Designing natural polymer based capsules and spheres for biomedical applications- A review

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ABSTRACT : Natural polymers, such as polysaccharides and polypeptides, are potential candidates to serve as carriers of biomedical cargo. Natural polymer-based carriers, having a core–shell structural configuration, offer ample scope for introducing multifunctional capabilities and enable the simultaneous encapsulation of cargo materials of different physical and chemical properties for their targeted delivery and sustained and stimuli-responsive release. On the other hand, carriers with a porous matrix structure offer larger surface area and lower density, in order to serve as potential platforms for cell culture and tissue regeneration. This review explores the designing of micro- and nano-metric core–shell capsules and porous spheres, based on various functions. Synthesis approaches, mechanisms of formation, general- and function-specific characteristics, challenges, and future perspectives are discussed. Recent advances in protein-based carriers with a porous matrix structure and different core–shell configurations are also presented in detail. Capsule coatings have a wide range of applications as they afford protection to active pharmaceutical ingredients. However, few studies have focused on capsule coating owing to the sensitivity of hard gelatin shells to solvents and high temperature. In the present study, we aimed to coat capsules using two thermoforming coating techniques: vacuum forming coating (VFC) and centrifugal forming coating (CFC). Rheological and mechanical properties were investigated to comprehensively elucidate the processes and mechanisms underlying the two coating techniques. The corresponding coating integrity and drug release behavior were characterized and compared. Herein, we observed that a lower temperature was more suitable for the VFC process than the CFC process. The drug release rate decreased with the film thickness increased. Both optimal VFC and CFC capsules revealed a 24 h sustained-release property following Fick's diffusion law. The coating thickness distribution was more homogeneous for the VFC capsule than the CFC capsule. With the advantage solvent-free of functional capsule coatings, thermoforming coating techniques are convenient and efficient solutions for small scale personalized coating of oral solid preparations.

Keywordes: Natural po;ymer, Generation, Biomedical, Biodegradation, Therapeutic use, Capsule formation.

I. INTRODUCTION

The field of biomedical engineering has witnessed a surge of interest in the development of innovative drug delivery systems and biomedical devices. Among these, natural polymer-based capsules have garnered significant attention due to their unique properties and versatile applications in targeted drug delivery, tissue engineering, and diagnostic imaging. Natural polymers, derived from renewable sources such as plants, animals, and microorganisms, offer distinct advantages over synthetic counterparts, including biocompatibility, biodegradability, and low immunogenicity[1]. In recent years, the design and fabrication of natural polymer-based capsules have evolved rapidly, driven by advances in polymer science, nanotechnology, and biomaterials engineering. These capsules, typically ranging from nano to microscale in size, can encapsulate a wide range of therapeutic agents, including small molecules, proteins, nucleic acids, and cells[2]. Moreover, their tunable physicochemical properties allow for precise control over drug release kinetics, enabling sustained release profiles tailored to specific therapeutic needs.This introduction sets the stage

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for exploring the various aspects of designing natural polymer based capsules, including the selection of suitable polymers, encapsulation techniques, core materials, and functionalization strategies. By harnessing the unique properties of natural polymers and leveraging innovative fabrication methods, researchers aim to develop next-generation drug delivery systems with enhanced efficacy, reduced side effects, and improved patient outcomes. In this review, we delve into the principles, advancements, challenges, and future prospects of designing natural polymer-based capsules for biomedical applications[3]. Conventional drug therapy involves administering the drug or pharmaceutical agent directly into the body, through oral, pulmonary, or parenteral routes. However, several demerits to this approach are the rapid release of the drug into the body at the site of administration, loss of drug dose on the way from the site of administration to the target site (due to biological degradation), the requirement for administering higher doses of the drugs to compensate for this loss, higher chances of over- or under medication, side effects due to the interaction of the drugs with untargeted sites, the requirement of frequent dosing, lower drug bioavailability, lower per-unit cost (but higher overall healthcare cost), and higher total dosage requirement into the body[4]. These demerits have led to the need for a different approach, which involves transporting the active pharmaceutical cargo (APC) and releasing it to the targeted (or affected) site in the body for therapeutic effect via drug delivery agents. Such a therapeutical approach has enabled the site-specific, slow, sustained, and controlled release of drugs, thus improving their bioavailability, pharmacokinetics, and increased efficacy, as well as minimizing the side effects to the untargeted sites and overall risk to the patient, thereby reducing the overall medication cost, due to the decreased frequency of drug administration and increasing patient compliance[5].

II. GENERATION OF DRUG DELIVERY:

1. FIRST GENERATION: The first generation of drug delivery (1950–1980) involved the study of controlled-release mechanisms and development of oral and transdermal sustained-release systems. Eventually, the first controlled delivery device, based on silicone rubber for delivering the drug isoproterenol, was reported in 1964 for its potential application as implants to treat heart block. This was followed by several studies on developing a variety of polymeric and liposomal systems for the controlled release of various drugs and their underlaying release mechanisms[6]. Describe conventional drug delivery methods such as oral tablets, capsules, and injections. Discuss their limitations and the need for further innovation[7].

2. SECOND GENERATION : The second-generation drug delivery (1981–1990) was basically focused on the study and development of constant-release, self-regulated drug delivery systems, and nanoparticle -based drug delivery systems. During this era, many sustained-release drug formulations (drugs-DDS), based on polymeric nanoparticles (Adagen, Gliadel, Copaxone), polymeric implants (Zoladex), liposomal carriers (Doxil, Abelcet), dendrimer-conjugates, and protein-based nanoparticles (Abraxane), were clinically tested and approved by the FDA[8]. The past decade has been focused on designing smart, stimuli responsive systems for targeted drug delivery[9]. These systems have been shown to actively deliver the drug to the target site and enable controlled drug release by undergoing physical and/or chemical changes, in response to biological or external triggers[10]. Examine modifications and improvements to conventional systems, including controlled-release formulations, transdermal patches, and liposomal formulations[11].

3.THIRD GENERATION: The third generation of drug delivery systems emerged primarily in (1991-2000)[12] . However, the exact years can vary depending on the specific technologies and advancements considered within this generation. Generally, the development and adoption of targeted drug delivery approaches, such as ligand-targeted systems and nanoparticle-based delivery, gained momentum.Research and innovations in this area continue to evolve, with ongoing efforts to improve precision, efficacy, and safety in drug delivery[13].

4.FORTH GENERATION: The concept of fourth-generation drug delivery systems is relatively recent and represents the cutting edge of drug delivery technology[15]. While there's no fixed timeframe for the fourth generation, it's typically associated with advancements in nanotechnology, biomaterials, and personalized medicine, which have gained significant attention since the early 2000s[14].

III. CORE MATERIALS FOR ENCAPSULATION:

In the past few decades, a wide variety of konovel drug delivery approaches, in the form of micro- and nanoparticles (core–shell capsules, as well as matrix-type spheres), transdermal patches, gels, dendrimers, micelles, microneedles, and microfluidics-based devices have been developed[16] .

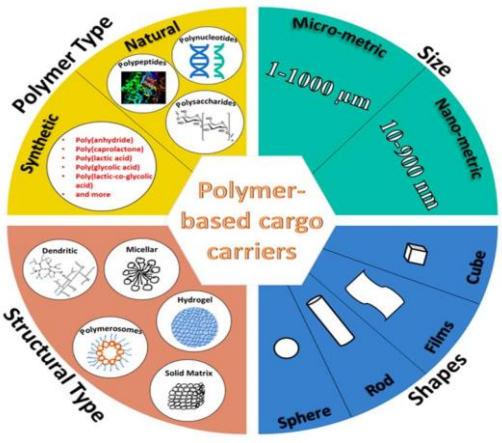

Figure-1: Core materials for encapsulation

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These were usually made of synthetic polymers (such as poly-lactic glycolic acid), natural polymers (such as polysaccharides, polypeptides, and polynucleotides) , liposomes, metallic formulations, metal oxides, carbon nanotubes, etc., aimed at a variety of functions, including site-selective, active, or passive targeted delivery of a wide variety of drugs for treating diseases, such as cancer and diabetes. Several parameters, such as the material of fabrication, size, shape, structural configuration, and surface characteristics of these APC carrier systems (ACSs), play a major role in their interaction with the in-vivo chemical environment, while passing, from the site of administration to the site of action, their function and in-vivo biodistribution. As such, these parameters are considered vital to designing better and smarter ACSs.

•Natural polymer utilized to develop biomedical carriers

POLYMER:

1. Polysaccharides:

1.1. Cellulose: It's found in plants and gives them structure and strength.Using cellulose as a natural polymer in biomedical capsules is a smart way to make use of its properties.

1.2. Alginate: It is derived from seaweed.Alginate is a natural polymer commonly used in pharmaceuticals, and textiles. It's known for its ability to form gels and films, making it useful in applications like food thickening, drug encapsulation, and wound dressings.

1.3. Pectin: The ability of pectin to form pH-sensitive and stimuli-responsive matrices further enhances its utility in controlled drug release formulations, enabling tailored drug delivery in response to specific physiological conditions.

1.4. Gellan Gum: It's derived from bacteria and has a unique ability to create gels at low concentrations.Gellan gum can be used as a polymer in certain applications, including as a capsule for encapsulating and delivering active ingredients. Its gel-forming properties make it suitable for creating controlled-release systems, where the active ingredient is gradually released over time.

1.5. Gum Arabica: Gum arabic, also known as acacia gum, is a natural gum derived from the sap of the Acacia tree.Gum arabic can be used as a polymer in certain applications, including as a capsule for encapsulating and delivering active ingredients. Its natural adhesive properties and ability to form a protective coating make it suitable for this purpose[17].

1.6. Gaur Gum: Gaur gum, also known as guar gum, is a natural gum derived from the seeds of the guar plant.Guar gum can be used as a polymer in certain applications, including as a capsule for encapsulating and delivering active ingredients. Its gel-forming properties make it suitable for creating controlled-release systems, where the active ingredient is gradually released over time[18].

1.7. Starch: It's a common carbohydrate found in many plants, like potatoes, corn, and wheat.Starch including drug delivery systems, encapsulation of active ingredients, and controlled release of substances. Capsules provide protection to the encapsulated material and can release it in a controlled manner[19].

1.8. Chiten: It's a fascinating substance found in the exoskeletons of crustaceans, insects, and the cell walls of fungi.Chitin can indeed be used as a polymer capsule[20]. Its unique properties make it suitable for encapsulating and delivering active ingredients in various industries. The chitin capsule provides protection to the encapsulated material and can release it in a controlled manner[21].

1.9. Carrageenan: It's a natural ingredient extracted from red seaweed.These polysaccharides can encapsulate and deliver active ingredients in a controlled manner[22].

1.10. Chitosan: It's a natural polymer derived from chitin, which is found in the exoskeletons of crustaceans[23]. Chitosan has various applications, including its use as a polymer capsule. It can be used to encapsulate and deliver active ingredients in a controlled manner, similar to other polymer capsules. Chitosan capsules have been studied for their potential in drug delivery systems[24].

1.11. Dextran: Dextran is sometimes used as a polysaccharide in capsule formation. It's valued for its ability to create a protective coating for drug delivery systems, helping to control the release of the active ingredient[25].

1.12. Xanthan gum: It's a polysaccharide that is commonly used as a thickening and stabilizing agent in various food products[26]. It's derived from the fermentation of sugars by the bacterium Xanthomonas campestris.Xanthan gum is mainly known for its applications as a thickener and stabilizer in food products. However, there are other materials, like polymers, that are commonly used for capsule production. These capsules can be used to encapsulate and deliver active ingredients[27].

1.13. Shellac: Shellac is a natural polymer derived from the lac beetle and is used as a coating material for pharmaceutical capsules. It provides a protective layer, enhances stability, and facilitates swallowing[28].

1.14. Pullulan: Pullulan is a polysaccharide produced from starch by certain fungi. It is utilized in the pharmaceutical industry as a capsule material, particularly for vegetarian and vegan capsules[29]. Pullulan capsules are known for their stability, solubility, and low moisture content, making them suitable for encapsulating various drugs and dietary supplements[30].

1.15. Cashew gum: Cashew gum, derived from the exudate of the cashew tree, has been explored for various pharmaceutical applications, including as a potential material for capsule formation. It offers adhesive properties and has been studied for its potential as a binder

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and coating agent in drug delivery systems[32]. However, its use in capsule formation may be less common compared to other materials like gelatin or cellulose derivatives. Research into its suitability and practical application in capsule formation continues[31].

2. Polypeptides

2.1. Egg albumin: Egg albumin, derived from egg whites, is sometimes used in capsule formation, particularly in the production of certain types of pharmaceutical capsules. It provides a protein-based alternative to gelatin capsules and can be suitable for specific dietary or religious restrictions. However, its use may be less common compared to other capsule materials[33].

2.2. Casein: Casein, a protein found in milk, is commonly used in capsule formation in pharmaceuticals[34]. While it has been explored for various applications in drug delivery systems due to its biocompatibility and controlled release properties, it is typically used in other forms such as nanoparticles or as a coating material rather than as a capsule material itself[35].

2.3. Gelatin: Gelatin is one of the most commonly used materials in capsule formation. It's a protein derived from collagen, usually sourced from animal bones and skin[36]. Gelatin capsules are widely used in the pharmaceutical industry for encapsulating medications, supplements, and vitamins. They are preferred for their ease of manufacturing, compatibility with a wide range of drugs, quick dissolution, and bioavailability. Gelatin capsules come in various sizes and colors, and they can be filled with both solid and liquid formulations[37].

2.4. Keratin: Keratin, a fibrous structural protein found in hair, nails, and skin, is not commonly used in capsule formation in the pharmaceutical industry. While keratin-based materials have been explored for various biomedical applications, including drug delivery systems, they are typically utilized in other forms such as hydrogels, nanoparticles, or as coatings rather than as capsule materials themselves[38].

2.5. Elastin: Elastin, another fibrous protein found in connective tissues like skin and blood vessels, is not commonly used in capsule formation in the pharmaceutical industry[60]. While elastin-based materials have been studied for potential biomedical applications, including tissue engineering and drug delivery, they are typically utilized in other forms such as hydrogels or scaffolds rather than as capsule materials themselves[55].

2.6. Soy protein: Soy protein is commonly used in capsule formation in the pharmaceutical industry. While soy protein has various applications in food and dietary supplements, it is not typically used as a capsule material. However, soy protein may be utilized in pharmaceutical formulations for its potential as a binder, filler, or coating agent in tablet manufacturing or as a component in drug delivery systems[50].

2.7. Resilin: Resilin, a rubber-like protein found in insects, particularly in their elastic tissues such as wings and joints, is not commonly used in capsule formation in the pharmaceutical industry[44]. While resilin has remarkable elastic properties and has been studied for potential biomedical applications, including as a biomaterial for tissue engineering and drug delivery, its use in capsule formation is limited due to its source and specialized properties[39].

2.8. Gliadin: Gliadin, a component of gluten found in wheat and other grains, is not commonly used in capsule formation in the pharmaceutical industry[40]. While gliadin has been studied for its potential as a biomaterial, particularly in drug delivery systems, it is typically utilized in other forms such as nanoparticles, films, or coatings rather than as a capsule material itself[45].

3. Hyaluronic acid:

Hyaluronic acid is commonly used in capsule formation in the pharmaceutical industry[49]. While it is widely used in various biomedical applications, including tissue engineering and ophthalmic formulations, it is typically utilized in other forms such as gels, creams, or injections rather than as a capsule material[47].

4. Phospholipids

4.1. Liposome: Liposomes are commonly used in pharmaceuticals as a drug delivery system. These are spherical vesicles composed of lipid bilayers, mimicking the structure of cell membranes[41]. They can encapsulate both hydrophilic and hydrophobic drugs, providing targeted delivery, improved drug stability, and controlled release[46]. Liposomes are utilized in various applications, including chemotherapy, vaccine delivery, and cosmetic formulations[43].

5. Polynucleotides

5.1. Ribonucleic acid: In pharmaceuticals, RNA-based therapies are gaining attention for their potential to treat diseases by targeting specific genes or cellular mechanisms. RNA-based drugs can include messenger RNA (mRNA) vaccines, small interfering RNA (siRNA) therapies, and antisense oligonucleotides (ASOs). These therapies hold promise for treating a wide range of diseases, including cancer, genetic disorders, and infectious diseases[42].

5.2. Deoxyribonucleic acid: Deoxyribonucleic acid (DNA) has been explored for its potential use as a natural polymer in pharmaceutical capsule formation[48]. DNA-based materials offer several advantages, including biocompatibility, biodegradability, and the ability to self-assemble into structures. While DNA capsules are not as common as other materials like gelatin or cellulose derivatives, research has shown promising applications for DNA-based capsules in targeted drug delivery, controlled release systems, and vaccine formulations. Additionally, DNA can be modified and engineered to enhance its

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stability, encapsulation efficiency, and targeting capabilities, making it a versatile option or pharmaceutical encapsulation[51].

IV. Encapsulation techniques

1. Spray drying: Spray drying is a technique in which a feed solution, which is a mixture of the core material and the wall material is atomized and formed into a mist inside a chamber, where hot air is applied to convert the mist into powder[58]. Depending on various factors like the characteristics of the feed solution and operating conditions, powder of varied particle size can be produced. In spray drying, the core material, that is, the material of interest gets trapped in the dried powder. Some of the advantages of this method: it can be used for different encapsulating agents, it is economical, flexible, can be used for many different types of materials and can be scaled up easily[52]. Many studies have shown successful implementation of this technique in encapsulation. Spray drying is a technique used to convert a liquid or slurry into a dry powder by spraying the liquid into a hot gas stream. The droplets quickly dry as they fall through the gas, resulting in a fine powder[53]. It's commonly used in the pharmaceutical, and chemical industries for products like capsule, tablets ,drugs in pharmaceuticals.

Some variations include spray drying like-

1.1. Pressure Spray Drying: This variant involves spraying the liquid into a drying chamber at high pressure, which can enhance drying rates and produce finer particles. It's commonly used for heat sensitive materials or when a finer powder is desired[54].

1.2. Centrifugal Spray Drying: In this method, the liquid is atomized using a centrifugal atomizer. The centrifugal force generated breaks the liquid into fine droplets, which then dry in the drying chamber[56].

1.3. Fluidized Bed Spray Drying: This variant combines spray drying with fluidized bed technology. The liquid is sprayed onto fluidized particles in a drying chamber, allowing for efficient heat transfer and uniform drying. It's often used for heat-sensitive materials and to produce agglomerated powders with controlled particle size distribution[57].

1.4. Freeze Spray Drying: In freeze spray drying, the liquid is first frozen into solid particles before being introduced into the drying chamber. This method is suitable for heat-sensitive materials and can produce powders with improved reconstitution properties[58].

1.5. Rotary Atomization Spray Drying: Here, the liquid is atomized using a rotary atomizer, which produces a fine mist of droplets. This method is known for its ability to handle viscous liquids and produce powders with narrow particle size distributions[61]. These variants offer flexibility and can be adapted to meet specific product requirements in various industries such as food, pharmaceuticals, and chemicals. [67].

2). Coacervation:

Coacervation is a simple technique which involves formation of a homogeneous layer of the polymeric wall material around the core material. This is achieved by altering the physicochemical properties of the wall material by change in temperature, pH, or ionic strength[62]. Here, the core material and the wall material are mixed to form an immiscible solution. Then, phase separation is carried out by changing the ionic strength, pH, or temperature to form coacervates, which are tiny liquid droplets, consisting of polymer-rich dense phase[63]. These coacervates then surround the core material, forming the microcapsules. Electrostatic interaction between two aqueous media is responsible for liquid to gel transition, that is, ionic gelation, hence, leading to the formation of coacervates. This technique is basically used for encapsulating hydrophilic molecules. Such coacervation, which involves only one polymeric material is called simple coacervation[65]. One example of such a polymer can be sodium alginate. In simple coacervation, sodium alginate is dissolved in water and the active compound that needs to be encapsulated, which is usually an oil, is mixed into it and the emulsion formed is released in drops into a gel-forming media like calcium chloride. Ionic interaction between sodium alginate and calcium chloride leads to formation of insoluble polymers, calcium alginate. Several studies have been reported showing successful use of this technique in microencapsulation. Sweet orange oil was encapsulated by Jun-xia et al. (2011) by coacervation using soybean protein isolate (SPI) as the wall material[68]. Coacervation can also involve more than one polymer, then it is called complex coacervation. One common example of complex coacervation includes polymers, gelatin, and alginate. Gelatin is solubilized in water at an acidic pH for obtaining positive charges and alginate is soubilized in water separately at a basic pH to obtain negative charges[66]. The active compound to be encapsulated is mixed into the alginate solution and homogenized properly. This alginate phase is then mixed intensively with the gelatin phase and the temperature is raised until chemical reaction between alginate and gelatin starts. The active compound gets encapsulated by the formation of polycationic-polyanionic insoluble polymer around it. Liu et al. (2010) used complex coacervation method for encapsulation and stabilization of flaxeed oil[69]. Here, gelatin and gum Arabic, the two oppositely charged polymers were used as the wall materials and the deposition of these coating materials around the core was initiated by changing the pH of the medium. However, the use of this method is limited as it best works only within a certain pH range and with certain electrolyte and colloidal solutions[70].

3). Spray cooling: Spray cooling is a technique used for encapsulation, especially in the pharmaceutical and food industries. It involves spraying a hot or warm solution or

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suspension of the material to be encapsulated into a cold or chilled medium. The rapid cooling of the droplets solidifies the material, forming microcapsules or particles with the core material encapsulated within a shell[71]. This method is effective for encapsulating heat-sensitive substances and can be used to produce controlled-release formulations, improve stability, and mask taste or odor. It's commonly employed for encapsulating drugs, flavors, fragrances, and nutritional supplements. Spray cooling method of encapsulation is very similar to spray drying in operation, the major difference being the use of cold air in it. Here, a mixture of core material and wall material is atomized to form a mist inside a chamber, inside which cold air flows. The low temperature within the chamber results in solidification of the micro droplets, leading to the formation of microencapsulated powder. This technique also has a huge potential in scaling up[72].

4). Extrusion: Extrusion technology for encapsulation can be used for producing highly dense capsules. To use this method, the core and the wall material should be immiscible. Here, the core and the wall materials are passed in such a way that the wall material surrounds the core and they are passed through concentric nozzles, thus, forming droplets containing the core surrounded by the wall material. Then solidification is done either by cooling or using an appropriate gelling bath wherein the droplets fall and solidify due to formation of complex[74]. The encapsulates formed using this method are relatively larger in size than formed using any other method and also, this technology is useful with limited wall materials. Extrusion techniques can be used for encapsulation by incorporating the core material within a carrier matrix and then extruding the mixture through a die to form desired shapes or profiles. Here are some common extrusion techniques for encapsulation:

4.1. Co-extrusion: This technique involves extruding multiple materials simultaneously through a single die to create a multilayered structure. The core material, along with the carrier matrix, is fed into the extruder, while additional layers can be added to provide protection, controlled release, or other functionalities[73].

4.2. Microextrusion: Microextrusion involves extruding small-scale structures or particles, typically with diameters in the micrometer range. It's suitable for encapsulating sensitive materials or for producing microcapsules with controlled release properties[75].

4.3. Hot-melt extrusion: Hot-melt extrusion is a process where a mixture of thermoplastic polymers and active pharmaceutical ingredients (APIs) is melted and extruded through a die to form solid dispersions or matrices. This technique is commonly used in pharmaceutical formulation development for controlled-release dosage forms and improved bioavailability[77].

4.4. Spheronization: While not strictly extrusion, spheronization is often used in conjunction with extrusion techniques. It involves shaping extruded material into spherical pellets or beads by tumbling them in a rotating drum. This process is used in pharmaceutical and food industries to produce uniformly sized particles for encapsulation purposes. These extrusion techniques offer versatility and flexibility in encapsulation processes, allowing for the production of a wide range of products with tailored properties and functionalities[76].

5). Emulsification: Encapsulation using emulsification technique is done by dispersing the core in an organic solvent, containing the wall material. The dispersion is then emulsified in the oil or water, to which emulsion stabilizer is added. Encapsulation of the core occurs by formation of a compact polymer layer around it, by evaporation of the organic solvent[78]. This is one of the frequently used techniques of encapsulation as the procedures involved are very simple. This technique is widely used for encapsulating enzymes and microorganisms. Song et al. (2013) reported encapsulation of probiotics in alginate-chitosan using emulsification and demonstrated better resistance of the probiotics under stimulated gastrointestinal conditions. Emulsification techniques are commonly used in encapsulation to disperse one immiscible liquid phase (such as oil) into another (such as water), creating small droplets of the dispersed phase within the continuous phase[79]. Here are some emulsification techniques frequently employed in encapsulation:

5.1. Homogenization: High-pressure homogenization involves forcing the mixture of immiscible liquids through a small orifice at high pressure, resulting in intense shear forces that break the dispersed phase into small droplets. This technique is often used in pharmaceutical and food industries to produce nanoemulsions or microemulsions for encapsulation purposes[80].

5.2. Ultrasonication: Ultrasonication involves the application of high-frequency sound waves to the emulsion, which disrupts the interface between the dispersed and continuous phases, leading to the formation of smaller droplets. Ultrasonication is particularly effective for producing fine emulsions and is used in various industries for encapsulation applications[80].

5.3. Microfluidization: Microfluidization involves forcing the emulsion through a narrow gap or channels at high pressure, causing intense shear and impact forces that break down the droplets into smaller sizes. This technique is suitable for producing stable emulsions with narrow size distributions and is widely used in pharmaceutical and biotechnology applications[85].

5.4. Spinning Disk Processing: Spinning disk processing involves dispersing the dispersed phase onto a rapidly spinning disk or surface, where it is sheared into small droplets by the centrifugal force generated. This technique

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is scalable and can be used to produce emulsions for encapsulation in large-scale industrial applications[81].

5.5. Phase Inversion : Phase inversion techniques involve changing the composition or properties of the emulsion system to induce phase inversion and form emulsions with desired properties. This can include methods such as temperature-induced phase inversion, solvent-induced phase inversion, or pH-induced phase inversion. These emulsification techniques offer precise control over droplet size, distribution, and stability, making them valuable tools for encapsulating active ingredients in various industries, including pharmaceuticals, food, cos metics, and personal care products[81].

V. CROSSLINKING

Cross-linking results in the formation of a pellicle on the internal or external surface of the gelatin capsule shell that prevents the capsule fill from being released. In vitro dissolution testing of cross-linked gelatin capsules can result in slower release of the drug or no release at all.Gelatin capsules are a widely used dosage form both for pharmaceutical drug products as well as dietary supplements. Gelatin in the presence of certain compounds, mainly aldehydes, or in high humidity and high temperature conditions can cross-link. Cross-linking involves covalent bonding of the amine group of a lysine side chain of one gelatin molecule to a similar amine group on another molecule. The covalent bonding is, for practical purposes, irreversible[82].

A). Cross linking in gelatin: The factors that can affect the properties of the gelatin capsule shell include moisture exchange between the shell and the fill material, which can potentially create brittleness in the gelatin shell, and chemical interactions between the fill material and gelatin or between the gelatin and the environment during storage, which can result in gelatin cross-linking. Cross-linking involves strong chemical linkages beyond simple hydrogen and ionic bonding between gelatin chains[84]. One of the strongest and most common types of cross-linking involves the covalent bonding of the amine group of a lysine side chain of one gelatin molecule to a similar amine group on another molecule. This reaction generally is catalyzed by trace amounts of reactive aldehydes. Formaldehyde, glutaraldehyde, glyoxal, and reducing sugars are the most common catalysts. The covalent bonding produced with this type of cross-linking is, for all practical purposes, irreversible, and dissolution of the shell must involve the breaking of other bonds, e.g., by enzyme-mediated breaking of peptide bonds in protein chains. It has been proposed that chemically modified gelatin —by adding succinic acid groups to the lysine side chains—may prevent or at least diminish aldehyde-mediated cross-linking. Another, weaker, type of cross-linking is complexation of free carboxylic acid groups on two different gelatin molecules with trivalent metal ions, such as Fe3+ and Al3+. These cations may be found in some of the dyes used as colorants or as low levels of contaminants in excipients. Higher bloom gelatin, which is normally associated with higher quality, facilitates efficient cross-linking because fewer links are needed to join greater lengths of gelatin chains[88].

Common causes of cross-linking include:

•Aldehydes present in active pharmaceutical ingredients, excipients, packaging materials, or degradants formed in situ during storage.

•High humidity

•Substances that facilitate a cross-linking reaction

•Substances that promote decomposition of stabilizer in corn starch (hexamethylenetetramine) resulting in the formation of ammonia and formaldehyde

•Rayon coilers that contain an aldehyde functional group (furfural)

•Polyethylene glycols that may auto-oxidize to form aldehydes

•UV light, especially in the presence of high heat and humidity

•Heat, which can catalyze aldehyde formation

Cross-linking is going to result in the formation of a pellicle on the internal or external surface of the gelatin capsule shell[86]. A pellicle is a thin, water insoluble clear membrane of cross-linked protein on the inner or outer surface of the capsule that prevents the capsule fill from being released. Cross-linking is evidenced by the observation of a thin membrane or gelatinous mass during dissolution testing because the pellicle itself may be difficult to observe in fig.2 and fig.3 Unpredictable dissolution and rupture of the softgel shell may become apparent upon aging, when capsules are exposed to extreme physical conditions, such as heat (Yannas & Tobolsky, Citation1967; Welz & Ofner, Citation1992) high temperature and humidity, UV radiation, gamma radiation (Bessho et al., Citation2007), rapid drying (Reich, Citation1995) and exposure to chemical substances such as aldehydes, ketones, imines and carbodiimides (Sheehan & Hlavka, Citation1957; Davis & Tabor, Citation1963; Digenis et al., Citation1994; Tomihata & Ikada, Citation1996; Bottom et al, Citation1997; Gold et al., Citation1998; Fan & Dash, Citation2001; Liang et al., Citation2004). These problems are attributed to cross-linking of gelatin (pellicle formation) which causes the gelatin shell to become swollen, tough, rubbery and insoluble in water. Chemically, aldehydes are known to form methylene bonds between two amino groups on adjacent gelatin chains or within the same chain. The aldehyde and other carbonyl impurities in softgels may originate from the auto-oxidation of materials containing polyoxyethylene moieties in their structures, e.g. polyethylene glycols, methoxypolyethylene glycols, polyoxyethylene fatty acid esters, polyoxyethylene

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sorbitan fatty acid esters, polyoxyl 40 hydrogenated castor oil (Azaz et al., Citation1973; Hamburger et al, Citation1975; McGinity et al, Citation1975; Donbrow et al, Citation1978; Johnson & Taylor, Citation1984; Bindra et al., Citation1994). The rate of cross-linking in gelatin by aldehydes is strongly influenced by humidity with maximum cross-linking occurring around 60–70% humidity (Albert et al., Citation1991; Roy et al., Citation2001). The cross-linking of gelatin in softgel shell can be reduced by using excipients with low aldehyde content in the fill formulation. Crosslinking of gelatin can also be reduced using excipients containing abundant free amino groups (e.g. glycine, lysine) in the shell formulation which can compete with amino groups present in gelatin chain for available aldehydes originating from components used in softgel (i.e. aldehyde scavengers) (Gullapalli, Citation2010). Masking the number of amino groups available along the molecular chain of the gelatin through covalent bonds with suitable masking agents is another approach to reduce gelatin crosslinking. Succinic acid is often used to mask the amino groups present in gelatin chain through covalent bonds (succinization). However, a disadvantage of succination approach is that gelatin shell prepared using succinated gelatin is usually highly permeable to volatile solvents (e.g. ethyl alcohol) and migratable ingredients (e.g. propylene glycol). Incorporation of both amino acid (e.g. glycine) and carboxylic acid (e.g. citric acid) into powder fill of hydrochlorothiazide hard gelatin capsule was found to provide a reduction in the cross-linking of gelatin (Adesunloye & Stach, Citation1998)[87].

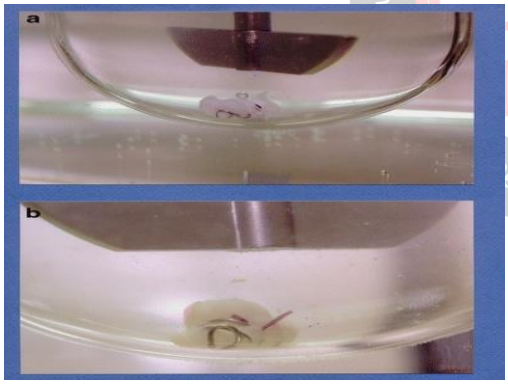

Figure 2:

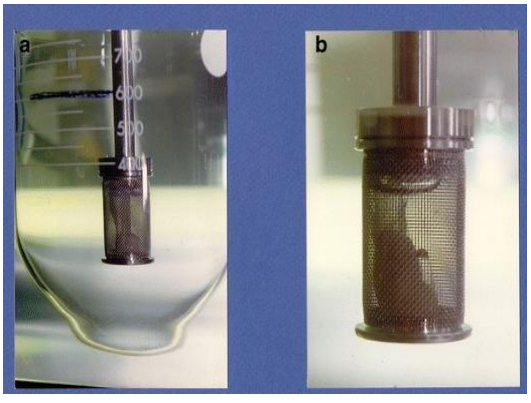

Figure 3

VI. NATURAL POLYMER BASED CAPSULE CHARACTERISATION

1). Genral characteristics:

1.1). Size: One of the primary characteristics of any biomedical formulation is its operating size. It is a critical parameter that determines the suitability of the capsules to penetrate the target biological site, as well as its applicability arising from in-vivo pharmacokinetics. In addition, the capsule size influences the drug-loading capacity, drug release rate and profile, and capsule stability. Smaller capsules may provide a larger surface area for the entrapment of a surface bound drug, leading to potentially higher loading capacity[89]. However, a smaller core, achieved due to smaller size capsules, may not ensure sufficient loading capacity for a drug-loaded in the capsule core as a reservoir. Alternatively, a larger capsule, with a thicker shell (or multiwalled shell), can have a higher loading capacity for a shell-bound drug but may or may not have a higher loading capacity for a core-bound drug, in which case the core size is of paramount importance. A shell-bound drug releases at an accelerated rate from smaller size capsules, due to the increased surface area. Larger polymeric capsules have been shown to degrade/dissolve faster than smaller capsules, due to bulk erosion. However, it has also been previously shown that the particle size had a minimal effect on the polymer degradation rate[88]. Hence, it is safe to draw that the dependence of capsule degradation on its size may be system- and parameter-specific. Capsule size can be affected by the type of precursor polymer and its concentration , emulsion homogenization speed, agitation rate, type and concentration of the emulsifying agent, volume of the aqueous and the oil phase, size of the solid template/core, type and concentration of the surfactant, storage conditions, thickness of the polymeric shell, and synthesis technique employed. Valot et al. studied process the influence of process parameters on the size distribution of ethyl cellulose microcapsules synthesized, using the emulsion–evaporation technique. They found that the mean capsule size decreases with the increase in the volume ratio of the dispersed organic phase to the continuous aqueous phase and an increase in the stirring rate. They also concluded that a decrease in the surfactant concentration leads to increased mean capsule size. Size distribution measurements are usually performed using the dynamic light scattering (DLS) method, wherein the micro- or nano-capsules are dispersed in a solvent media during measurements. Size and morphological studies are also conducted using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). However, care must be taken during sample preparation. We have observed that the liquid core microcapsules are prone to bursting during air drying and vacuum conditions in the SEM instrument. Lyophilization of the sample for ESEM

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measurements can be an option to avoid such a scenario[90].

1.2). Stability: The stability of micro- and nano-capsule concerns their storage, as well as operating in-vivo stability. After synthesis and purification, microspheres are either stored as colloidal solutions at lower temperatures, solid freeze-dried samples, lyophilized into powders, or in the form of spray-dried or vacuum-dried powders. Proper capsule storage ensures a better shelf-life of capsule formulations and their subsequent usage. Sonochemically prepared liquid-core human serum albumin capsules have shown to be stable for long-terms in suspension, as well as in freeze-dried conditions. In-vivo stability of a capsule can be increased to avoid the initial burst release of the drug, which is usually an undesirable feature of a drug delivery formulation, and to extend the drug release rate. Moreover, the capsules can be stabilized and programmed to release drugs that target particular conditions, as in the case of stimuli-responsive release systems[90].

1.3). Moisture content: Moisture content is an important physical property for the dried micro- and nano-capsules and spheres that influences the stability of the core after drying and affects the processibility, shelf-life, usability, and quality of the pharmaceutical product. Furthermore, the maximum permissible moisture content in certain products depends on the guidelines established by regulatory bodies, such as the FDA. In general, products with moisture content between 3–10 g/100 g possess good storage stability. Moisture content is determined using a thermogravimetric approach by measuring weight loss upon drying. Many moisture content measuring instruments are available. During a typical measurement procedure, the sample is heated, and the weight loss, due to moisture evaporation, is recorded[89].

1.4). Surface Charge: Another important property of any micro- or nano-capsule is its surface charge, which is usually determined by zeta potential measurements. The surface charge establishes the in-vivo capsule distribution and affects the drug release rate from the capsules. The surface charge can be modified using functionalizing polymers to enable targeted delivery of micro- and nano-capsules, for instance, to the cell nucleus[67].

1.5) Encapsulation Efficiency: The efficiency of the drug encapsulation is calculated using the expression: $Encapsulation\ Efficiency\ (\%)=\{(\ Ct-\ Cun\ )/\ Ct\ \}\times 100\%$ Ct is the total concentration of the drug initially present in the precursor solution before capsule or sphere formation, and Cun is the drug concentration measured in the residual precursor solution after the capsule or sphere formation[92].

1.6) Drug-loading capacity: The drug-loading capacity is defined as the amount (weight) of drug loaded per unit weight of micro- or nano-capsules and is calculated by the expression $Loading\ Capacity = Wd / Wc$ in which Wd is the total entrapped drug and Wc is the total weight of the capsules[98].

1.7) Cytotoxicity: To determine the suitability and biocompatibility of capsule formulations, in-vitro cytotoxicity analysis is done in-vitro on tissue cells using cell viability and cytotoxicity assays. These assays measure the cellular or metabolic changes associated with viable or nonviable cells and detect structural changes, such as loss of membrane integrity upon cell death or physiological and biochemical activities, indicative of living cells. Various types of cytotoxicity assays are available on the market, including MTT (methyl thiazolyl tetrazolium) and CCK-8 (Cell Counting Kit-8). The testing protocol for each is different and is explicitly defined by the assay manufacturers. In a typical procedure, the cells are incubated in 96-well plates at 37 °C, until adherent to the culture plates, followed by the addition of sterilized capsule suspensions. To these capsule-containing culture wells, prescribed volumes of cytotoxicity assay are added each day, incubated for 2 h, and scanned for absorbance at a particular wavelength to measure the optical density for counting the number of surviving cells and analyze their metabolic activity . Zhou et al. describe various methods for cytotoxicity analysis of medical devices[99].

1.8) Blood Compatibility: For any biomedical device or formulation, especially those intended to be introduced in-vivo through intravenous route and blood vessels, embolizing agents must have blood compatibility and should not cause hemolysis and blood coagulation. For blood compatibility analysis, the capsule formulation must undergo five stages of screening tests, which include thrombosis (blood clotting index, coagulation analysis, and platelets), hemolysis rate (nonhemolytic (0–2%), slightly hemolytic (2–5%), or hemolytic (>5%)) [121], and immunology testing[100].

1.9). Flowability: Flow properties of the dried micro- or nano-capsule powder is an important parameter that establishes the powder quality[87]. Usually, flow properties are analyzed by calculating the bulk and the tapped densities of a powdered sample. The procedure involves transferring a measured amount (m) of the powdered sample into a calibrated measuring cylinder and noting the bulk volume (VL) occupied by the powder to calculate the bulk density, $\rho\ b$

by mVL .

After this, the cylinder with the m amount of powdered sample is manually tapped for a certain amount of time to reach the tapped volume VT for calculating the tapped density, $\rho\ T$

by mVT .

The flowability of the power is then indirectly predicted using

Carr's index $(\%)=\{(\rho\ T-\rho\ b\ )/\rho\ T\ \}\times 100$

Hausner Ratio $=\rho\ T\ /\rho\ b$

 DOI : 10.35291/2454-9150.2024.0038

Carr's index ratings up to 10% are deemed excellent, between 10–15% are good, 16–20% are poor, 32–37% are very poor, and greater than 38% are abysmal. A Hausner ratio ≤1.25 indicates that the powdered sample is free-flowing, while a ratio ≥1.25 indicates poor flowability[101].

1.10) Pore Size and Porosity: Depending upon the pore diameter size, micro- and nano-spheres can be microporous (200 nm). The pore size can be measured during morphological analysis using SEM, TEM, or confocal laser scanning microscopy. Porosity is the ratio between the pore volume and total volume of the microsphere. It can be calculated using a variety of methods[91].

2). Function-Specific Characteristics:

2.1) Drug Release and Kinetics: To understand the release behavior of the drug from a sustained-release capsule formulation, it is essential to study its release kinetics in-vitro. This is usually done by dispersing the drug-loaded capsule formulations in a release media under constant stirring and by measuring the drug concentrations in the release media at set time intervals[95]. Conditions, such as the selection of proper release media, pH, temperature, and stirring speed, must be maintained and monitored throughout the in-vitro release experiments. The in-vitro release media is generally composed of the route- and target-specific biomimicking fluids at various pH values and bodily temperature (~37 °C). For example, orally administered capsule formulations are tested in-vitro in the gastrointestinal-mimicking release media. However, simulating exact in-vivo conditions is difficult. D'Souza reviewed various in-vitro drug release study methods, including 'sample and separate', 'continuous flow', and 'dialysis method'. The 'sample and separate' method involves retrieving a certain amount of sample from the release media at certain time-intervals, separating the retrieved sample from capsules (via filtration, ultrafiltration, centrifugation, ultra-centrifugation, or their combination), and, finally, measuring the drug concentration in the filtrate or/and the evaluating the filtered capsules. This method, although straightforward, poses many challenges, including the clogging of filters during filtration and absorption of the drug molecules into the filters. We also faced similar challenges during drug release studies from organic-core BSA microcapsules. In addition, we observed that BSA microcapsules ruptured several times during sample ultrafiltration, which resulted in the premature drug release in the filtrate leading. In a continuous flow method, the release media flows through a column containing immobilized drug-loaded capsule formulation, and the effluent is collected and monitored by detectors. Several types of apparatus are available for the continuous flow method. However, it is a costly method and requires complicated set-up assembly. The dialysis method is straightforward. Generally, the sample is placed in a dialyzing membrane and suspended into the release media. Samples are retrieved from the release media and analyzed. The method is simple and advantageous over the 'sample and separate' and 'continuous flow' methods, with the exception that a few drugs can bind to the dialysis membrane, affecting their concentration in the release media. In addition, the behavior of the dialysis membrane in the release media must be monitored prior to their employment for drug release studies. Finally, the drug release concentration in the release media vs. time profile is generated and compared to theoretical and computational models to predict the drug release behavior from the capsules and ascertain the underlaying release mechanisms[96]. The drug release process typically involves the migration of drug molecules from their initial location in the capsule to the external surface of the capsule and then, eventually, into an in-vitro release media or at the in-vivo target site. The movement and release of the drug via this route are facilitated by various mechanisms, which are briefly discussed below. In-vivo drug release is usually governed by a combination of two or more of these mechanisms, depending upon the type and design of the capsules or the spheres[97].

2.2) Swelling ratio: he diameter of the micro- and nano-capsules is measured before and after the swelling of the capsules. During swelling experiments, the capsules are dispersed in an aqueous media under stirring at varying pH and temperatures conditions. Their diameters are measured at each interval of time, and the swelling ratio (%) is calculated using the equation: $\{(- D\ 0)/\ D\ 0\}\times 100\ t$

(1)where, D0 is the initial diameter and Dt is the diameter of the capsules after swelling at time ( ).It is vital to build a swelling ratio profile prior to in-vivo testing, in order to understand the swelling behavior of micro- and nano-capsules, especially for their utility as embolizing agents operating at different diameters of blood vessels, as well as osmosis-controlled drug release systems[100].

2.3). Cell Survival Number: For determining the efficacy of the capsule as a protective enclosure to probiotic bacterial cells against the harsh gastric environment, in-vitro incubation of cell-encapsulating capsules and free cells in a simulated gastric fluid (SGF) is carried out for a set period to evaluate the cell survival number[58].

2.4). In-Vivo Bioavailability: Capsules prepared for aiding the solubility characteristics of the encapsulated drug are tested, in comparison to the unencapsulated free drug, for its in-vivo oral bioavailability. The procedure involves live subjects (such as male or female rats in a similar weight range), divided into test and control groups. A certain amount (by weight of the live subjects) of drug-encapsulating capsules and the free drug are administered orally in the test and the control groups, respectively. Fixed volumes of blood samples are then drawn from the test and control groups at fixed time intervals (t0, t1, …, tn), through the experimentally preferred vein type (for

 DOI : 10.35291/2454-9150.2024.0038

example, the retro-orbital, the saphenous vein, or the tail vein in rats). Blood samples from a second control group of live subjects, to which no drug is administered, can also be studied for conducting an accurate evaluation. The collected blood samples from each group are analyzed for the blood plasma drug concentrations. Pharmacological analyses are carried out by generating the mean plasma concentrations of drug vs. time profile and analyzing the maximum plasma concentration (Cmax) at the time (tmax) and area under the curve (AUC), to evaluate drug bioavailability from free drug and capsule-encapsulated drug[67].

2.5). Dissolution Profile of the Capsules: The dissolution profile of a capsule formulation is built based on in-vitro experiments, which usually involve incubating the capsules in water/simulated gastric fluids over a definite period. In such as case, the dissolution behavior is evaluated by observing the change in the absorbance intensity and optical density with time at the absorbance frequency of the capsule-forming polymer. The dissolution profile of capsule formulations reflects the capsule erosion over time in the release media and, as a result, indicates its biodegradation and elimination fr om the body, and affects the release behavior of the encapsulated APC[65].

VII. SOLIDIFICATION STRATEGIES

Solidification strategies in capsule spheres are crucial for controlling the properties and characteristics of the final product. Here are some common strategies[45]:

1).Cooling Rate Control: Regulating the rate at which the capsule sphere cools can influence its solidification behavior. Slow cooling rates can promote the formation of larger crystals, while rapid cooling rates can result in finer microstructures.

2).Nucleation Control: Nucleation refers to the initiation of solidification from the liquid phase. By controlling nucleation, either through additives or thermal treatments, one can influence the size, distribution, and morphology of crystals within the capsule sphere.

3). Alloy Composition: The composition of the material inside the capsule sphere plays a significant role in its solidification behavior. Alloying elements can alter the solidification temperature range, phase transformations, and microstructural evolution.

4). External Pressure: Applying external pressure during solidification can modify the crystalline structure and mechanical properties of the capsule sphere. Pressure can influence nucleation kinetics, crystal growth rates, and the formation of defects.

5). Stirring or Agitation: Agitation techniques such as stirring or vibration can promote uniform mixing of components within the capsule sphere, leading to homogeneous solidification and improved material properties.

6). Controlled Atmosphere: Modifying the atmosphere surrounding the capsule sphere during solidification can prevent oxidation or other unwanted reactions that may affect the final product's properties**.**

7). Additives or Inoculants: Introducing specific additives or inoculants can refine the microstructure of the capsule sphere, enhancing its mechanical properties, corrosion resistance, or other desired characteristics.

8). Thermal Gradient Control: Creating controlled thermal gradients within the capsule sphere can influence the direction and rate of solidification, allowing for tailored microstructures and properties.

By implementing these solidification strategies, manufacturers can fine-tune the characteristics of capsule spheres to meet specific performance requirements for various applications.

The storage of phase change material in the macro-capsules used for a latent thermal energy storage system significantly enhances the thermal performance compared to the conventional shell and tube heat exchanger. The geometrical shape and dimensions of these capsules have a major impact on the melting and solidification characterization. Most of the research is, however, carried out using a spherical capsule only. Hence, the influence of the differently shaped macro capsules is required to be evaluated to obtain thermal performance enhancement. An experimental setup is developed to validate numerical observations. The primary objective of the present study is to visualize the phase change phenomenon and compare the thermal behavior of differently shaped capsules (spherical, cubical, triangular, and plus-shaped) during the melting and solidification processes. Results show that the triangular capsule exhibits better thermal performance with melting and solidification time of 41 min and 133 min, respectively. In addition, the increase in the heat transfer fluid temperature increases the melting rate. Furthermore, it is found that the 27% reduction in the capsule size decreases melting and solidification time by 12.19 and 19.17%, respectively. Hence, the capsule size has more influence on the solidification process compared to the melting process.

•Solidification Techniques:

•Chemical Cross-linking: Some polymers can be cross-linked to form a solid network, encapsulating the core material. Cross-linking agents like glutaraldehyde or calcium ions are often used to induce cross-linking.Cooling: For thermoplastic polymers, solidification can occur by cooling the polymer solution or suspension. This leads to the formation of a solid shell around the core material.Drying: In the case of emulsions or suspensions, drying techniques such as freeze drying or spray drying can be used to remove the solvent and solidify the shell material.

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VIII. BIODEGRADATION MACHANISM

Capsule coatings have a wide range of applications as they afford protection to active pharmaceutical ingredients. However, few studies have focused on capsule coating owing to the sensitivity of hard gelatin shells to solvents and high temperature. In the present study, we aimed to coat capsules using two thermoforming coating techniques: vacuum forming coating (VFC) and centrifugal forming coating (CFC). Rheological and mechanical properties were investigated to comprehensively elucidate the processes and mechanisms underlying the two coating techniques[98]. The corresponding coating integrity and drug release behavior were characterized and compared. Herein, we observed that a lower temperature was more suitable for the VFC process than the CFC process. The drug release rate decreased with the film thickness increased. Both optimal VFC and CFC capsules revealed a 24 h sustained-release property following Fick's diffusion law. The coating thickness distribution was more homogeneous for the VFC capsule than the CFC capsule. With the advantage solvent-free of functional capsule coatings, thermoforming coating techniques are convenient and efficient solutions for small-scale personalized coating of oral solid preparations[97].

•Degradation properties:

Polymer degradation is a change in the properties-tensile strength, color, shape, etc-of a polymer or polymer based product under the influence of one or more environmental factors such as heat, light or chemicals. Degradation can also be induced deliberately to assist structure determination. Polymeric molecules are very large (on the molecular scale), and their unique and useful properties are mainly a result of their size.7 Any loss in chain length lowers tensile strength and is a primary cause of premature cracking. Surgeries are most common in India. Mostly metal plates are kept as the supporting material but now it is replaced by degradable polymer materials[60].

IX. RECENT ADVANCES IN PROTEIN – BASED SPHERICAL CAPSULES TOWARDES BIOMEDICAL APPLICATION

In the past few decades, various types of animal- and plant-based proteins and peptides have been studied for their use as drug and growth factor carriers, embolizing agents, and cell culture platforms, in order to enable sustained drug release, protection from the biological environment, enhanced bioavailability, targeted delivery, pH- and temperature-responsive release, embolization of blood vessels, better cell integration into the body and toxicity moderation. The interest in protein-based drug carriers stems from several of their advantages, namely higher biocompatibility and lower toxicity, biodegradability, high drug-binding capacity leading to a good drug-loading efficiency, possibility of straightforward and cheaper production due to their abundance in nature, the feasibility of structural modifications, due to the presence of several functional groups, non-immunogenicity, etc[103]. Protein-based systems in the form of hydrogels, micro and nanoparticles, micro- and nanocapsules, implants, microneedles, bio-adhesives, fibers, rods, and films have been developed and tested for various applications in cancer therapy, nutritional therapy, diabetes, bone diseases, neurological conditions, and stem cell therapy. Spheres and capsules made of animal- and plant-proteins having liquid (organic or aqueous), hollow and solid cores have been developed for the above applications. In addition, the past decade has seen a considerable evolution of composite capsules made of two or more proteins, protein–polymer composite capsules, and composite capsules of protein conjugated with other materials, such as ceramics and metallic nanoparticles. Protein capsules have also been functionalized using other polymers to develop drug delivery formulations for targeted delivery. Herein, we focus on the advances made in the past decade towards developing micrometric and nanometric capsules with liquid, solid, and hollow core encapsulated by shells made of functionalized proteins and protein–protein composites, protein–polymer composites, protein composites with other materials, and multiwalled capsules. Our discussion revolves around protein capsules and spheres developed for biomedical applications, under the designing aspects discussed hitherto[108].

X. Function-Specific Characteristics

1). Drug Release and Kinetics: To understand the release behavior of the drug from a sustained release capsule formulation, it is essential to study its release kinetics in-vitro. This is usually done by dispersing the drug-loaded capsule formulations in a release media under constant stirring and by measuring the drug concentrations in the release media at set time intervals. Conditions, such as the selection of proper release media, pH, temperature, and stirring speed, must be maintained and monitored throughout the in-vitro release experiments. The in-vitro release media is generally composed of the route- and target-specific biomimicking fluids at various pH values and bodily temperature (~37 °C). For example, orally administered capsule formulations are tested in-vitro in the gastrointestinal-mimicking release media. However, simulating exact in-vivo conditions is difficult. The drug release process typically involves the migration of drug molecules from their initial location in the capsule to the external surface of the capsule and then, eventually, into an in-vitro release media or at the in-vivo target site. The movement and release of the drug via this route are facilitated by various mechanisms, which are briefly discussed below. In-vivo drug release is usually governed by a combination of two or more of these mechanisms, depending upon the type and design of the capsules or the spheres[119].

 DOI : 10.35291/2454-9150.2024.0038

1.1. Diffusion: This process involves the mass transfer of the molecules of a substance (solute) from one part of a system or solution to another, driven by the solute concentration gradient. In other words, it is the movement of solute molecules from their higher concentration to their lower concentration in a solution, as long as this concentration gradient is maintained. After the concentration difference is equalized, the system reaches a state of equilibrium where no more solute diffusion from one part of the system to another takes place. This mass transfer of molecules is facilitated by thermal and Brownian motion, which results in random and repeated collisions between molecules. Usually, in a gradient of solute concentration, not all the solutemolecules have a preference to move in one direction. Hence, while studying mass transfer by diffusion, a solution is divided into volume groups of solute molecules. One group of molecules may move in one direction, while another group in the reverse direction[118]. If the concentration of the f irst volume group is more than the second one, overall, more particles will move from the first group to the second, leading to a net flow of molecules from their higher concentration in group one to their lower concentration in group two. For releasing from a polymeric capsule, the drug molecules must diffuse from their initial position (inside the core drug reservoir or matrix, or the polymer matrix) to the outer surface of the polymer matrix and, eventually, into the release media.

1.2. Erosion: Drug release, by polymeric capsules, sometimes involves the erosion or disintegration of the polymer matrix by the kinetic degradation of the appropriate links between polymer polymer molecules or polymer–APC molecules, due to the hydrolysis of bonds. The hydrolysis of a bond depends upon the local environment (acidic or basic). In a drug reservoir system, erosion controlled drug release occurs when the polymer matrix degrades, releasing the APC that it physically encapsulates. In the case of a matrix system, the APC is usually chemically linked to either the polymeric shell or the core and is released after the breakage of those chemical links, accompanying the degradation of the matrix. Erosion can occur at the surface, or in bulk, of the capsules. When water invasion is slow and the hydrolysis of polymeric bonds is rapid, surface erosion occurs, which reduces system dimensions. In a matrix-type system, the surface erosion of the polymeric SDDS is accompanied by the release of the APC molecules. When water invades the SDDS more rapidly throughout the system than the hydrolysis of the surface bonds, several polymeric chains are broken, leading to the bulk erosion of the system. During the bulk erosion, the drug is initially released from the system through the surface and pores. This initial release is followed by a dormant stage (almost no drug release), where broken polymer chains, triggered by water invasion, form crystallites that are resilient against hydrolysis. Finally, the drug is released rapidly, due to the accelerated degradation of the polymer and polymeric crystallites, due to autocatalysis[101].

1.3. Osmosis: Osmosis involves the movement of solvent (biological fluid) from its higher concentration (i.e., lower concentration of the solute) to its lower concentration (i.e., the higher concentration of the solute) through a semi-permeable membrane, which allows the transport of smaller solvent molecules into the system but prevents bigger solute molecules from leaving the system. The process is controlled by osmotic pressure, which develops when two solutions of different solute concentrations are separated by a semi-permeable membrane. The higher the osmotic pressure, the higher the chemical potential, which leads to an increased rate of transport of the solvent molecules through the semi-permeable membrane. In osmotically-driven drug release, the polymer matrix of the capsules or spheres acts as a semi-permeable membrane. Due to the built-up osmotic pressure, the water outside the DDC/S starts to permeate the capsule polymer matrix, resulting in its hydration and swelling. Eventually, due to the permeation of water molecules into the matrix, the drug (solute) concentration inside the SDDC starts lowering, which results in a decrease in the osmotic pressure. The hydration and swelling of the polymer matrix result in the matrix becoming partially permeable to the drug molecules, which decreases the osmotic pressure and drives the drug molecules to slowly escape the system through the now partially permeable polymer matrix of the SDDC. The process is repeated alternatively on both sides of the polymer matrix on account of osmotic pressure and chemical potential, leading to a slow and controlled release of the drug. The rate of osmotic flow depends upon the concentration and nature of the drug, temperature, and hydraulic permeability of the polymer matrix[105].

1.4. Swelling: Swelling of the polymeric membrane of an SDDC usually depends upon the hydrophilic behavior of the polymer or water–molecule interaction. When the polymer is surrounded by water, the polymeric network expands because water enters the DDC rapidly, as opposed to polymer dissolution, which is slow. This leads to the swelling of the polymeric shell. The mechanism is similar to swelling, in the case of osmotically driven drug release from an SDDC. The primary parameters that control swelling are ionic content, cross-link content, and hydrophilic content of the polymeric shell[106].

2).Swelling Ratio: The diameter of the micro- and nano-capsules is measured before and after the swelling of the capsules. During swelling experiments, the capsules are dispersed in an aqueous media under stirring at varying pH and temperatures conditions. Their diameters are measured at each interval of time, and the swelling ratio (%) is calculated using the equation: {(Dt - Do)/Do}*100 (1)

where,

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Do is the initial diameter and Dt is the diameter of the capsules after swelling at time. It is vital to build a swelling ratio profile prior to in-vivo testing, in order to understand the swelling behavior of micro- and nano-capsules, especially for their utility as embolizing agents operating at different diameters of blood vessels, as well as osmosis-controlled drug release systems[107].

3). Cell Survival Number: For determining the efficacy of the capsule as a protective enclosure to probiotic bacterial cells against the harsh gastric environment, in-vitro incubation of cell encapsulating capsules and free cells in a simulated gastric fluid (SGF) is carried out for a set period to evaluate the cell survival number[110].

4). In-Vivo Bioavailability: Capsules prepared for aiding the solubility characteristics of the encapsulated drug are tested, in comparison to the unencapsulated free drug, for its in-vivo oral bioavailability. The procedure involves live subjects (such as male or female rats in a similar weight range), divided into test and control groups. A certain amount (by weight of the live subjects) of drug-encapsulating capsules and the free drug are administered orally in the test and the control groups, respectively. Fixed volumes of blood samples are then drawn from the test and control groups at fixed time intervals (t0, t1, …, tn), through the experimentally preferred vein type (for example, the retro-orbital, the saphenous vein, or the tail vein in rats). Blood samples from a second control group of live subjects, to which no drug is administered, can also be studied for conducting an accurate evaluation. The collected blood samples from each group are analyzed for the blood plasma drug concentrations. Pharmacological analyses are carried out by generating the mean plasma concentrations of drug vs. time profile and analyzing the maximum plasma concentration (Cmax) at the time (tmax) and area under the curve (AUC), to evaluate drug bioavailability from free drug and capsule-encapsulated drug[112].

5). Dissolution Profile of the Capsules: The dissolution profile of a capsule formulation is built based on in-vitro experiments, which usually involve incubating the capsules in water/simulated gastric fluids over a definite period. In such as case, the dissolution behavior is evaluated by observing the change in the absorbance intensity and optical density with time at the absorbance frequency of the capsule-forming polymer. The dissolution profile of capsule formulations reflects the capsule erosion over time in the release media and, as a result, indicates its biodegradation and elimination from the body, and affects the release behavior of the encap sulated APC[108].

XI. CHALLENGES AND LIMITATIONS

Natural polymer-based capsules and spheres offer numerous advantages, including biocompatibility, biodegradability, and low toxicity. However, they also pose several challenges and limitations:

1). Structural stability: Natural polymers may have lower mechanical strength and stability compared to synthetic polymers, leading to limitations in their use for certain applications requiring robust capsules[106].

2). Control over properties: Achieving precise control over the size, shape, and surface properties of natural polymer-based capsules can be challenging, impacting their uniformity and functionality.

3). Limited loading capacity: Natural polymers may have lower loading capacities compared to synthetic polymers, which can restrict their use for encapsulating and delivering certain types of payloads such as drugs or active ingredients[113].

4). Variability in composition: Natural polymers sourced from biological materials can exhibit variability in composition and properties, leading to batch-to-batch inconsistencies and affecting the reproducibility of encapsulation processes[114].

5). Polymer-based capsules and spheres have some challenges and limitations. One challenge is achieving precise control over their size and shape. Additionally, the mechanical properties of the polymer can affect the stability and integrity of the capsules. It's also important to consider the compatibility of the polymer with the encapsulated materials[114].

6). Compatibility with target applications: Natural polymer-based capsules may not be suitable for all applications due to factors such as compatibility with specific solvents, processing techniques, or target environments[115].

7). Cost and scalability: Natural polymers may be more expensive to produce than synthetic polymers, and scaling up production processes can be challenging, impacting the cost effectiveness and commercial viability of natural polymer-based capsules.

Addressing these challenges requires ongoing research and development efforts to optimize natural polymer-based capsule formulations, enhance their properties, and expand their applicability across various industries, including pharmaceuticals, food, cosmetics, and materials science.

Polymer-based capsules and spheres have some challenges and limitations. One challenge is achieving precise control over their size and shape. Additionally, the mechanical properties of the polymer can affect the stability and integrity of the capsules. It's also important to consider the compatibility of the polymer with the encapsulated materials. These are just a few factors to keep in mind when working with polymer-based capsules and spheres[112].

XII. SCALES IN POLYMER

To set the stage, we begin with discussing the different scales that are involved in our multiscale picture of polymers and introduce classes of polymer models that are

 DOI : 10.35291/2454-9150.2024.0038

used to study polymer materials at these different levels[110].

1). Monomer/Oligomer Scale: The basic building blocks are the monomers. They can have a simple chemical structure, as in the case of many commodity polymers such as polystyrene, or a rather complicated structure, as in the case of biopolymers such as RNA, DNA, or proteins. The structure of the monomers on the monomer scale determines local properties such as the charges and the polarization, the solubility in a solvent. the existence and structure of a hydration shell, the local affinity to surfaces, or, in studies of polymer reactions, the monomer reactivity. In general, these properties are also influenced by the larger-scale structure of polymer systems. For example, the effective monomer reactivity depends on the accessibility of the reactive sites, which is determined not only by the local electronic and steric monomer structure but also by the polymer conformation. Likewise, the effective charges and/or polarization of monomers depend on the local environment. In most cases, however, the corrections due to the larger-scale environment are small compared to the intrinsic value imposed by the monomer structure[104]. To study polymers on the monomer scale, atomistic models are used, and in some cases quantum mechanical modeling in necessary.

2). The Scale of Conformations: The second level, the polymer scale, is the realm of classical polymer physics, where generic statistical mechanics approaches have celebrated successes. At this level, scaling laws have scored victories, both regarding static and dynamic properties of polymeric systems, and simple calculations based on ”scaling blobs” can make meaningful predictions. This is because polymer molecules consisting of many identical monomer units start to exhibit universal behavior beyond a certain molecular weight. Therefore, renormalization groups concepts can be applied, according to which the fractal large-scale structure of polymer conformations does not depend on details of the local monomer structure. This results in the paradigm of the ”Gaussian chain model”, (18) which describes a polymer molecule as a random walk in space. In the case of complex heteropolymer molecules such as intrinsically disordered peptides (IDPs), applying scaling concepts is more challenging, but still at least partially successful. Theoretical models at this level are mostly based on effective phenomenological parameters (18) such as the Kuhn length, the famous Flory–Huggins χ-parameters characterizing polymer–solvent or monomer–monomer interactions, the monomer mobility, the effective monomer charge, and possibly the Debye screening length[107].

3).The Blob Scale: The properties of polymer systems containing many polymers are often determined by conformational restructuring on scales that are much larger than the monomeric scale. On such scales, polymers behave in many respect like single soft, interpenetrating ”blobs” or chains of such blobs. In polymer physics, the term blob often refers to a theoretical framework that allows for simple intuitive derivations of crossover phenomena between different scaling regimes in polymer solutions. Here we will use it more generally to describe the soft character of overlapping polymers[103]. To complete the definition of a density-based model, one must also specify how to determine the local densities $\rho\alpha$ and how to formulate the corresponding spatially discretized version of the equations of motion. Often, the local densities are evaluated on a grid, but other off-lattice variants based on weighted densities have also been proposed. When using a grid-based model in dynamical simulations, a second practical issue is how to determine the resulting forces on monomers ─ whether to directly take the derivative of the discretized Hamiltonian with respect to the monomer positions or whether to calculate a discretized force field and interpolate that. The former strategy guarantees that the simulation is grounded on a well-defined Hamiltonian, but it introduces lattice artifacts. The latter strategy gives more freedom to reduce the lattice artifacts and (approximately) restore momentum conservation in molecular dynamics simulations, but it does not guarantee that one samples a rigorously defined statistical ensemble in the limit of zero time step[105]. Thus, the former approach is better suited for studying the statistical mechanics of the system, and the latter for studying processes where hydrodynamics is important**.**

4). Mesoscopic Scale: The next level is the scale of mesoscale organization, i.e., structure formation in inhomogeneous polymer systems. Emerging phenomena at this scale are the nucleation of crystallites in semicrystalline polymers, phase separation and demixing, wetting phenomena, or self-assembly[104].

XIII. ECONOMIC AND ENVIRONMENTAL CONDITIONS

Capsule formation, whether in the pharmaceutical or other industries, involves various economic and environmental considerations:

1. Raw Material Selection: - Economic: Choosing raw materials with consistent quality and competitive pricing ensures cost-effectiveness in production.- Environmental: Opting for sustainable and biodegradable materials, such as plant-based or recycled polymers, reduces reliance on fossil fuels and minimizes environmental impact[107]**.**

2. Energy Efficiency:- Economic: Implementing energy-efficient machinery and processes reduces operational costs and improves overall productivity.- - Environmental: Utilizing renewable energy sources like solar or wind power decreases greenhouse gas emissions associated with energy consumption during manufacturing[109]**.**

3. Waste Reduction:- Economic: Implementing lean manufacturing practices to minimize material wastage and streamline production processes lowers production costs.-

 DOI : 10.35291/2454-9150.2024.0038

- Environmental: Recycling and reusing materials wherever possible reduces landfill waste and conserves natural resources[117].

4. Water Management:- Economic: Implementing water-saving technologies and efficient recycling systems reduces water usage costs and minimizes utility expenses.- - Environmental: Employing water treatment systems to purify wastewater before discharge mitigates water pollution and protects local ecosystems[107].

5. Transportation Optimization: - Economic: Consolidating shipments, utilizing efficient logistics networks, and optimizing transportation routes minimize fuel costs and transportation expenses.- - Environmental: Reducing carbon emissions from transportation by using eco-friendly vehicles, consolidating shipments, and favoring local suppliers decreases the carbon footprint associated with capsule distribution[105]**.**

6. Compliance and Risk Management:- Economic: Investing in compliance with regulatory standards and certifications mitigates the risk of fines, penalties, and legal liabilities.- Environmental: Implementing proactive environmental management practices reduces the risk of environmental incidents, reputational damage, and potential legal consequences[110].

7. Lifecycle Assessment:- Economic: Conducting a comprehensive lifecycle assessment identifies opportunities for cost savings, process optimization, and resource efficiency.- Environmental: Analyzing the entire lifecycle of capsules helps quantify environmental impacts, prioritize sustainability initiatives, and improve overall environmental performance[104].

8. Innovation and Research:-

Economic: Investing in research and development to innovate new materials, technologies, and processes enhances competitiveness and fosters market differentiation.-

Environmental: Developing eco-friendly alternatives, such as biodegradable capsules or novel manufacturing techniques, reduces environmental footprint and supports sustainability goals. By integrating these detailed considerations into capsule formation processes, companies can achieve a balance between economic viability and environmental sustainability, fostering long term profitability and responsible stewardship of natural resources.-

ECONOMICS

The cost of biopolymers needs to be looked into objectively and addressed, because as biopolymer is developing, more ideas about biopolymers and the need to embrace their usage is necessary and important, therefore, Economic concerns must be addressed, because the future of each biopolymer product is solely dependent on its cost competitiveness, and society's ability to pay for it because most of the biopolymers are costly and since petroleum based polymers are cheaper, industries embark on their usage without considering the environmental factors rather the profit. In developed and developing countries, governments and NGO'S are introducing initiatives designed to promote, enlighten people and promote education by giving research grants, provide room for application and adequate development of biopolymers. Most countries all over the world and their policy makers support work in the area of biopolymer research, with government's universally interested e.g. German government being particularly interested.3 This literature review provides information providing awareness and progress made available in the production, application and development of biodegradable polymer materials and some important information needed to be explored about biodegradable materials[102].

The circularity assessment follows the Material Circular Indicator (MCI) methodology (Ellen MacArthur Foundation, 2015), comparing the results for the three selected materials (PP, aluminium and tinplate). Although there are other sets of indicators and tools to measure the company's shift toward a circular economy, and they are at an initial stage of development, the MCI approach enables users to measure the circular state of a product. Combining the MCI results with a complementary analysis, such as LCA, the MCI becomes a powerful indicator in comparing manufacturing alternatives for the product under study. The MCI tool takes into consideration the following aspects of a product: the feedstock (source of material used in the manufacture of a product); destination after use (sent to landfill, reused or recycled) and the product utility (length of the material lifespan and intensity of use). Regional recycling rate conditions and industry data were considered, for the production and after the use of the package, when available[107].

The economic effects of natural polymer-based capsules in biomedical applications can be substantial. These capsules are often utilized in drug delivery systems, tissue engineering, and medical diagnostics due to their biocompatibility, biodegradability, and controlled release properties.

1). Cost-effectiveness:

Natural polymers, such as chitosan, alginate, and gelatin, can often be sourced from renewable biological materials like crustacean shells, seaweed, or animal by products. This can result in lower material costs compared to synthetic polymers derived from petrochemicals. Additionally, the manufacturing processes for natural polymer-based capsules may be simpler and more environmentally friendly, further reducing production costs[117].

2).Therapeutic efficacy:

Natural polymer-based capsules offer advantages in drug delivery, such as controlled release and targeted delivery.

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By encapsulating drugs within these capsules, it's possible to achieve sustained release profiles, improving the efficacy of the treatment while potentially reducing side effects. This can lead to better patient outcomes and potentially lower healthcare costs associated with managing adverse effects or disease progression[117].

3).Market competitiveness:

In the biomedical industry, there is growing demand for sustainable and biocompatible materials. Natural polymer-based capsules align with these trends, making products incorporating these capsules more attractive to consumers, healthcare providers, and regulatory agencies. Companies investing in these technologies may gain a competitive edge by offering innovative solutions that meet both therapeutic and environmental criteria[118].

4). Research and development:

The development of natural polymer-based capsules requires investment in research and development (R&D) to optimize formulations, manufacturing processes, and scalability. While initial R&D costs can be significant, successful development can lead to intellectual property assets and proprietary technologies that provide long-term economic benefits through product sales, licensing agreements, or partnerships[118].

5). Regulatory considerations:

Regulatory approval is a critical aspect of bringing biomedical products to market. Natural polymer-based capsules may benefit from regulatory pathways that recognize their biocompatibility and safety profiles. Additionally, regulatory agencies increasingly prioritize sustainability and environmental impact assessments, which can favor the use of natural polymers over synthetic alternatives.

Overall, the economic effects of natural polymer-based capsules in biomedical applications are intertwined with their ability to offer cost-effective, therapeutically efficacious, and environmentally sustainable solutions. As the demand for personalized medicine, targeted drug delivery, and sustainable healthcare continues to grow, the economic significance of these capsules is likely to increase[109].

XIV. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Natural, polymer-based APC carriers, especially proteins and polysaccharides, have been utilized widely in biomedical applications, mainly due to features such as biodegradability, biocompatibility, functionalization capability, low-immunogenicity, and blood compatibility. Amongst polysaccharides, chitosan (and derivatives), cellulose (and derivatives), and alginate have been the most commonly utilized shell candidates in core–shell capsules, whereas BSA, HSA, collagen, gelatin, silk fibroin, and zein proteins rule the polypeptide family. Keratin, resilin, and gliadin are some of the less explored polypeptides as shell-forming polymers for core–shell capsules[5]. Recent research trends indicate an accelerated rate in the development of APC carriers with various core–shell structural configurations. Compared to non-porous and porous sphere structures, core–shell capsule configurations have been proven superior, as they enable the introduction of multifunctionalities, higher cargo loading capacity, and encapsulation efficiency. A variety of hydrophobic and hydrophilic cargo can be simultaneously encapsulated and entrapped in the single- and multiwalled core–shell capsules. Porous spheres, on the other hand, were proven to be advantageous as platforms for cell culture. The majority of research and development in cell carrier platforms seems to utilize porous microspheres, possibly due to the availability of a larger surface area for culture within the pores, as well as the polymer matrix surface[60].

Several approaches and techniques have been utilized to synthesize porous spheres and core shell capsules. The majority of these techniques have been utilized for many decades and have undergone slight modifications over the years to meet the system-specific needs[10]. It is also evident that these techniques largely utilize templating approach, wherein either solid or emulsion templates are prepared and used to guide the formation of core–shell-type, as well as sphere-type structural configurations. Solid templating is the easiest and most direct approach for synthesizing solid- and hollow-core, as well as single- and multiwalled capsules[22]. There are many reports on utilizing the solid templating approach for solid- and hollow-core–shell capsule synthesis. Liquid-core capsules have also been indirectly prepared using solid templating. However, the number of such studies is relatively low[88]. Emulsion templating is another commonly used method of synthesis, especially for oily core capsules and porous spheres. An important difference between sphere and capsule synthesis using emulsion templating is that the latter generally requires the formation of o/w emulsion, as opposed to w/o emulsion, especially when the polymer is hydrophilic and soluble in water[82]. Ultrasonication-assisted emulsification has also been established as one of the leading capsule synthesis approaches, due to its facile and time efficient methodology. Several studies have utilized the ultrasonication approach for the synthesis of liquid-core capsules. However, the proportion of studies involving the ultrasonic synthesis of oily-core capsules is higher than that of the aqueous-core capsules. Thus, ultrasonication can be further explored towards the synthesis of aqueous-core capsules[100].

The stability of polymeric carriers, especially core–shell single- and multiwalled capsules, has been a concern. For their long-term stability, covalent crosslinking has been exploited. However, as mentioned earlier, a balance between covalent and non-covalent interactions must be achieved to ensure capsule stability but must enable

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stimuli-responsive cargo release. Storage is another concern when it comes to core–shell capsules. Liquid-core and hollow core capsules are highly prone to structural deformations and bursting when dried for storage and characterization as dry powders[118]. Liquid-core capsules can be stored as colloidal solutions, instead, to avoid these issues. However, it must be noted that if the colloidal conditions are not appropriately maintained, the capsules suffer aggregation, which results in the loss of shell functionalities. More efforts are needed in the direction of purification and proper storage in addition, alternatives, less invasive approaches for preparing characterization samples of liquid-core capsules are needed[119].

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