controlled release of a drug.

Water insoluble polymers are used as encapsulation matrix using this technique.

Biodegradable polymer PLGA (poly (lactic-co-glycolic acid)) is frequently used as encapsulation material.

4. Polymer Encapsulation By Rapid Expansion Of Supercritical Fluids

Supercritical fluids are highly compressed gases that possess several properties of both liquids and gases.

The most widely used being supercritical CO2 and nitrous oxide (N2O).

A small change in temperature or pressure causes a large change in the density of supercritical fluids.

Supercritical CO2 is widely used for its low critical temperature value, in addition to its nontoxic, non flammable properties; it is also readily available, highly pure and cost effective.

This technology also applicable to prepare nanoparticles also.

5. Hydrogel Microspheres

Microspheres containing gel-type polymers including alginate are prepared through a simple process of dissolving the polymer in an aqueous solution.

Then, mixing the above solution while placing the active ingredient inside the mixture.

Coming out from a precise organ with micro droplets being created

After that, immerse it to a hardening bath, which is allowed to stir slowly. The hardening bath is normally a solution of calcium chloride.

6. Spray-Drying

Spray congealing could be carried out by the use of spray drying equipment where the shield of the coated will be mushy.

A ('core material') is dispersed in such a way as to allow a coating material melt rather than a coating solution.

The cooling down of the hot mixture is achieved by directing the spray towards a cooler air stream which could be anything of a cool stream.

7. Fluidized-Bed Technology

In addition, fluid bed coating, another mechanical encapsulation method, can only be used for the encapsulation of solid core materials including the liquids absorbed into porous solids.

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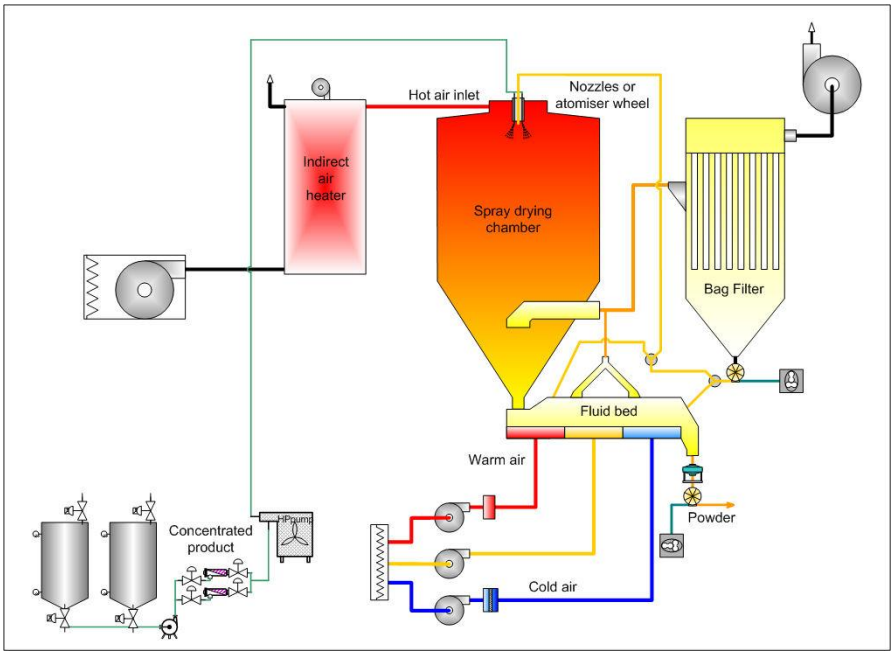
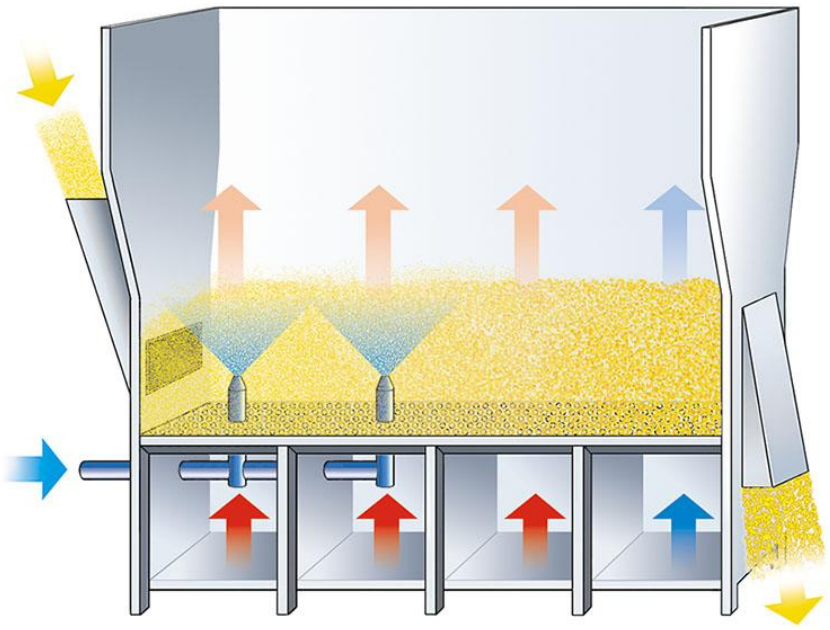
Solid particles are used to encapsulate pharmaceutical injection powders and bulk intermediate products very often. Suspended solid particles to be encapsulated are taken along a jet of air and thereafter by a spray of liquid coating material.



Capsules are moved along to an area where shells are solidified either by cooling or the vaporization of solvent. Process: the Suspension is atomized and cooled repeatedly until desired thickness of capsules' walls is achieved. This process is called a Wurster process when the spray nozzle is positioned at the bottom of the fluidized bed of particles.



8. Pan Coating

The coating material is slowly applied over the particles in a pan or similar device while they are being tumbled.

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Solid particles are blended with a dry coating material and temperature increased in pan daycare providing core materials that end up encased by the flavoring realtor, subsequently cooled down to set this finishing.

9. Centrifugal Extrusion

Centrifugal extrusion processes All fundamental principles of centrifugal liquid encapsulation we explained produce capsules in the larger size range starting from 250 µm up to a few mm and are defined by the specific process.
The core and the shell materials, which are non-mixable must flow through a spinning two-fluid nozzle.
This action creates a continuous rope that instantly breaks into round beads just after leaving the nozzle.
The cooling or gelling bath solidifies the continuous walls of these droplets, depending on whether composition and properties of coating material. [5]

III. BENEFITS OF MICROENCAPSULATION

Sr.No.	Benefit	Description
1	Microorganism and enzyme Immobilization	Enzymes have been encapsulated in cheeses to accelerate ripening and flavour development. The encapsulated enzymes are protected from low pH and high ionic strength in the cheese. The encapsulation of microorganisms has been used to improve stability of starter cultures.
2	Protection against UV, heat, oxidation, acids, bases	Chemical agents like colorant sand vitamins Eg. Vitamin A / monosodium glutamate
3	Improved shelf life	due to preventing degradative reactions dehydration, oxidation
4	Masking of taste or odours	Mask unpleasant test and odour.
5	Improved processing, texture and less wastage of ingredients	Control of hygroscopy enhance flowability and dispersibility dust free powder enhance solubility
6	Handling liquids as solids	Liquid drug can be encapsulated and used as solid formulation.
7	Nutritious Foods	Microencapsulation could deliver the vitamins and minerals in children friendly and tasty way.
8	Textile industry	enhance the properties of finished goods
9	Controlled and targeted release of active ingredients	extend the shelf-life of flavouring volatile products Mask the taste of nutrients added to fortify a product without compromising the product's intended taste
10	Encapsulated Pesticides	Allow farmers to apply the pesticides less amounts than requiring.
11	Ingredients in foods are encapsulated for several reasons	Both oral and injected formulation, release over longer periods of time or at certain locations in the body

IV. RECENT PROGRESS IN MICROENCAPSULATION

Various methods and techniques are available for creating polymeric microparticles, which are essential in microencapsulation. The chosen method affects the microparticle's size, type, and interactions between components. Microparticles, larger than one micrometer, encompass both microcapsules and microspheres. These drug-containing microparticles serve multiple purposes, including controlled release, taste and odor masking, drug protection from degradation, and protection from toxic effects. Polymeric carriers, used in fabricating microparticles, come from diverse fields and can be either erodible or non-erodible[8]

Researchers have recently developed innovative methods for delivering drugs. Hughes, for example, created a method for delivering active drugs to the back of the eye using biodegradable microparticles. This approach uses ester prodrugs, such as tazarotene, to avoid high systemic concentrations. Similarly, Lee et al. developed a thin film or strip containing microspheres loaded with antibiotics, made from biodegradable polymers. This film is designed for sustained release in periodontal pockets and is coated with a cationic salt solution. Traynor et al. also used a similar method to create positively charged microcapsules containing sunscreens, using cationic additives like polymers.[9,10,11]

Some methods developed injectable, slow-release formulations using poly(D,L-lactide) microspheres for opioid agonists/antagonists. Tice et al. and Markland et al. created these microspheres using an oil-in-water (o/w) emulsion,

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with ethyl acetate and polyvinyl alcohol. The microspheres were recovered through water extraction. Wen and Anderson prepared single-wall, biodegradable microspheres containing anti-inflammatory agents using a similar o/w emulsion method.[12] These microspheres can be immobilized in an implantable matrix or in situ formed matrix. Additionally, hydrophilic capsule materials like gelatin can be solidified through rapid temperature reduction and dehydration. However, this method can be challenging to achieve rapid solidification of the microencapsulating material.

[13]Wen and Anderson developed a method to create double-walled microspheres using two biodegradable polymers through the oil-in-water emulsification solvent extraction process. Meanwhile, Futo et al. utilized a high molecular weight lactic acid polymer (ranging from 11,000 to 27,000) or its salt to produce microspheres that achieve prolonged release over an extended period. This method effectively suppresses the initial excessive release of a water-soluble LHRH derivative, allowing for a more controlled release profile through either single or double emulsion techniques.

Innovative methods for encapsulating DNA and hormones in microparticles for oral administration. Jones et al. created a method using water-in-oil-in-water (w/o/w) emulsion and biodegradable polymers to encapsulate DNA, preserving its ability to induce gene expression. [14,15,16]Little et al. developed a high-throughput method for preparing multiple microparticle formulations containing plasmid DNA using double emulsion/solvent evaporation. Woo et al. achieved sustained release delivery of hormones like calcitonin using biodegradable microspheres. Additionally, microspheres with release-modifying agents and pH-stabilizing agents, such as basic amino acids like L-arginine, were prepared using oil-in-water (o/w) emulsion. The unique combination of components in these microspheres enables sustained release, resisting changes in pH.

Johnson et al. successfully encapsulated nucleotides and growth hormone using simple and double emulsification methods, respectively. In addition to synthetic polymers like poly(lactic acid) and polyorthoesters, proteins have also been utilized to form microparticles or microspheres for drug delivery.[17,18] These protein-based microparticles are typically cross-linked using glutaraldehyde or hardened at high temperatures. However, significant challenges remain, including the loss of biological activity of the incorporated materials and the inability to control particle size and in vivo degradation rates.

Reslow et al. developed a novel method for encapsulating vaccines using starch as the encapsulating material. The process involves suspending the vaccine in an aqueous starch solution with a high amylopectin content (over 85% by weight). [19]This mixture is then combined with an aqueous solution of a polymer that can form a two-phase aqueous system. The starch droplets containing the vaccine are allowed to gel, leveraging the natural gelling properties of starch.[20] This innovative approach enables the encapsulation of vaccines in a biocompatible and biodegradable material.

MARKETED FORMULATION OF MICROENCAPSULATION [21-48]

Active ingredient	Category of drugs	Purpose of that encapsulation	Final product of microencapsulation
Aspirin	Anti-arthritic	Taste masking, Sustained release, Gastric irritation	Tablet
Paracetamol	Anti-inflammatory	Taste masking	Capsule
Menhol	Anti-bacterial	Reduction in volatility, Sustained release	Lotion
Islet of langerhans	Endocrinr cells	Sustained normali-zation for diabetics	Injection
5-fluorouracil	Anti-metabolite	Reduced irritation	Cream
Vitamin A palmitate	Anti-aging	Stabilization to oxidation	Dry-powder

V. FUTURE PROSPECTS OF MICROENCAPSULATION

Microencapsulation – The process of producing a small capsule (or more specifically, many small capsules), normally just few microns in size that includes any specific substance; In concept, microencapsulation is a process by which an

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ultra-thin spherical shell, made of natural or synthetic polymer encapsulates another chemical literally insulating it from its immediate environment. One shell reduces or slow it from getting through. The polymer shell dissolves or is broken with pressure and releases the encapsulated material.

Microencapsulation is not new. · Spray drying, spray chilling, freeze-drying and coacervation have existed for decades. However, scientists argue that the field has evolved quickly. Consequently, the microencapsulation market is rapidly becoming a leading industry of recent food and beverage flavor innovation. In future, flavours and flavour systems may be based even more on the use of nanotechnology — research work with materials at millionths of a mm sizes.

The advent of microencapsulated flavors represents a new realm of food development possibilities never seen before "The Franken food that improves you" in UK's., with encapsulation technologies being key to their vision of future foods.There are also possibilities of microencapsulating oil ingredients, such as omega-3, with sugar beet pectin as a possible alternative to more traditional encapsulating agents such as milk proteins and gum Arabic, which have been commonly used in the past.

Additional workis needed for microencapsulation, to investigate the oxidative stability of the microcapsules over time along with flavour retention for aromatic compounds.

Future work for microencapsulation of islets of Langerhans utilised sodium alginate and poly-l-lysine (PLL) to construct the microcapsules.

Apart from the above familiar applications, microcapsules have been used in pharmaceutical, agricultural, cosmetic and food industries.. As examples, microencapsulations have been performed with oils, aqueous solutions, alcohols and a variety of solids.

VI. CONCLUSION

Microencapsulation technology has significantly advanced the field of controlled drug delivery systems, offering numerous benefits such as enhanced bioavailability, targeted drug release, and protection of active pharmaceutical ingredients. The ability to convert liquids to solids, modify surface properties, and control drug release through various mechanisms like diffusion, dissolution, osmosis, and erosion highlights its versatility and effectiveness. Recent developments in both chemical and mechanical microencapsulation techniques have opened new opportunities for creating more efficient drug delivery platforms. These innovations allow for better customization of drug release profiles, improving patient outcomes and therapeutic efficacy. As research progresses, microencapsulation will continue to be a key technology in the development of next-generation drug delivery systems, offering potential solutions for complex medical challenges.

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