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Encapsulation of active ingredients in polysaccharide–protein complex coacervates

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ABSTRACT

Polysaccharide–protein complex coacervates are amongst the leading pair of biopolymer systems that has been used over the past decades for encapsulation of numerous active ingredients. Complex coacervation of polysaccharides and proteins has received increasing research interest for the practical application in encapsulation industry since the pioneering work of complex coacervation by Bungenburg de Jong and co-workers on the system of gelatin-acacia, a protein–polysaccharide system. Because of the versatility and numerous potential applications of these systems essentially in the fields of food, pharmaceutical, cosmetics and agriculture, there has been intense interest in recent years for both fundamental and applied studies. Precisely, the designing of the micronscale and nanoscale capsules for encapsulation and control over their properties for practical applications garners renewed interest. This review discusses on the overview of polysaccharide–protein complex coacervates and their use for the encapsulation of diverse active ingredients, designing and controlling of the capsules for delivery systems and developments in the area.

Contents

1. Introduction

Encapsulation technology has received considerable interest in polymer science in wide range of disciplines and in numerous fields of applications. Over the past few decades, advances in biopolymer encapsulation based technologies have spurred development in many important fields such as pharmaceutical, foods, cosmetics, agricultural, electronic, and molecular diagnostic applications. Various novel and intelligent delivery matrices and vehicles have been designed and fabricated by using the encapsulation technology to fulfill the ever-increasing needs of different fields. The process of encapsulation involves the entrapment of a substance (active agent) within a carrier material (wall material). The material encapsulated can be called the core, fill, active, internal or payload phase. The encapsulating material is generally called as the coating, membrane, shell, capsule, carrier material, external phase, or matrix [1–4]. By using encapsulation technology the active agents can be protected from several drastic

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conditions such as light, shear, oxygen, moisture, heat or other extreme conditions, thus enhancing their stability and maintaining viability. Encapsulation is also utilized for achieving various goals such as for masking of any unpleasant odours or tastes [4], transforming liquid droplets into solid particles, safe handling of the toxic materials, reducing the evaporative loss and flammability of liquids, reducing the reactivity of the core material, and extending the duration of the activity of the active agent. Encapsulation is a useful tool to improve the delivery of the encapsulated material to the required site with the required rate or optimal kinetics. Conditions for the encapsulation of active molecules depend on the sensitivity (thermal and redox stability) and nature (solubility in oil and water) of the active components but release can be controlled by mechanical process, pH variations (acidic conditions in the stomach, near neutral in the intestine), enzymatic actions [5] or can be triggered by other external stimuli. For example, the "smart" wall material polymers respond to small changes in their environment with dramatic changes in their physical properties [6]. Smart polymeric encapsulated delivery systems are able to release the entrapped active agents at the appropriate time and site of action, in response to specific physiological triggers [6,7]. Broadly divided methods of encapsulation are chemical methods, physico-chemical methods and physico-mechanical methods [8]. Within these broadly classified processes, various specific techniques are employed for encapsulation of active agents to form the capsules, including coacervation and phase separation, interfacial polymerization, sol–gel encapsulation, solvent evaporation, supercritical CO_2 assisted encapsulation, spray drying, spray chilling or spray cooling, extrusion coating, fluidized bed coating, pan coating, liposome entrapment, inclusion complexation, centrifugal extrusion, melt injection and rotational suspension separation [4,8].

Encapsulation by the coacervation method has garnered increasing attention in the recent past owing to its practical applications in the agriculture, food, cosmetic, pesticide, printing, adhesive and pharmaceutical industries. Historically, the word 'coacervate' is taken from the Latin word "acervus" which means heap or aggregate and the prefix "co" means the union of the colloidal particles. Generally, the term 'coacervate' signifies the metastable suspension of macro ion-rich drops. It is the electrostatically-driven dense liquid–liquid phase concentrated relatively on macro molecules. More concentrated phase is the coacervate phase and the other phase is the equilibrium solution [9]. Coacervate is sometimes used to define spherical particles of colloidal droplets connected together by hydrophobic forces. Scientist Tiebackx was the first to report the term coacervation [10]. There are two types of coacervation: simple and complex coacervation. Simple coacervation is achieved by changing the conditions causing molecular dehydration of the macromolecules and can be realized by changing different parameters like addition of micro ions, a non-solvent, a temperature change or a change in pH. A macromolecular solute can be brought to coacervation phase separation by adjusting the solvent conditions, such as bringing mixtures of water and various alcohols to different mixing ratios. In a ternary solution of a water soluble macromolecule and two solvent components, demixing at a particular range of alcohol/water ratios would lead to two phases, with a high concentration of macromolecule in one phase which is in equilibrium with a more dilute phase of the macromolecule having a higher water concentration resulting in simple coacervation [11].

Complex coacervation is the separation of a macromolecular solution and composed of two oppositely charged macro ions into two immiscible liquid phases. Bungenberg de Jong and Kruyt first introduced the name "complex coacervation" in order to distinguish it from the simple coacervation of a single polymer. Bungenberg de Jong first investigated systematically the complex coacervation of gum arabic-gelatin [12], a polysaccharide–protein system. Scientist Aleksander Oparin cited his work and mentioned the similarity of proto-cells and coacervates suggesting that life first generated in coacervate droplets. The first theoretical analysis of complex coacervation was provided by Voorn and Overbeek [13]. Subsequent theoretical models were stated by Veis and Aranyi [14], and others [15,16]. Complex coacervation can be achieved in biopolymer pair of protein–polysaccharide mixtures by exact controlling of the external parameters producing electrostatic interactions [17] of oppositely charged macroions. Among the polymer pairs, polysaccharide–protein complex coacervation has attracted much attention in the past few decades particularly in the area of encapsulation of active ingredients.

Present review focuses essentially on the versatility of encapsulation of the active ingredients in the protein–polysaccharide complex coacervate systems. Moreover, review regarding the segregate and conjugate protein–polysaccharide systems is beyond the scope of this article although few complex forming examples of interest are mentioned when necessary. Additionally, an overview on the structure of proteins and polysaccharides with examples of some frequently used proteins and polysaccharides in complex coacervative encapsulation practice, and a few aspects of complex coacervation are included in the first part of the article.

2. Polysaccharides and proteins

2.1. Polysaccharides

Polysaccharides are carbohydrate molecules comprising long chains of monosaccharides linked by glycosidic bonds which upon hydrolysis give their constituent monosaccharides and oligosaccharides. Polysaccharides are largely found in various resources like plant origin, microbial origin, algal origin, and animal origin [18]. They have a large number of reactive functional groups, variable chemical composition, and different ranges of molecular weight, which define their diversity in property and in structure. Different derivatives of polysaccharides can be prepared by chemically modifying the various reactive groups present on their molecular chains [19,20]. They are insoluble in water and generally amorphous in nature. Depending on the structure, they have different physical and chemical properties from their monosaccharide units. Polysaccharides have linear to branched structure comprising structural polysaccharides such as cellulose and chitin and also the storage polysaccharides such as starch and glycogen [21]. Among several polysaccharides cellulose, chitosan, carrageenan, gum arabic etc. are widely used in complex coacervation of polysaccharides and proteins.

Cellulose, a natural polymer, is considered as the most renewable and abundant polysaccharide. It is naturally prepared as microfibrils linked together to form cellulose nanofibers. Biochemically, cellulose, an organic compound with the formula $(C_6H_{10}O_5)_n$, is a straight carbohydrate polymer chain consisting of $\beta \rightarrow 1$–4 glucosidic linkages (Fig. 1). It is biosynthesized by several living organisms such as sea animals, different plants, bacteria, and fungi. It has other different main components like hemicelluloses, pectins and lignin [22]. Sodium carboxymethyl cellulose (SCMC), an anionic derivative of cellulose interacts with protein to form complex coacervates under different conditions [23,24]. Pectin, an anionic polysaccharide, is chiefly found in primary cell walls of terrestrial plants. It is known to form coacervates with globular protein like β-Lactoglobulin using different parameters [25]. Cellulose and its derivatives are useful in many industries such as wood and paper, veterinary foods, fibers and clothes, cosmetic and pharmaceutical industries as excipient [26]. Semi-synthetic derivatives of cellulose has widely used in cosmetic and pharmaceutical industries. Derivatives such as cellulose ethers and cellulose esters are largely used in the design of different drugs and healthcare products [27]. In recent years, cellulose based polymers and their derivatives have gained an extensive status in encapsulation technology and become more important in finding new applications in different fields.

Chitosan is the deacetylated form of chitin. Aqueous alkali is added to chitin at a high temperature of 100–160 °C to remove the N-acetyl groups of chitin. The resulting deacetylated chitin comprising various degrees of deacetylation is called chitosan (Fig. 2) which is slightly soluble in acidic medium. Thus, chitosan is a natural polymer composed