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Polymers used in Novel Drug Delivery System with special reference to Microencapsulation

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ABSTRACT: Microencapsulation has emerged as a crucial technique in the area of novel drug delivery systems (NDDS), revolutionizing pharmaceutical formulations. This methodology involves encapsulating active pharmaceutical ingredients [APIs] within microscale particles, offering numerous advantages such as controlled release, enhanced stability, targeted delivery, and protection of sensitive compounds. The versatility of microencapsulation enables customization of drug release kinetics to match specific therapeutic requirements, facilitating sustained, pulsatile, or triggered release profiles. Various methods are employed in microencapsulation, including spray drying, coacervation, solvent evaporation, and emulsion techniques, each tailored to suit the physicochemical properties of the drug and desired characteristics of the final formulation. Additionally, advances in materials science have led to the development of innovative encapsulation matrices, such as biodegradable polymers, lipids, and proteins, further enhancing drug bioavailability and biocompatibility. Microencapsulation has found applications across diverse therapeutic areas, including oral, transdermal, pulmonary, and injectable drug delivery systems. It has significantly improved the safety and efficacy profiles of conventional medications, minimizing side effects and maximizing patient compliance. Moreover, microencapsulation has facilitated the delivery of challenging drug molecules, such as peptides, proteins, and nucleic acids, overcoming issues of poor solubility, instability, and rapid clearance. To sum up, microencapsulation is a significant development in pharmaceutical science that provides a flexible and efficient method of drug administration. Prolonged investigation and creativity in this domain may result in the creation of innovative treatments that yield better therapeutic results and increase the welfare of patients.

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INTRODUCTION:

The term "novel drug delivery systems" describes cutting-edge techniques and tools for precisely delivering pharmacological substances to the intended location inside the body. Enhancing therapeutic efficacy while reducing side effects and raising patient compliance is the main objective of NDDS. The creation of drug delivery methods that can accurately regulate the active pharmaceutical ingredient's (API) release kinetics is one of the main components of NDDS [1]. Conventional drug delivery techniques frequently use formulations with instant release, which release the full dosage of the medication quickly after administration. Nonetheless, NDDS provides a range of approaches,

including as stimuli-responsive release, targeted delivery, controlled release, and sustained release, to adjust drug release kinetics. Formulations with sustained release are intended to release the medication gradually over a longer lowering the frequency of dosage and preserving therapeutic levels in the bloodstream. Enhancing patient compliance and minimising drug concentration changes can result in increased efficacy and decreased negative effects. Precise control over the rate and duration of medication release is possible with controlled release devices, allowing for customised dosage schedules based on the patient's requirements. Numerous processes, including diffusion, osmosis, and delivery system biodegradation, can accomplish this. Another key component of NDDS is targeted drug delivery, which entails delivering the medication precisely to the body's site of action with the least amount of exposure to healthy tissues [2]. The use of ligands, antibodies, or other targeting moieties that bind to receptors or antigens on the target cells or tissues selectively can accomplish this. Drug delivery systems that are responsive to external stimuli, such as changes in pH, temperature, or enzyme activity, can release the drug. By delivering the medication at the intended location on demand, these devices increase therapeutic efficacy and lessen systemic side effects.

Table 1. Classification of NDDS.

Carrier based Drug Delivery System	Transdermal Drug Delivery System
Liposomes	Sonophoresis
Nanoparticles	Osmotic pump
Microspheres	Microencapsulation
Niosomes	
Resealed erythrocytes as drug carriers	

NDDS is essential for by passing several physiological barriers, including the blood-brain barrier, and for increasing the bioavailability of poorly soluble medications in addition to increasing drug delivery efficiency [3]. All things considered, NDDS is a quickly developing field at the nexus of biomedical engineering, materials science, and pharmaceuticals that has the potential to completely transform drug therapy by offering better, safer, and more patient-friendly treatment alternatives. Sustained investigation and advancement in this field are imperative to propel medication delivery innovations and enhance global patient outcomes [4].

For over two decades, scientists have acknowledged the potential benefits of nanotechnology in providing notable breakthroughs in drug delivery and targeting. Better delivery strategies that lower toxicity and boost efficacy will benefit patients tremendously and open up new markets for the pharmaceutical and drug delivery industries [5]. Other drug delivery strategies concentrate on finding safe and effective ways to deliver protein drugs outside of the gastrointestinal tract, where they may be degraded, or on overcoming particular delivery barriers, such as the blood-brain barrier BBB, to better target the drug and increase its efficacy. Classification of NDDS as shown in Table 2 [6].

The objective of this review is to explore the role of polymers in novel drug delivery systems (NDDS), with a special emphasis on microencapsulation. This study aims to analyse different types of polymers, their properties, and their suitability for microencapsulation techniques. It also examines the impact of polymer-based microencapsulation on drug stability, bioavailability, controlled release, and targeted delivery. Additionally, the review highlights various microencapsulation methods, their advantages, and applications in pharmaceutical sciences to enhance therapeutic efficacy while minimizing side effects.

ADVANTAGES OF NDDS:

Controlled Delivery:

NDDS makes it possible to keep the medicine at the appropriate concentration and with a controlled rate of release. This guarantees more reliable therapeutic outcomes.

Accurate Dosing:

Using NDDS makes exact dosing possible. For treatment outcomes to be optimised, this accuracy is essential.

Enhanced Safety and Efficacy:

By guaranteeing that the appropriate dosage of medication reaches the target place, NDDS enhances pharmacological efficacy. It reduces toxicity and adverse effects at the same time.

Site-Specific distribution:

Targeted medication distribution to particular bodily areas is made possible by NDDS. This accuracy minimises unfavourable consequences elsewhere while maximising therapeutic advantages.

Lessened Toxicity and Side Effects:

NDDS lessens the possibility of toxicity and unfavourable reactions by regulating drug release and focusing on particular tissues.

Enhanced Patient Compliance:
NDDS can improve patient satisfaction and compliance with treatment regimens, leading to better overall outcomes [7].

DISADVANTAGES OF NDDS:
Inactivation by Gastric Juice:
The stomach's gastric juices have the ability to inactivate NDDS, potentially decreasing their efficacy.

Metabolism before Target Cell Reaching:
It is possible for certain NDDS formulations to go through metabolism before meeting the target cells. For example, drug availability may be impacted by first-pass metabolism that takes place in the liver, intestines, or lungs.

Adverse Reactions:
Despite NDDS's goal to improve medication administration, these devices may nevertheless have unfavourable effects.

Big Amount of Drug Delivery:
It can be difficult to consistently deliver a comparatively big amount of the drug when using certain NDDS procedures.

Repeated Dosage Requirement:
In order to sustain therapeutic levels, NDDS frequently require repeated doses, which may have an effect on patient compliance.

Reduced Patient Compliance:
Patients may be less compliant with NDDS due to its complexity and frequent dose regimens.

Potential Toxicity in the Event of a System Failure:
An uncontrolled medication release from a malfunctioning or failing NDDS system may be toxic.

Increased Cost:
Compared to traditional drug delivery techniques, developing and implementing NDDS may be more expensive [8].

MICROENCAPSULATION:
A system of encasing covering micron extend influential particles or beads of fluid or gases, which as a result concentrate and jam them from the outside world, is what defines microencapsulation as a dormant shell. When the particle size is less than 1 mm, it is categorised as a microparticle, a microcapsule, a microsphere, or a particle with a diameter between 3 and 800 mm. Macro Particles are defined as particles larger than 1000 mm. Microparticles or microcapsules consist of two components: the base layer and the cover or shield composition. When coating or securing the core material - the paint or hell material - core content needs an active component. Various materials, including hormones, peptides, reactive lipids, meat products, paints, pigments, and active medicine additives. May be embedded with a variety of shell or covering materials, including polyester, chitosan, ethyl cellulose (EC), HPMC, Na CMC, and PLGA. The technique known as "micro-encapsulation" creates tiny capsules by enclosing microscopic particles or droplets in a covering. A microcapsule is in its most basic form, a microscopic spherical shell surrounded by a homogeneous wall. While the wall of the microcapsule is sometimes referred to as a shell, coating, or membrane, the material inside is known as the core, internal phase, or fill. The majority of microcapsules range in diameter from a few micrometres to a few millimetres. There are now more foods included in the definition. Each kind of food ingredient has been contained. Tastes are the most prevalent [5]. The process of microencapsulation as shown in the Fig 1.

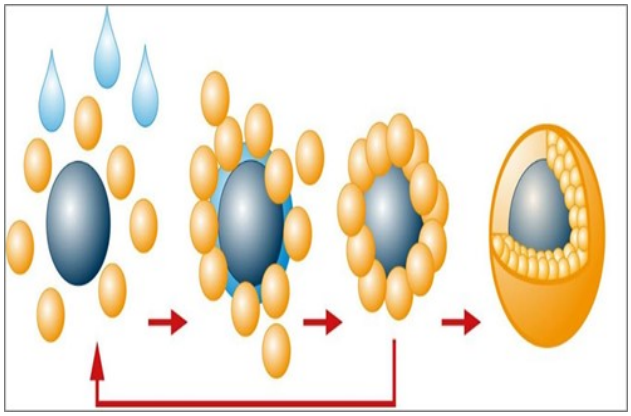

Fig 1. Process of microencapsulation.

The physical and chemical characteristics of the material to be enclosed determine the microencapsulation process. These microcapsules offer several advantages, including enhanced material handling capabilities, environmental protection, the ability to separate reactive substances, and the ability to transform liquids into solids. Next barrier polymers (such as gelatine, plastic, wax, etc.) micronized capsules containing active ingredients are added. Nonetheless, many microcapsules

Table 2. Coating materials, their sources, properties, and the techniques they are suitable for Polymers used/ Material used.

Coating Material	Source	Properties	Techniques Used
gums	Gum Arabic, sodium alginate, carrageenan	From soft elastic gels, poor tensile strength, hydrocolloid	Extrusion, phase separation Spray drying. coacervation, emulsification
Carbohydrates	Starch, dextran, sucrose	Hydrocolloid, comparatively higher tensile strength than gums	Spray drying, fluidized bed coating, extrusion, freeze drying
Proteins	Starch, dextran, sucrose	Emulsification, gelation, foaming, and water binding capacity	Spray drying, extrusion, coacervation, freeze drying emulsification
Lipids	Beeswax, stearic acid. Phospholipids	Plasticizing properties, Good barrier to gases and water vapor	Fluidized bed coating, spray chilling/cooling, extrusion
Celluloses and their derivatives	Plant cells	Hydrophilic, good film forming ability and surface activity	Spray drying, fluidized bed coating. extrusion, emulsification/ precipitation Coacervation
Chitosan	Shells of crustaceans	Good barrier to gases and water vapor	Spray drying, coacervation, emulsification

are not much like these straightforward spheres. An emulsion, a suspension of solids, a crystal, a jagged adsorbent particle, or a suspension of smaller microcapsules can all be the core. The microcapsule might possibly have more than one wall [7]. Various coating materials, their sources, properties, and the techniques they are

Suitable for Polymers Used/Material Used shown in the Table 2 [9-12].

Large molecules known as polymers [molecular weight: 10,000 to 1,000,000 g/mol] are made up of monomers, which are smaller repeating units. Natural polymers are those that are produced by living things like fungi, bacteria, algae, plants, and mammals. Polymers that undergo laboratory manufacturing are referred to as synthetic polymers. In numerous industries, including textile, cosmetics, pharmaceutics, medical, and food, polymers - both natural and synthetic - have found widespread application. The process of encapsulating anything involves enclosing it in a wall material and keeping it isolated from its surroundings. Therefore, by using this technique to transport and protect biomolecules, it is possible to increase their bioavailability. Similarly, encapsulation can be used to lessen the unwanted sensory effects that come with adding a bioactive to a food matrix can give [13].

Because of their great biocompatibility, affordability, and accessibility, natural polymers are the most often utilised polymers for encasing bioactive substances and incorporating them into food products. In this sense, alginate, chitosan, gelatin, albumin, carrageenan, starch, and guar gum are the most naturally occurring polymers utilised in pharmaceuticals for bioactive encapsulation. However, because synthetic polymers like poly-lactic-co-glycolic acid (PLGA), polyvinylpyrrolidone (PVP), or polyglycerol polyricinoleate (PGPR) can form more stable structures that offer better protection and isolation of bioactives, there is interest in using them for bioactive encapsulation. However, the high cost, difficult synthesis procedures, and potential negative effects on consumer health when ingested in large amounts have restricted the usage of synthetic polymers [14].

NATURAL POLYMERS:

The most popular polymers for creating encapsulation systems are natural ones. Their numerous physicochemical and biological characteristics, such as their great biodegradability, biocompatibility, and availability, are mostly to blame for this. However, the high likelihood of contamination and hydrolysis by microorganisms, as well as the variability in their structure and properties, are some drawbacks of natural polymers. They are listed below [15]. Process for preparation of natural polymers as shown in the Fig 2.

Starch:

It is a glucose polymer and a plant's food store. Cellulose is the polymer that makes up plants. Additionally, fibres that we can twist into threads and weave into garments, such as cotton and hemp, are made

of cellulose. Moreover, many plants produce starch. Grains, potatoes, corn and rice are high in starch.

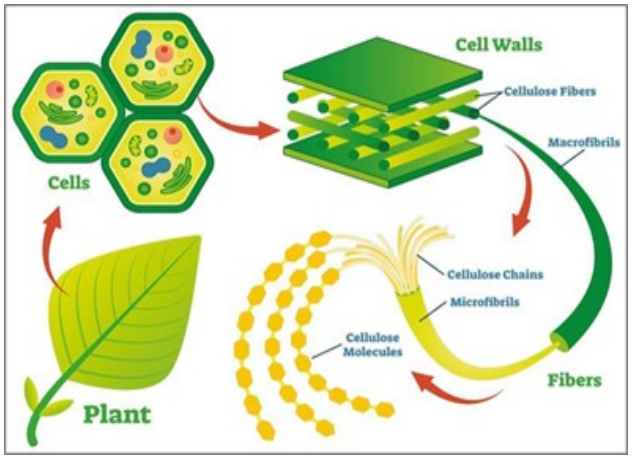

Fig 2. Natural polymers.

Cellulose:

It is also a glucose polymer. It is the main structural element found in plants. Cellulose and starch are synthesized by plants from the glucose generated during photosynthesis. Cellulose, an organic molecule with the formula [C6H10O5]n, is a polysaccharide composed of a linear chain of several hundred to over ten thousand β[1→4] linked D-glucose units. Certain bacteria may convert cellulose into a fuel called cellulosic ethanol.

Proteins:

These are α-amino acid polymers, usually consisting of 20 to 1000 α amino acids arranged in a highly ordered fashion. These are the fundamental components of an animal's body and are present in all of our diet.

Nucleic acids:

These polymers are distinct nucleotides. For example, DNA and RNA are examples of common nucleotides. Biopolymers are another name for polymers that control many elements of plant and animal life, such as proteins, nucleic acids, and polysaccharides (cellulose, starch). Nucleic acids are linear polymers, or chains, of nucleotides. Each nucleotide is composed of a pentose sugar, a phosphate group, and a purine or pyrimidine nucleobase (referred to as a nitrogenous base or simply base).

Silk:

Silk is another fantastic protein that is produced by unique caterpillars. For thousands of years, this material has been used to create exquisite textiles for garments. Furthermore, nothing compares to silk, even if people have created nylon, a substitute for silk [16].

Enzymes:

Enzymes are a unique class of proteins that function within the body. Every single enzyme is a unique tiny glob of protein that performs a specialised function in the body really quickly. Enzymes are necessary for these tasks to occur, or they would go far too slowly, to support life. Enzymes can even synthesise other enzymes [17].

SYNTHETIC POLYMERS:

As synthetic polymers were first introduced to the practical market around the beginning of the 20th century, they can be regarded as relatively new materials. The rules of chemistry and thermodynamics are the sole limits to the virtually limitless possibilities for manufacturing different forms of synthetic polymers, which are created by chemical processes. Moreover, polymer-based membranes that may expand or contract in response to pH and temperature changes can be used to create responsive drug release systems. Although they might be elastomers, fluids, or resins, silicone polymers, also known as polysiloxanes, are inorganic organic polymers. Polymers can be given a wide range of properties by introducing different side groups, crosslinking, and chain lengths [18].

Novel Classes of Polymers:

The term "smart polymers" refers to novel kinds of polymeric materials that are stimulus-sensitive, meaning that their physicochemical characteristics alter in reaction to outside stimuli. In the past two to three decades, there has been a considerable interest in smart polymers due to their unique qualities, which include being soluble or insoluble, stimuli-sensitive, and environmentally sensitive. Dagani first used the term "smart" in 1995 because of the visible resemblance to biopolymers. In the diagnosis of gastrointestinal ischemia, which is a condition that occurs in numerous diseases, a pH sensor can be used to measure the partial pressure of CO_2 in the stomach. Certain disorders can also induce physical variables within the biological system, such as changes in temperature and pH. The production of dual-stimulus responsive polymeric systems involves copolymerizing monomers with these functional groups or by developing a new type of monomers that can respond simultaneously to two stimuli [19].

pH-Sensitive Polymers:

The polyelectrolytes that make up the pH-sensitive polymers have an ionizable group linked to a hydrophobic backbone chain. These ionic functional groups can be basic, like pyridine, amines, and imidazole, or weakly acidic, like sulfonic and carboxylic acids. The net charge and degree of ionisation of the polymer chains are altered by the protonation and deprotonation of these ionic groups. Under specific pH ranges, such ionic functional groups will ionise, which will alter the polymer's structure and cause swelling or dissolution. The carboxylic groups of polyacrylic acid, for example, ionise in a pH media above its dissociation constant (pKa 4.25). The polymer chains' electrostatic repulsion as a result of ionisation can make water swell [20, 21].

Temperature Sensitive Polymers:

The ability of thermoresponsive polymers to change from a solution to a gel state above a specific temperature gives them a special quality. It is also possible to modify these polymers to exhibit a sol gel transition at a specific temperature. The two kinds of thermoresponsive polymers are negative temperature-sensitive polymers and positive temperature-sensitive polymers are distinguished by how they react to varying temperatures. Poly(N-isopropyl acrylamide) (PNIPAM), a negative temperature-responsive polymer, becomes insoluble above its critical temperature, also known as the lower critical solution temperature (LCST). Applications of PNIPAM are limited because of its toxicity. Nevertheless, other thermoresponsive materials are now being developed using the insights gathered from PNIPAM research. Nowadays, poly(N-vinyl caprolactam) [PNVCL] is seen as a promising substitute because its LCST is similar to that of PNIPAM.

Mucoadhesive Polymers:

Mucoadhesive polymers have properties that make it easier for them to interact with mucus. These polymers' chain flexibility is appropriate for mucus's ionic strength and pH. Water-soluble and water-insoluble polymers are both possible for mucoadhesive polymers. These polymer networks are swellable and are bonded together by cross-linking agents through a variety of mechanisms, such as mucus and polymer interpenetration, mutual adsorption, and wetting. Collagen, albumin, and gelatin are examples of natural mucoadhesive polymers. Polysaccharides include hyaluronic acid, alginates, chitosan, dextran, agarose, starch, and cellulose.

Furthermore, polyesters such as PGA, polyhydroxy butyrate, PLA, PCL, polydioxanone, polyanhydride, polyadipic acid, polyterphthalic acid, polysebacic acid, PAs, cellulose derivatives, silicones, and poloxamines are examples of synthetic mucoadhesive polymers. Mucoadhesive polymers can be formed as gels, tablets, lozenges, wafers, films, pessaries, viscous solutions, nano and micro particulates, in situ gelling systems, sprays, and suspensions. These polymers are employed in drug delivery systems. The majority of the dosage forms previously mentioned include polymeric excipients, which play a significant part in the mucoadhesive quality of the formulation.

Bioadhesives Polymers:

Polymers that are bioadhesive can adhere to particular biological locations, including epithelium tissues. For a considerable amount of time, bioadhesive polymers have been utilised in a variety of biomedical applications, including surgical and denture adhesives. The primary benefit of these polymers is their capacity to generate noncovalent binding to the mucosal tissue, which extends the time the drug remains at the site of polymeric material attachment. Since 1980, there have been bioadhesive polymer imitations on the market, particularly for topical use in the gastrointestinal system and oral cavity (GIT). Nonetheless, different mucosal surfaces, such as the vaginal mucosa, have been the focus of bioadhesive formulation development.

Vaginal delivery products on the market, like Postin E2 pills that contain dinoprostone for inducing labour and Medabon tablets that contain misoprostol for terminating pregnancy, contain polysaccharides like maize starch and microcrystalline cellulose. Investigations are being conducted on the vaginal delivery of chitosan and other polysaccharides in various formulations (e.g., solution, gel, pill, and insert) [22].

BIODEGRADABLE POLYMER:

Biodegradable polymers have gained popularity over the past 20 years as a means of delivering drugs orally as well as proteins and peptides during oral vaccinations. Both natural and artificial biodegradable polymers have a number of benefits, including tissue compatibility, biodegradability, low toxicity, and prolonged release properties when used in conjunction with particular target-oriented delivery strategies. Biodegradable polymers have a wide range of uses, including oral

immunisation and innovative drug delivery systems. When considering the use of different biomolecules, such as proteins and peptides, for oral vaccination, biodegradable polymers are important because they shield these substances from the harsh acidic environment of the stomach or provide sustained release, which can help lower the frequency of oral vaccination (either booster or maintenance dose). These kinds of tactics have been used in the treatment of autoimmune disorders including atrophic rhinitis and water-borne illnesses like cholera. One of the main concerns with oral delivery of many medicinal compounds is bioavailability. Drugs with low solubility and minimal permeability through biological membranes have problems with oral bioavailability. However, in addition to these two factors (solubility and permeability), presystemic metabolism can also have a substantial impact on the bioavailability of therapeutic compounds [5].

Before entering the systemic circulation, medications taken orally [apart from those meant to be taken buccal and sublingual] often need to transit through the liver's portal circulation and intestinal wall. Drugs are considerably metabolised by hepatic and intestinal enzymes, which might lead to low bioavailability since the necessary plasma concentration for the intended therapeutic response may not be reached. Studies are being conducted on the significance and contrast between the functions of intestinal and hepatic enzymes in the bioavailability of different medicinal compounds. According to the research, intestinal enzymes play a more significant part in pre-systemic metabolism than hepatic enzymes due to the liver's comparatively higher blood supply than the intestine's. Because the digestive tract has a longer residence time for therapeutic molecules than the liver, medications stay in contact with intestinal enzymes longer, which increases metabolism and decreases bioavailability [23].

Biodegradable polymers have demonstrated a multitude of encouraging uses in enhancing the bioavailability of medicinal compounds that have low bioavailability. Although curcumin from turmeric (*Curcuma longa*) has many health benefits, its therapeutic effectiveness is limited by its low solubility in water. Curcumin has low bioavailability because of its hydrophobic nature. Encasing curcumin in biodegradable polymer preparations such as cyclodextrin-encapsulated curcumin and PLGA-curcumin [poly lactic acid-co-glycolic acid curcumin] has effectively changed its bioavailability.

Biodegradable polymers have been effectively used to encapsulate a number of bioactive compounds that are beneficial in treating various diseases. This has led to enhanced bioavailability, controlled release, targeted distribution, and a decrease in adverse effects. To prevent side effects from arising from systemic delivery of the drug alone into the vitreous cavity, Gomez-Gaete et al. encapsulated dexamethasone into biodegradable poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles. Both the targeting efficiency and medication retention in the vitreous cavity were enhanced by the created nanoparticulate delivery technology.

In the past ten years, microencapsulation with polymer matrices has gained a lot of popularity. Salmonella typhi outer membrane proteins have been protected from degradation in an acidic environment and their mucosal immunity has strengthened thanks to PLGA microencapsulation. Strong B cell responses specific to S. typhi were induced by the PLGA-encapsulated vaccine. Following oral vaccination administration, the polymeric micro- and nanoparticles have demonstrated a marked improvement in both the mucosal and systemic immune responses. Additionally, it is shown that oral antigen delivery stimulates B and T cell mediated immune responses at the mucosal location where the antigen is approaching as well as in various other immunological components [24].

PREPARATION OF MICROCAPSULES (PHYSICOCHEMICAL TECHNIQUES):

Coacervation and Phase Separation:

In order to deposit polymer around the center, the "coacervation" process modifies the medium's physicochemical properties, including its pH, polarity, ionic strength, and medium temperature. Complex coacervation is the term used to describe the presence of opposing charges for two or more molecules. There is only one macromolecule involved in the basic conservation process. The acervation method is easier, less costly, and doesn't call for organic solvents or high temperatures. This technique usually works well for covering up flavored oils. One of its main drawbacks is that the coacervation only happens at low pH, colloidal, and/or electrolyte concentrations [25]. Coacervation and phase separation shown in the Fig 3.

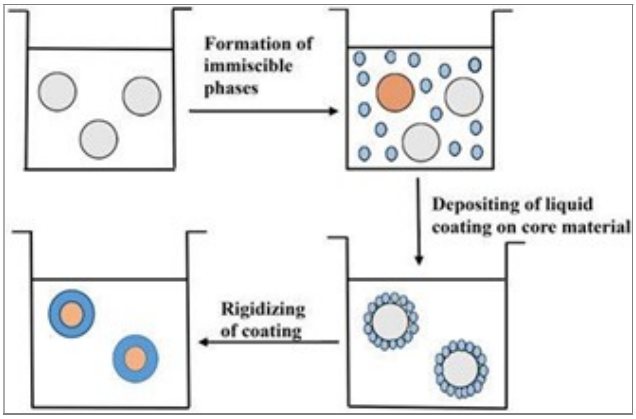

Fig 3. Coacervation and phase separation.

Examples:

- Soy protein coating coated with sweet orange oil.
- Micro embedded B. L. and lactis. When acidophilus is combined with coating materials like pectin and casein, it may more effectively withstand the in-process product from liquids and juices from the stomach and intestine region.
- Aspartame is co-encapsulated which improves protection up to 80°C.

Supercritical Fluids Quickly Expand to Encapsulate Polymer:

Supercritical fluids, which are highly compressed gases, have a number of advantageous liquid and gas features. The most often used are supercritical carbon dioxide, nitrous oxide, and alkanes (Carbon no. 2 to 4). At the critical point, a small change in stress or temperature causes a large change in the supercritical liquid volume. In addition to being non-toxic and non-flammable, supercritical carbon dioxide is frequently helpful at low critical temperature values. It is also widely accessible, very pure, and reasonably priced [26].

Supercritical Approach Quick Expansion:

In this procedure, the supercritical fluids containing the coat material and API are kept at high pressure before being released at atmospheric pressure through a small nozzle. A coating material film is created on the API by the shell content dispersing and dissolving due to the abrupt drop in stress. The drawback of this approach is that the coating material content and the API must both be significantly soluble in supercritical fluids. Furthermore, relatively few tiny stable energy density polymers exist [e.g., polymethacrylates (PMA) and polydimethylsiloxanes (PDMS). Among the liquids in that are carbon dioxide soluble. Utilising co-solvents can improve the polymer's solubilization in the solvent. Non-solvents are useful in certain situations because they improve solubilization in supercritical fluids, but dissolving shell material at atmospheric pressure is challenging. Previously, ethanol was used as a polymer shell non-solvent, such as polyethylene glycol (PEG) or methyl methacrylate, for the RESS microencapsulation of TiO2 nanoparticles.

***Application of Gas Antisolvent [Gas] Process*:**

Supercritical fluid with anti-solvent (SAS) is exclusive to this technique. In that case, an API and a shell material solution are combined with supercritical fluid, which is maintained at an excessively high pressure [as required by the procedure]. The result is an increase in solvent size, which causes supersaturation and causes the solute to precipitate. As a result, the solution needs to become soluble in water; it should not be diluted in an oil and supercritical fluid mixture. However, the liquid solution and the supercritical fluid should dissolve in one another. Water-soluble components are not well suited for this system since liquids do not dissolve well in supercritical fluids. This technique can be used to create particles in the submicron range.

***Gas-Saturated Solution Particles (GSSP)*:**

Using high-pressure supercritical fluid, the core and shell components are combined in this approach. During this process, supercritical liquid enters the shell material and causes expansion. When the solution is heated above the glass phase, the polymer liquefies. After the stress is removed, the shell content can collect on the active ingredient. It is possible that in this phase the materials in the super-critical liquid's centre and shell won't dissolve [27].

CHEMICAL METHODS FOR MICROCAPSULE PREPARATION:

Polymerization:

***Interfacial Polymerization [IFP]*:**

Two common types of monomers are multifunctional acid chlorides and multifunctional isocyanates. It will be applied collectively or independently. The multifunctional monomers will dissolve in a liquid core material and then scatter it in the water phase using the dispersing agent. The mixture is treated with an amine co-reactant with multiple functions. Accelerated surface polymerization and the formation of capsule shells are the outcomes. A polyurea shell is created when isocyanate interacts with an amine, poly nylon, or polyamide shell. It also occurs when acid chloride reacts

with an amine. As the isocyanate reacts with the hydroxyl that contains the monomer, a polyurethane layer is formed. For instance, diammonium hydrogen phosphate was enclosed by a polyurethane urea membrane with an interfacial polymerization technique.
Based on basic examination calculations, it was discovered that a microencapsulated powder form production with a content packed of 62 % DAHP had an elevated synthesis yield (22 %). DAHP microcapsules are typically 13.35 mm in size. Moreover, 95% of the molecules were less than 30.1 mm in diameter [28].

***Polymerization in situ*:**
When applied to the embodiment framework, the monomers' polymerization activity causes the container shell to structure similarly to IFP. Receptive experts are not extensively used in the framework. Only in the framework's continuous stage and on the stage side of the interface created by the ceaseless stage and diffuse centre can polymerization take place. Formaldehyde reagent in water is used to generate the shell material, carboxy-functionalized magnetic microcontrollers are used to prepare the solution, and a large number of lipophilic liquids are first capsulated to create a strong capsule shell. A pre-polymer with a low molecular weight is the end result of this [29].

***Solvent Evaporation*:**
The pharmaceutical industry frequently uses solvent evaporation microencapsulation to deliver drugs with controlled release. With a particular release profile, the polymer microspheres that were created with trapped material within will eventually break down and release the substance that was enclosed [30].

PHYSICAL MECHANICAL METHODS:

Spray Drying:
This method entails the creation of structures such as emulsions, suspensions, arrangements, and dividers that are then nebulized in a sightseeing circulation chamber. The water instantly evaporated when it came into contact with the heated air, and the material enveloped the heart. Compared to other techniques, atomization has the following advantages: a large number of facilities are available, a variety of microencapsulating agents may be used, and subsequently large-scale output may be possible, simple machinery, reasonable performance, lower transportation and storage costs, and cost-effective manufacture. The creation of unevenly made items is the main disadvantage of atomized [31].

One of the most widely used microencapsulation techniques, spray drying has been around for ten years. It is mainly used to microencapsulate flavouring agents, fats, and pigmenting agents. However, it can also be used for temperature-sensitive materials like microbes and essential oils, where it can be limited to the necessary elevated temperature that allows the material to volatilize and/or destroy.
Spray-drying cardamom oleoresin in gum Arabica, maltodextrin, and modified starch successfully microencapsulated the taste of sumac in salt-tasting cookies, salads, and crackers. This enhanced the safety of oleoresins. Raspberry juice with optimal probiotic microencapsulation achieved through 91.15 % spray drying.
Spray-drying fats in potato starches, tapioca, and maize has effectively encapsulated the fats, preventing any conflicts between the encapsulated components and the wall [28]. Spray drying process shown in the Fig 4.

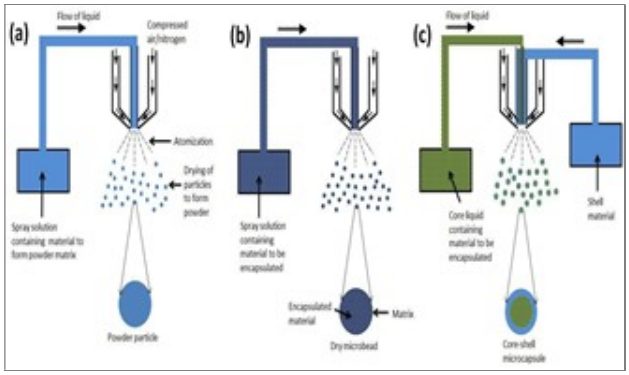

Fig 4. Spray drying.

Spray Cooling / Congealing:
Spray microencapsulation focuses on cold air injection to promote particle solidification. Microparticles are made up of a mixture of droplets made up of the base and surface components. Low-temperature air flows through a hollow after the atomizer nebulizer the fluid. The product solidifies in the structure as a result of temperature decreases, encapsulating the substance. The result is accelerated surface polymerization and capsule shell development. If isocyanate interacts with the amine, poly nylon, or polyamide shell and an acid chloride reaction takes place with the amine, a polyurea shell will form on top of the core material.
As the isocyanate reacts with the hydroxyl that contains the monomer, a polyurethane layer is formed. For instance, encapsulated (DAHP) by a polyurethane urea membrane by an interfacial polymerization procedure. By using elementary examination, a microcapsule

powder with a fill content of 62 weight percent of DAHP was created with an elevated synthesis yield (22 %). The average size of DAHP microcapsules is 13.35 mm. Furthermore, the best encapsulation engineering is said to be spray cooling microencapsulation since it uses lower temperatures and a high scale-up capacity. Microparticles might, nevertheless, provide certain processing challenges, such as limited centre expulsion and encapsulation capability. Minerals and vitamins were mostly encapsulated by spray chilling. Microencapsulated tocopherols in a lipid matrix using spray cooling, with encapsulation quality levels above 90 %. Using salt from hydrogenated palm oil, magnesium, iodine, and retinol were added to create microcapsules that were created by spray chilling. Microcapsules that have been collected are more stable, and no differences in perception have been noted. Through spray chilling, it has been demonstrated that the encapsulating agent maltodextrin effectively inhibits linseed oil oxidation [9]. Spray cooling / congealing process shown in the Fig 5.

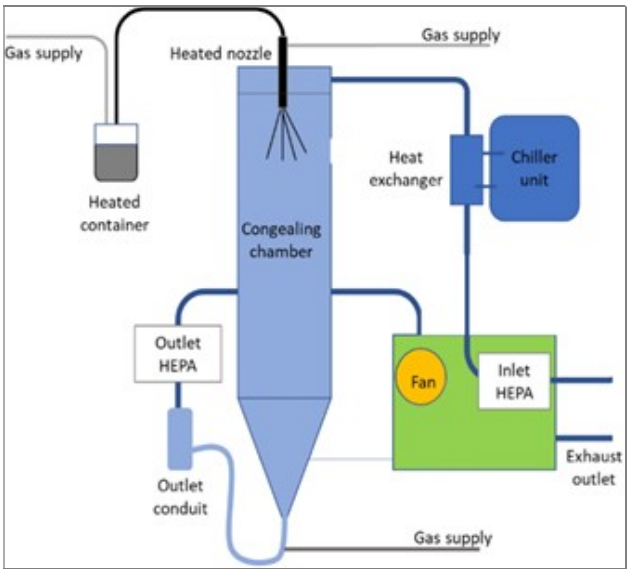

Fig 5. Spray cooling / congealing.

Fluidized Bed Technology:

The particles are covered in water, and rapid dissipation creates an outside surface in most cases. As needed, the coating formulas and thickness can be gathered. There are three different kinds of liquid mattress coaters: tangential, foundation, and top spray. In the top spray process, the cover surface is drawn down into the liquid bed, allowing hard or porous particles to be incorporated into the sheet region. The uneven streams of surface materials and particles enable improved enclosure performance and cluster development protection. The arrangement of the covering substance determines how the covered particles drip. Fluid-bed coaters with a spray nozzle at the top produce more particle scores than by tangential or lower sprays. Fluidized bed technology process shown in Fig 6.

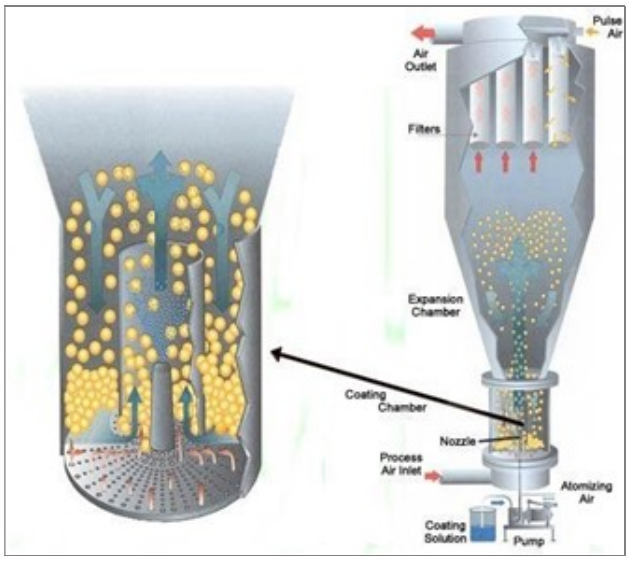

Fig 6. Fluidized bed technology.

DETAILS OF CERTAIN OTHER METHODS OF ENCAPSULATION:

Extrusion:

This is centred on a polysaccharide gel associated with multivalent ions that immobilises the centre. In order to extrude, the kernel must be inserted into a sodium alginate solution. Next, a combination must be squeezed through a syringe or pipette of reduced calibre to fall extrusion into a hardening liquid, like calcium chloride. One limitation of this method is the relatively big extrusion particles (about 500–1,000 mm), which makes it unsuitable for usage in situations where mouth filling is crucial. As such, wall products for extrusion encapsulation are extremely restricted. L. Tiny. L survival rates are enhanced by calcium alginate gel acidophilus and extrusion-resistant starch. After digesting acidophilus in Iranian white savoury milk for six months. Extrusion-based β-cyclodextrin microencapsulation has been demonstrated to provide an active oxidation remedy.

Lyophilization:

Under the sublimation vacuum cycle, which extracts compound water without applying high temperatures for testing, frozen compounds become dehydrated. Since it reduces extreme temperature changes and is frequently

employed in essences or fragrances, this procedure yields high-quality products. The high expenses and laborious considerations hamper the commercial application. Extra virgin olive oil is microencapsulated when maltodextrin, carboxymethylcellulose, and lyophilizing are present. This means that the oil has been shake-free for nine to eleven months, extending its shelf life. Garcinia extract is encapsulated using lyophilization, whey protein separation, and maltodextrin. This results in a product with improved volume, finer crumb consistency, eye-catching colour, and pleasing sensory attributes [28].

EVALUATION PARAMETER

The pharmaceutical sector uses the intriguing technique of microencapsulation to envelop or contain different components [solids, liquids, or gases] in a continuous layer of polymeric materials. The resulting minuscule particles can have sizes ranging from several hundred microns to less than one micron [32]. Schematic representation of the factors influencing the properties of microcapsules shown in the Fig 7 [33] .

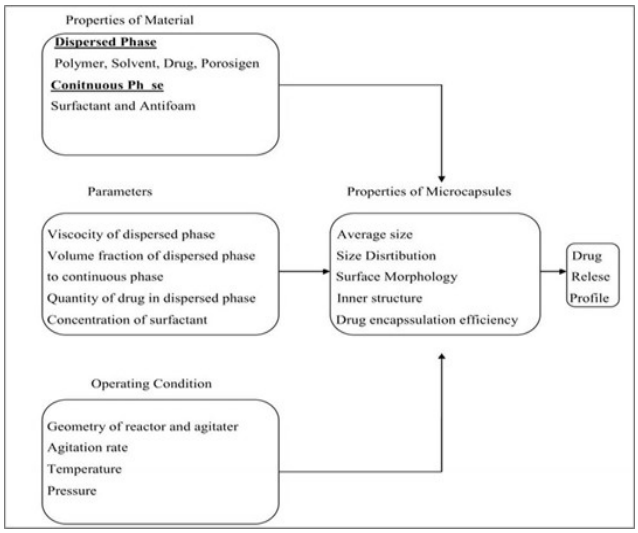

Fig 7. Schematic representation of the factors influencing the properties of microcapsules.

Process Variables and Parameters [32,34]:

- Core Material:
  - Density, surface area, melting point, solubility, friability, crystallinity, and flowability.
- Coating Material:
  - Concentration and rate of application.
- Air Volume:
  - Required for support and fluidization during the process.
- Amount of Coating Material:
  - Determines the thickness of the coating.
- Temperatures:
  - Inlet and outlet temperatures influence the process.

APPLICATIONS OF MICROENCAPSULATION:

- Microencapsulation is widely used for masking the organoleptic properties like taste and odour of many drugs.
- The drugs can be protected which are sensitive to moisture, light and oxygen. e.g.: Nifedipine
- It prevents the incompatibility between the drugs.
- The drugs which are volatile in nature may vaporize at room temperature like Aspirin and Peppermint oil can be prevented by micro encapsulation.
- It is also used in thermal energy storage [35].
- It is used for the sustained release or prolonged action of drugs [36].
- Cell immobilization in plant cell cultures microencapsulation, provides cell natural environment, and 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.
- It is the most acceptable technique in the food industry like production of yoghurt from propolis extract [37].
- Beverage production Using immobilization technologies beverage products are beer, wine, vinegar and other food drinks production to boost yield, improve quality, change aromas, etc. [38].
- It is used in manufacturing of powders and suspensions.
- Immobilization of microbes and microorganisms to prevent oxidative degradation.
- Is used to separate incompatible substances.
- It protects the gastrointestinal tract.
- It is used in genetic engineering [14].
- Microencapsulation is used to lessen the potential danger of toxic substance handling. The toxicity owing to handling of herbicides, insecticides, pesticides and fumigants, etc., can be usefully lessened after microencapsulation [38].

CONCLUSION:

In conclusion, microencapsulation is a crucial technique in the field of novel drug delivery systems (NDDS). By encasing active medicinal ingredients in protective shells, microencapsulation offers numerous advantages that enhance patient compliance, stability, and the effectiveness of medicine delivery. One of the key benefits of microencapsulation is its ability to protect drugs from degradation and ensure their stability throughout storage and transportation. This extends the shelf life of medications and reduces the need for preservatives, both of which may be harmful to patients. With the aid of microencapsulation, medications can be administered to specific sites inside the body, improving their efficacy and reducing systemic exposure and associated toxicity. This targeted approach has considerable promise for treating various conditions, including cancer, where precise medication localization is essential.

Additionally, by improving the solubility and bioavailability of poorly soluble medications, microencapsulation makes it possible to formulate them. This creates new opportunities for drug development, especially for drugs with difficult physicochemical characteristics. Microencapsulation has enormous potential to revolutionize drug delivery and therapy and maybe enhance healthcare outcomes globally as long as research and innovation in this field continue.

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