THE PARALLEL LIVES OF POLYSACCHARIDES IN FOOD AND PHARMACEUTICAL FORMULATIONS

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Abstract

The present opinion article discusses how polysaccharide structures can be used in both food and pharmaceutical formulations. We distinguish two regions depending on moisture content where polysaccharides form structures with distinct functional properties. Some trends in key areas of active research are assessed and in particular edible films, encapsulation, polycrystalline polysaccharides, protein-polysaccharide coacervation and fluid gels. We unveil that the physicochemical principles that are shared across the food and pharmaceutical disciplines provide a great opportunity for cross-disciplinary collaboration. We finally argue that such co-operation will help tackling polysaccharide functionality issues that are encountered in both areas.

1. Introduction

Polysaccharides are carbohydrate polymers that are extracted from various natural sources including plants, algae, bacteria, fungi and arthropods. The structural complexity and variability of their fine structure provides a toolbox with a wide spectrum of chemical and physical functionalities to address technological issues in both food and pharmaceutical industries for a range of applications. Established applications include viscosity enhancement of fluid formulations or stabilization of dispersions such as emulsions or suspensions of colloidal solid particles (Figure 1). The ability of polysaccharides to undergo sol-gel transition and structure aqueous solutions is also exploited in both fields. This process results in soft solids that are in a jammed metastable state [1]**. The food industry utilizes gelation events to replace, for instance, fat in low-fat formulations or generate new structures with distinct textural properties. The pharmaceutical industry also employs gelation to fabricate, for example, sustained release drug delivery systems [2] or wound dressings to assist healing [3]. Furthermore, various concepts from material science (e.g., glassy state, phase diagrams, non-equilibrium dynamics, etc.) are frequently employed in both disciplines to analyze and interpret the behavior of polysaccharides when they occur as condensed matter. Apart from established applications that are used in both fields, encapsulation and delivery of compounds is another area, which has advanced at fast pace in the last ten years or so. This technology usually involves engineering the interface of a dispersed system to make it responsive or resistant to the operating environment. For instance, encapsulation of edible oils can be achieved to protect them from environmental parameters (e.g., oxygen) [4]. Similarly, it is feasible by intelligent manipulation of polysaccharides to prepare systems that are responsive to environmental parameters (e.g., pH). Such systems can be used for drug delivery at locations where pH discrepancies may occur (e.g., along the gastrointestinal tract) [5]. Controlling the particle size of the delivery system is one of the most important and challenging factors that need to be addressed when designing such systems. [6]

Figure 1 illustrates the various theoretical concepts and their implementations that are encountered in both food and pharmaceutical disciplines of science. Interaction occurs at multiple levels as the underlying physics or chemistry share common characteristics. For instance, emulsification or encapsulation of either a hydrophobic drug or a flavor compound is governed by exactly the same physical principles, as hydrophobicity is the fundamental quality that determines behaviour. Furthermore, the environment that these systems are required to be functional is remarkably intricate. For example, a drug may be required to withstand the chemically aggressive environment of stomach. Similarly, a flavor compound should resist the processing conditions and chemical environment of the usually complex food matrices.

Present work identifies some common current trends in polysaccharide research in food and pharmaceutical areas and argues that the two seemingly distant scientific areas have common grounds for utilization of these intricate biopolymers.

2. Low moisture polysaccharide systems

The level of solids to promote polysaccharide gelation rarely exceeds 2%. In the solid polysaccharide state water is usually below ~10% thus failing to sufficiently hydrate the chains resulting in restricted molecular mobility and conformational rearrangements.

Such a state of affairs precipitates in a material with distinct structural and physicochemical properties than its high-moisture counterparts. The formed amorphous solid-state structure has the characteristics of glass and it usually forms on cooling or rapid water removal. The solid state of polysaccharides is mostly amorphous although crystalline state may also be observed within the same system (*e.g.,* amylose or cellulose crystals).

2.1 Edible films and coatings

Edible films consist of a thin layer of polysaccharide in the glassy state that provides barrier to moisture, oxygen and aroma diffusion in foods. The main advantage over the synthetic polymer films is their sustainability, as they minimize the need for synthetic packaging. Edible films and coatings can be fabricated using a diverse range of biopolymers including proteins, polysaccharides, waxes or mixtures thereof resulting in composite materials. Antimicrobial agents [7], flavours [8]* or drugs [9] can be also added in the film depending on the application. In the last few years, nanotechnology is exploited to enhance the functionality of the films and create composite materials using nanoparticles from various sources, as for instance, inorganic fillers, [10, 11] chitosan nanoparticles, [12] cellulose nanocrystals, [13] nanoemulsions [14] or drug nanoparticles [15].

2.2 Encapsulation

Polysaccharides can be also used to encapsulate active ingredients such as flavours, pigments, nutrients or drugs. This technology protects the encapsulated compound from oxidation, light, loses due to volatility or interactions with other ingredients in food or pharmaceutical formulations. In the operating environment (*e.g.*, mouth, stomach or packaging) the active component will be released in a controlled manner from the matrix or be protected from environmental perturbations for the duration of the shelf life. Encapsulation usually proceeds with immobilization of the desirable component into a glassy polysaccharide matrix. This is most commonly achieved with spray drying [6, 16] or electrospinning [17, 18] where fine particles or fibers are generated with the active compound entrapped a glassy matrix.

2.3 Polycrystalline materials

Polycrystalline materials are those that are composed of aggregated small crystals of different size and orientation. In polysaccharides and some synthetic polymer systems these materials also include amorphous regions in their structure. In cellulose and chitin for instance, acid hydrolysis of the amorphous regions results in fabrication of a new materials that consist of aggregates of cellulose or chitin crystals at various length scales. Typical polysaccharides that acquire a polycrystalline character during their biosynthesis are starch [19], cellulose [20, 21] and chitin [22] that find applications in food and pharmaceutical industries as fat substitutes, texture modifiers, tablet binders or additives to reinforce biopolymer composites.

3. High moisture polysaccharide systems

On the other side of the spectrum when water molecules are abundant, hydration of the chains is facilitated and promotes interactions that result in distinct structures compared with their low moisture counterparts. Gelled structures and protein-polysaccharide coacervates are the most notable examples of such molecular embrace.

3.1 Polysaccharide - protein complexes

Active agents often need to be incorporated into aqueous-based products to be protected during storage prior to controlled release of, for example, lipophilic drugs, antimicrobials or flavours [23]**. Biopolymer complexes, such as those formed by protein and polysaccharide interactions, form micro- or nano- capsules, particles and hydro-gels and are used in both the pharmaceutical and food industries in the encapsulation of active ingredients [24]. Therefore, a fundamental understanding of the factors underpinning the formation of these materials is essential to optimise their functionality. When polysaccharides are mixed with proteins (Figure 2) there are three possible results:

(i) a homogeneous solution

(ii) a two-phase system where both macromolecules are essentially separated from one another (simple coacervation)

(iii) a two-phase system where both macromolecules are concentrated in the same phase (complex coacervation). This is more common if the biopolymers are oppositely charged thus forming two phases. One phase is the so-called "coacervate phase" composed of electrostatically or non-specifically stabilised polymer complexes and the other is a dilute phase containing large amounts of solvent [25].

Complexes can be soluble or insoluble in aqueous solvent depending on biopolymer concentration(s), ionic strength, pH and temperature [23**, 26-30] as well as the physicochemical properties of biomacromolecules such as the charge on the polysaccharide chains and distribution of surface charge in proteins [31]. Therefore, these complexes have great potential as a bioresponsive material for controlled release [23**, 24, 27, 32] or in the reduction of salt, sugars or fats in foods, as the sensory perception of taste and flavour can be altered by tuning the microstructures [33-35]. Protein-polysaccharide complexes have also been shown to exhibit "better" functional properties than proteins and polysaccharides alone, for example, hydration and interfacial properties [25]. There are two alternative procedures for emulsion formation using polysaccharide–protein complexes in emulsion stabilisation [36]*. The first consists of preparing a solution of both biopolymers, and using the resulting protein–polysaccharide complex for the emulsification. The second method, that is named layer-by-layer (LBL) electrostatic deposition technique [36]*, consists in forming a primary protein-stabilized emulsion followed by addition of the polysaccharide. This leads to the formation of a secondary interfacial layer that frequently results in surface-charge reversal. Polyelectrolyte complexes of β-lactoglobulin and alginate formed using this approach have been shown to suppress lipid digestion in model systems [37].

Ternary systems containing a third biopolymer in the complex may result in a wider range of functionalities and greater resistance to changes in, for example, ionic strength or pH [38]. At least in synthetic systems ternary complexes maintain similar characteristics to binary coacervates; however the choice of the third polymer has an influence on both the material properties and (bio)responsiveness [38]. Finally, many polysaccharides are mucoadhesive (interaction with mucous or mucin) but the effect of complexation with proteins on mucoadhesion has not been fully explored yet.

3.2 Fluid Gels

Subjecting a gel forming biopolymer to a shear field during gelation can result in the formation of particulate micro gels that can be prepared to behave in bulk, as viscoelastic liquids. Microgels exhibit fluid-like behavior while having a cross-linked gel microstructure. These microgels, often referred to as fluid gels (or sheared gels), were first described in the 90's and were produced using polysaccharides, proteins or even synthetically produced polymers [39, 40]. The mechanism by which these gel particles form, was originally described as nucleation and growth process with the molecular ordering limited to within individual gel by the shear imposed on the system. The shear forces that are applied physically are thought to enable the gel nucleation sites to remain distinct from one another resulting in the formation of microgel particles [41]. These fluid gels have received renewed interest recently within food and pharmaceutical systems as a relatively simple method to structure liquid formulations and impart additional functionality. Furthermore, the wide variety of gelling biopolymers to choose from and their different material properties opens up several potential applications with physiologically responsive biopolymers of particular interest. The microstructure of fluid gels can be easily controlled by adjusting processing parameters [42]*. Indeed, changes in the concentration of the polymer, rate of cooling in thermally gelling biopolymers, and/or shear rate during fluid gel formation, controls their particle size and shape (Figure 3) [43-45*]. Moreover, the ability to change the particle size and shape allows the bulk rheology to be tuned and facilitate the application (pouring, spreading spraying etc.). Fluid gels tend to have a significant yield stress and once this stress is exceeded pseudoplastic flow occurs. The bulk viscosity also increases with an increase in the gel strength of the particles due to its greater capacity to resist deformation and subsequent flow [46].

Fluid gels produced from acid insoluble polysaccharides such as alginate [44, 47] and gellan gum have been of most recent interest with gellan gum fluid gels in particular finding applications in both food [48] and pharmaceutical formulations [45]*. In pharmaceutical applications low acyl gellan gum has been investigated as a modified release oral liquid and demonstrated to have the potential to be formulated with a similar viscosity profile to that of a marketed pediatric oral liquid. In addition, it was shown that due to the acid insolubility of gellan gum, it was possible to modify the release of a model drug entrapped in the fluid gel. The drug release, however, was dependent on the acidity and exposure time in simulated gastric fluids [45]*. The acid gel behaviour of low acyl gellan gum and of blends of high and low acyl fluid gels have been explored in food systems as a method to increase satiety [48, 49]. Currently, in our laboratories are under investigation blends of high acyl and low acyl gellan gum fluid gels as a mucoadhesive nasal spray formulations. Incorporating high acyl gellan appears to improve mucoadhesion compared with using low acyl gellan fluid gels alone. Additionally, a further advantage of forming a fluid gel is that the bulk viscosity is sufficiently reduced to enable spraying from a mechanical nasal spray device which was not possible with the non-crosslinked quiescently produced high acyl/low acyl blend.

Fluid gels have also been investigated as a potential fat replacement in low calorie foods as the microgels can be produced to mimic the some of the physical properties of fat droplets [50]. Furthermore, fluid gels have been investigated to deliver enhanced sensory attributes to foods improving mouth feel and textural properties. These properties have been modeled using thin film rheology (tribology) [51] and were influenced by the physical properties of particles such as size and elasticity [46, 52]. Controlling the particle properties, therefore, not only impacts on bulk rheological behaviour but also allows lubrication properties to be manipulated, which may also have potential advantages in topical pharmaceutical formulations.

4. Conclusions

In the present review some current theoretical and applied aspects of polysaccharide research have been discussed. We have identified that polysaccharide structures can be divided into two distinct classes depending on the moisture content of the matrix. Structures that are formed in the high or low moisture regimes of the systems present an opportunity for cross-disciplinary investigation. This holds true, as similar theoretical and technical approaches are shared between food and pharmaceutical disciplines to tackle functionality issues. Understanding and exploiting the underlying molecular mechanisms that govern polysaccharide functionality will result in further integration of these two outwardly distant areas of science.

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Figure Captions

Figure 1: Established and current concepts from engineering, physics and chemistry interact at various levels to interpret the behavior of polysaccharide-based systems across food and pharmaceutical scientific disciplines.

Figure 2: Phase diagram for mixtures of gum arabic (GA) and bovine serum albumin (BSA) as a function of pH and mixing ratio (GA: BSA). Adapted from reference [25] and reproduced with permissions.

Figure 3: Light microscopy images of 0.75% w/v gellan gum loaded with 20 mg/ml ibuprofen prepared at a shear rate of 500 s^{-1} using different cooling rates (a-c). (a) 0.5 °C/min, (b) 2 °C/min, (c) 10 °C/min and different shear rates cooling at 2 °C/min (d-f), (d) 100 s^{-1}, (e) 500 s^{-1} and (f) 1000 s^{-1}. Reproduced from [45] with permissions.

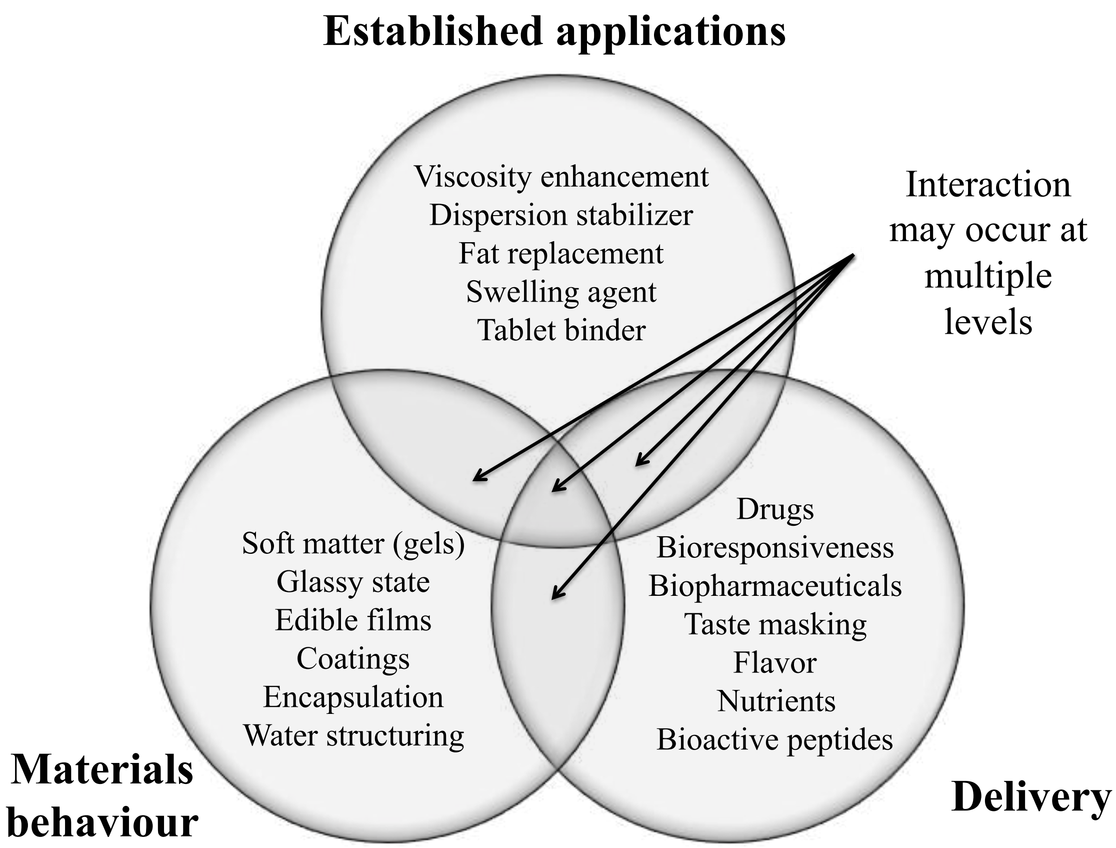
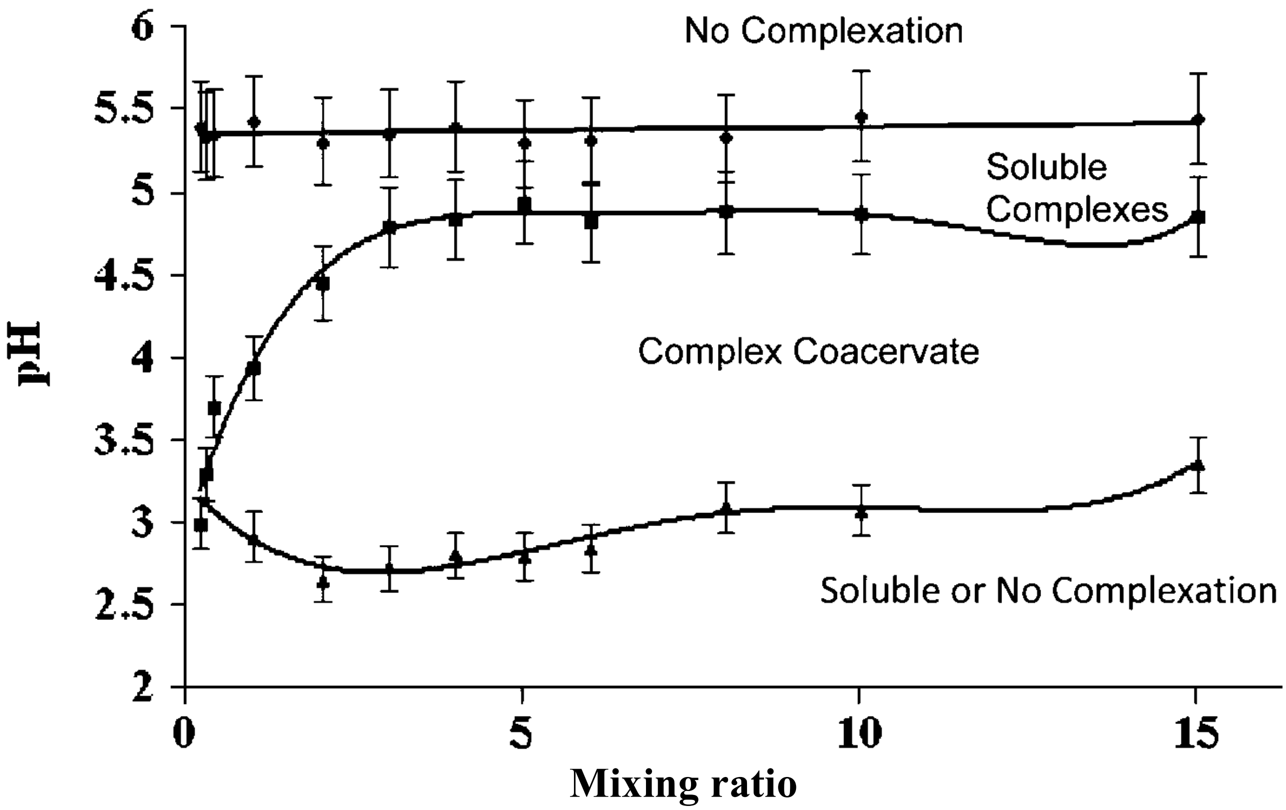

Established applications
Viscosity enhancement
Dispersion stabilizer
Fat replacement
Swelling agent
Tablet binder
Interaction may occur at multiple levels
Soft matter (gels)
Glassy state
Edible films
Coatings
Encapsulation
Water structuring
Drugs
Bioresponsiveness
Biopharmaceuticals
Taste masking
Flavor
Nutrients
Bioactive peptides
Materials behaviour
Delivery

Figure 1


No Complexation
Soluble
Complexes
Complex Coacervate
Soluble or No Complexation
pH
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Mixing ratio

Figure 2

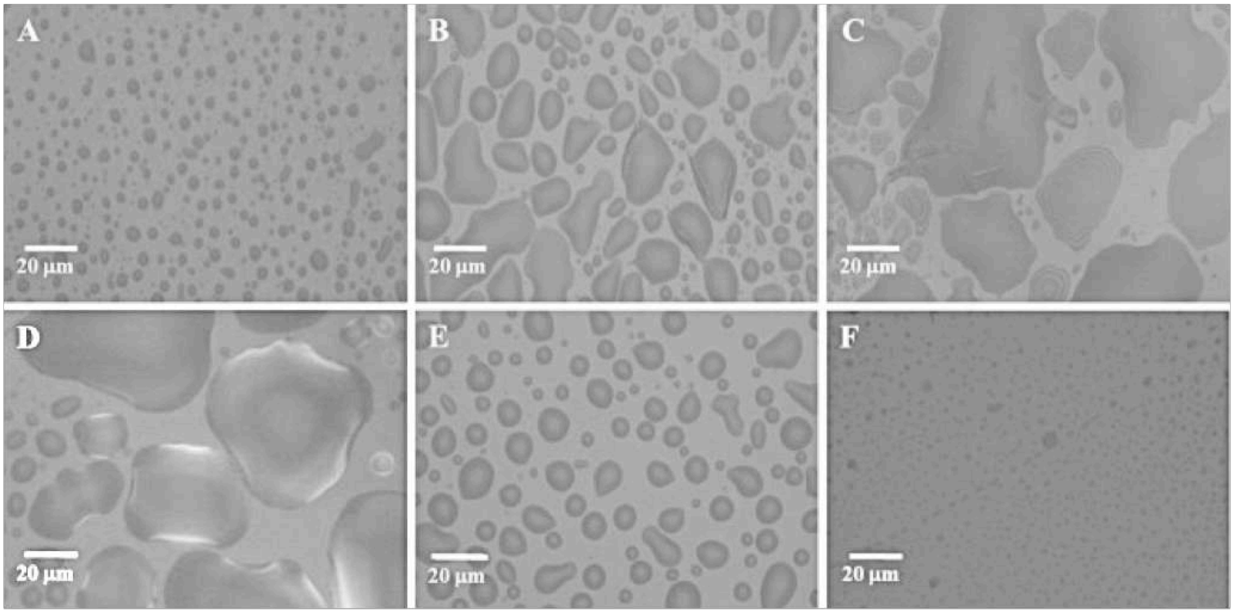

Figure 3