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Review Article

Self-Assembling Phenomena: From Excipients to Drugs

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Abstract

The universality of self-assembly can be illustrated by an extensive range of examples found in all categories of materials present in Nature. Inspired by its principles, multiple scientists have synthesized new self-assembled materials, many of them having pharmaceutical and biomedical applications. This review tries to bring some significant insights related to how minor modifications at molecular level are translated, via self-assembling phenomena, in major macroscopic changes expanding the range of practical applications. Based on the principle of weak forces interactions which didn't involve chemical modifications, self-assembly is an interdisciplinary approach able to generate complex aggregates, some of them comparable to living structures. The advantages of self-assembly consist in generation of organized systems that cannot be made by other procedures and in understanding the phenomena occurring in living organisms. Various examples of self-assembly phenomena were given for starch and its derivatives with the aim to illustrate how the same chemical entity can generate by minor modifications an extensive range of new compounds with divers features. Based on the principle of weak interactions between building blocks, the self-assembly proved its benefits in preparation of more efficient drug delivery systems and anti-cancer treatments. The review also includes some methods that can be used for characterization of self-assembled compounds discussed. More recently, the approaches based on supramolecular self-assembly processes are also used for fabrication of nanometer-scale objects, one of the major fields of research for the current technology.

Keywords

Drug-Drug Interactions; Excipients; Hydrogels; Polyelectrolyte Complex; Polymers; Self-Assembly; Starch Derivatives

General Considerations

Self-assembly of various types of molecules in complex supramolecular structures represents an extensively explored avenue in the development of new entities useful for applications including drug delivery systems, more efficient drugs or diagnostic agents. Furthermore, the fabrication of nanometer-scale objects is one of the major challenges in current technology and several disadvantages including size-restrictions can be solved only by alternative approaches based on supramolecular self-assembly processes. The universality of the self-organized structures is proven by examples found in all categories of materials unifying polymers, proteins, lipids or inorganic molecules which are already present in living organisms or were synthesized. Based on the principle of weak forces interactions which didn't involve chemical modifications, self-assembly transcends the traditional divisional borders of science offering a highly interdisciplinary approach able to generate complex aggregates some of them comparable to living structures. The advantages of self-assembly consist in generation of structures that cannot be made by other procedures and in understanding the phenomena of life [1].

Focused on a wide range of discrete molecules or molecular assemblies (considered as building blocks) and involving physical transformations, the molecular self-assembly is a process by which noncovalent, weak interactions formed between the molecules drive their assembly and organization, affording supramolecular structures that define the final features of the material. In addition to the advantages offered by traditional materials, self-assembled materials provide versatility and functionality for a full range of applications (i.e.,theranostics) by their capacity to be tailored, sometimes at monomer level, with specific properties that suit an intended application [2]. If initially self-assembly was used to develop products as microspheres, micelles and

liposomes based on polymers and lipids, in the last two decades more sophisticated structures appeared proposing nanogels, cubosomes, nanofibers, polyelectrolyte capsules, quantum dots [3], nanocrystals, supramolecular inclusion complexes [4].

The driving forces of the self-assembly are weak physical interactions including hydrophobic associations, hydrogen bonding, electrostatic interactions and van der Waals forces. They are occurring in wet phase and the self-assembly either must be reversible or must allow the components to adjust their positions within an aggregate once it was formed. Therefore, the strength of the bonds between the components must be comparable to the forces tending to disrupt them [5]. Without the intervention of external forces, the process must lead to a lower Gibbs energy, to more thermodynamically stable self-organized structures compared with individual ones.

From the huge variety of possible self-organized structures this review tries to bring some significant insights related to how minor modifications at molecular level are translated, via self-assembling phenomena, in major macroscopic changes expanding the range of practical applications. From ever-increasing number and diversity of applications only part of them will be discussed as examples. The versatility of self-assembling concept will be illustrated in polymeric systems which generated new excipients and in new drug molecules for pharmaceutical or biomedical applications. This review could be considered as a source for pharmaceutical scientists wishing to explore the concept of self-assembling and find practical and elegant solutions to create new structures.

Key Points

Molecular self-assembly is characterized by:

- Non-covalent interactions
- Spontaneity
- Increased thermodynamic stability
- Building blocks
- Order
- Reversibility
- Nano and micro-size

How Self-Assembly Works?

Despite the huge variety of generated structures, two common characteristics are involved in the self-assembly of systems a) hydrophilicity/hydrophobicity or b) ionic charges present on each specie. These two parameters would influence the geometry of the respective systems inducing complementarity in shapes among the self-assembling components which is a crucial aspect [6]. Geometry seems very important for circulatory persistence of anticancer drug (paclitaxel) and cellular uptake. Shuvaev et al., [7] showed that filomicelles (obtained from amphiphilic block copolymers self-assembled into worm-like micelles) can effectively deliver the paclitaxel and shrink human-derived tumors in mice being long circulating vehicles. It was found that filomicelles persisted in the circulation up to one week - about ten times longer than their spherical counterparts [8]. This aspect may give some insights into possible impact of filamentous shape of natural viruses.

Most of self-assembled molecules are amphiphilic containing hydrophobic and hydrophilic domains where the hydrophilic part can carry charges (anionic, cationic or zwitterionic) or be polar but uncharged. The presence and distribution of hydrophilic and hydrophobic characteristics in a molecule is directly related to its chemical composition. Considering general categories of substances i.e., polysaccharides, lipids and peptides there is evident that the interplay of hydrophilicity/hydrophobicity and presence of ionic charges will impact a full range of properties as packing between themselves or external interactions [9,10]. Intramolecular interactions are responsible for the conformation of the molecule conducting to a specific secondary structure (helix, coil, sheet) while the intermolecular non-covalent interactions are responsible of self-assembled macromolecular structures (i.e., micelles, vesicular tubes, lamellar sheets). Figure 1 is illustrative for the self-assembling to limited category of substances and the impact of the distribution of hydrophilic and hydrophobic segments [11].

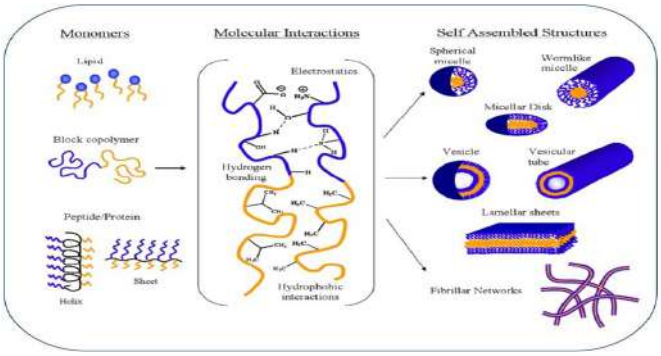

Figure 1: Illustration of self-assembly established by hydrophobic associations and polar interactions. Blue - hydrophilic portions; Orange - hydrophobic regions [11].

In lipids the amphiphilicity is distributed along the length of the molecule. Similar repartition along the molecule length can be found in synthetic block copolymers containing distinct blocks of hydrophilic and hydrophobic polymers [11,12]. In peptide and proteins, the repartition of amphiphilicity is different (Figure 1), allowing an alternation of hydrophilic and hydrophobic features in one face or another of the helix or β-sheet conformation [13]. The stabilization of systems via intra- or inter-chain self-assembling is a common characteristic of polysaccharides and proteins: α-helix and the β-sheet secondary structures in proteins ensure an overall globular subunit while the helical and ribbon-like structures of polysaccharides help them to perform their natural roles in maintaining the hydration and integrity of biological tissues [14].

The folding-unfolding of hydrophobic polymers in water was investigated in order to get some insights of the hydrophobic interactions in the context of realistic self-assembly processes. Hydrophobic polymers are interfacially active preferring locations at aqueous interfaces relative to bulk water, consistent with their low solubility. Molecular dynamics simulations showed that at the solid-water interface, polymer conformations are quasi-bi-dimensional, with folded states pancake-like structures. Some similarities between thermodynamics of polymer collapse and of protein folding, showed the role of hydration and fluctuations in the folding kinetics [15].

Other important aspects on self-organization phenomena are the contribution of interfacial energy when particles (nanoparticles) interact only weakly at flat interfaces and will assembly into more robust arrangements [16] and the interactions of biopolymers with the solvent. These are specific and nonspecific interactions occurring in an aqueous media. The polar Acid-Base (AB) interactions represent about 90% of all the non-covalent interactions in water, they can be attractive or repulsive. Together with AB interactions, the classical theory of non-covalent short-to long-range macroscopic-scale interactions between apolar and/or polar surfaces immersed in a liquid takes into consideration also apolar Lifshitz-van der Waals (LW) attraction and Electrical Double Layer (EL) repulsion. Whilst both AB and EL forces decay exponentially as a function of distance, LW interactions, decay quite gradually, i.e., proportionally to the distance [17].

Irrespective if the polysaccharidic chains are linear (i.e., pullulan) or branched (i.e., scleroglucan, xyloglucan) neutral or ionic, their self-association will be highly dependent on steric conditions issued from chain-chain and chain-solvent interactions [18]. As in all polymer systems, there is an entropic drive to the disordered (random coil) state which must be balanced by sufficiently favourable non-established interactions before a new ordered form can be adopted [19]. In case of polysaccharides, the alignment and interaction of two or more chain segments, usually with long regions of regular covalent sequence, will conduct to secondary structures and supramolecular associations. Using the same concepts of stabilization via weak but extensive and cooperative forces (i.e., hydrogen bonding, ionic interactions) various dosage forms based on polysaccharides, polysaccharides derivatives or polysaccharides and proteins were prepared in previous decades and successfully used to control the drug release [20-22].

Key Points

Features that can influence self-assembly:

- Hydrophilic/hydrophobic ratio
- Interfacial free energy
- Presence of ionic charge
- Specific interactions
- Interaction with solvent
- Complementarity in shapes

Self-Assembly in Polysaccharides

Carbohydrates like starch and cellulose, having the chemical composition based on similar repetitive glucose units, exhibit totally different properties due to the alpha or beta position of the linkage between the glucose block units. With alpha 1-4 orientation starch adopts helical conformations such as V- type single or A-, B-double helix which are packed in circular grains, whereas cellulose, having beta 1-4 links, has a stiff rod-like conformation. In both cases, the self-assembly occurs via hydrogen bonds established between the multiple hydroxyl groups present on the glucosidic chains. In case of cellulose, inter- or intra- chain hydrogen bonds hold the chains firmly together side-by-side conducting to microfibrils with high tensile strength [23].

In starch, various conformations will be translated in different morphologies and consequently in various behaviors of the material [24]. The polyglucosidic chains could be stabilized either in single helix which exhibit a hydrophilic surface and a hydrophobic inner channel or by alternation of hydrophilic and hydrophobic segments in double helices (Figure 2). Furthermore, not only physical but chemical modifications may induce the conversion of B to V-type helices. Such conversion was found by starch cross-linking and carboxylation and will be discussed in the next section.

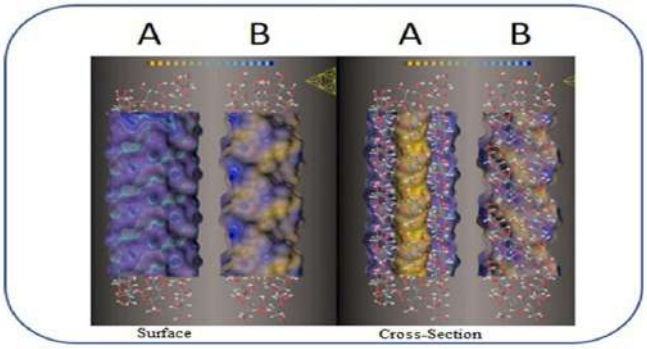

Figure 2: Molecular lipophilic patterns for starch single helix V-type (A) and double helices (B).

For both the left represents the surface; the right is the cross-section. The outside surface area of V-type amylose is uniformly hydrophilic (blue color) whereas the center channel is distinctly hydrophobic (yellow) and able to incorporate equally hydrophobic guests such as iodine or fatty acids. By contrast, the double-helical form of amylose, devoid of a center channel, exhibits an irregular distribution of hydrophilic and hydrophobic regions over the entire surface [25].

The presence of these helical forms and their level of organization in starch composition is the key element for its functionality. If in dry grains the polyglucosidic chains are packed very tightly, in wet phase and at light heating (50°C) this compact organization is disrupted and helical forms are disorganized (Figure 3B), chains adopting a random coil conformation (gelatinization). The process is the result of novel hydrogen bond interactions established between starch chains and water molecules. During

time, in this metastable preparation, the polyglucosidic chains will self-assembly spontaneously and stabilize themselves in double and single helices.This physical process known as starch gelation consists in creation of an extended and stable polymeric network obtained by self-assembling phenomena.

In case of cellulose, a vast number of its derivatives are presently used as pharmaceutical excipients. One important category of gel forming materials are obtained by grafting hydroxylic (hydroxypropyl HP) and hydrophobic (methyl M) groups on cellulosic chains. By modulation of hydrophilic/hydrophobic ratio in the obtained derivatives known as HydroxyproylMethyl Cellulose (HPMC), the hydration of polymer can be controlled and implicitly the drug release via mechanisms driven by diffusion and/or erosion. The main element to control the drug release from tablets based on HPMC is related to polymer self-organization (chains entanglement, relaxation) and their capacity to self-assembly in stable polymeric networks called hydrogels [26].

In case of chitosan, which is strongly stabilized by hydrogen bonding associations, the N-acylation with fatty acid chains, changes the type of self-assembling from hydrophilic to hydrophobic stabilization resulting in longer sustained release time of active agents [27].

Same chemistry and different properties due to self-assembly in starch derivatives

There is a vast number of usages in food and pharmaceutical fields related to gel formation and its structure as a main element defining the kind of application. The self-assembly of starch polymeric chains is largely used in drug delivery systems to delay, sustain, control or target the drug into gastro-intestinal tract.

Minor chemical modifications (i.e., low differences in crosslinking degree) can greatly impact the capacity of organization under helical forms and offer an additional tool to promote or limit self-assembly phenomena. A low degree of crosslinking will allow a lot of flexibility of polyglucosidic chains which can self-organize as double helices and create a stable gel network able to ensure a controlled drug delivery for up to 20h (Figure 3) [28-32]. As soon as the frequency of crosslinking (transversal bridges between the chains) will be too high this will hinder chains closeness and their stabilization [33].Thus, the polymeric chains will be less flexible and the spontaneous enrollment in double helices will decrease. The structure becomes amorphous and starch loses its matrix-forming capacity. This change will be reflected in a drastic modification of its properties: from a matrix-forming material at low crosslinking it becomes a powerful disintegrant at higher crosslinking. Practically the hydroxyl groups will be easily hydrated favoring a fast disintegration. In both cases the self-assembly involves hydrogen bonding between hydroxyl groups of polyglucosidic chains and water molecules [34]. Starch water interactions play a crucial role role on its self-organization [20,35,36].

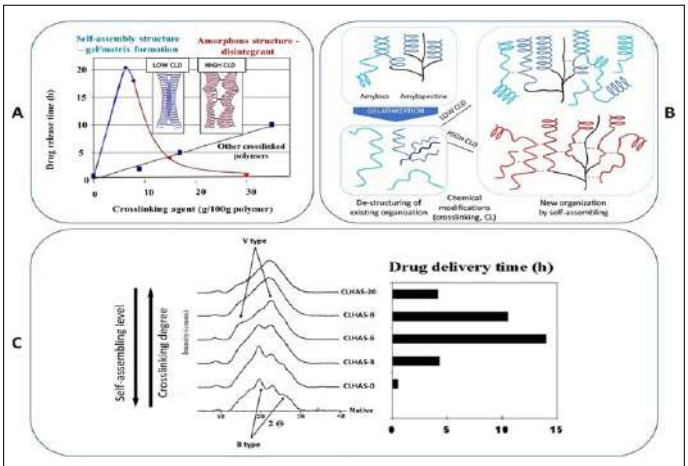

Figure 3: The impact of self-assembly phenomena on starch excipients used in drug delivery.

A) Drug release properties of starch with low (in blue) and high (in red) crosslinking degree (CLD); B) Self-assembly phenomena occurring during starch gelatinization and reorganization following chemical crosslinking; C) X-ray diffractograms associated with the presence of double helices and single helix organization; Increase of Cross-Linking Degree (CLD) avoid self-assembling generating more amorphous structures [29].

The capacity of starch to self-assembly in helical forms distinguishes completely its behavior compared to synthetic polymers where an increase of crosslinking degree generates smaller size of polymeric mesh and consequently a longer release time of drugs (Figure 3A other polymers [37]). In crosslinked starch the variation of drug release time is non-monotonous because only a narrow window (i.e., 3 - 6 g crosslinker/100 g of polymer) of crosslinking allows enough flexibility of chains to adopt spontaneously stable structures (Figures 3A and B). X-ray diffraction technique is an useful tool able to capture organization of polyglucosidic chains as B-double or V-single helix morphological forms and a good structure-properties correlation can be established [31] for such systems (Figure 3C).

More generally, the ratio between order (i.e., presence of helices, sheets, crystals, etc.) and disorder (amorphous structures, individual species, etc.) of a system will be an essential aspect ensuring its stabilization by self-assembly phenomena and a key element to modulate it and obtain specific properties [38].

Ionic charges: Carboxymethyl starch from gastric stability to intestinal chrono-delivery

Based on non-covalent forces, the self-assembling could be reinforced or weaken by the presence of electrostatic charges. Stimuli-responsive hydrogels, including thermo- and pH-sensitivity, are also considered with particular focus on self-assembled structures with pharmaceutical applications. Depending of the type of charge (anionic, cationic) and its location (on the same or different chains) the attractions or repulsions electrostatic forces

will impact conformation of the chains and consequently their geometry, proximity and solubility [39]. In polysaccharides the abundance of hydroxyl groups is responsible for intra and intermolecular H-bond interactions that will conduct to a supramolecular organization [19]. The presence of ionic substituents on the polysaccharidic chains will contribute mainly to the same phenomena: stabilization of helical conformation and gel formation but in these systems the electrostatic forces will also participate in the self-assembling (Figures 4 and 5).

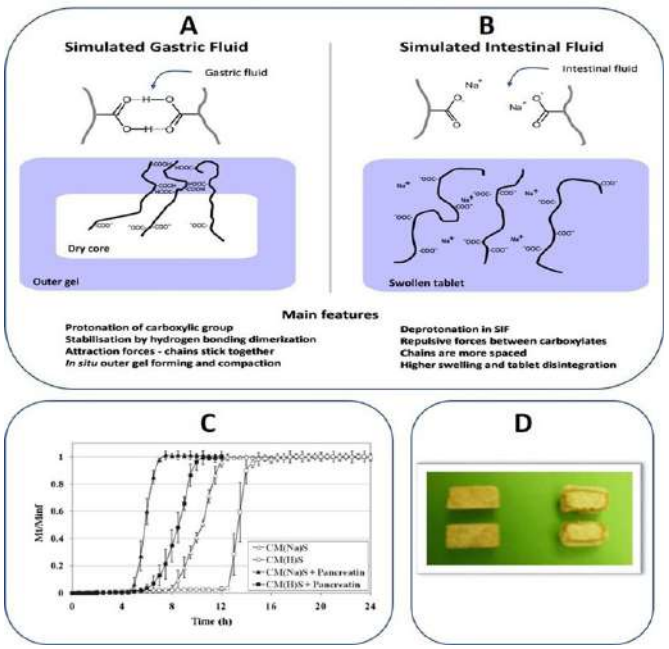

Figure 4: Illustration of self-organization in an ionic starch derivative and in pancrelipase tablets when exposed to simulated gastric and intestinal fluids.

A) CMS in SGF; B) CMS in SIF; C) Diclofenac release profiles obtained from double core CMS tablets; D) cross section of pancrelipase excipient-free tablets exposed for 1 h to SGF [40,41].

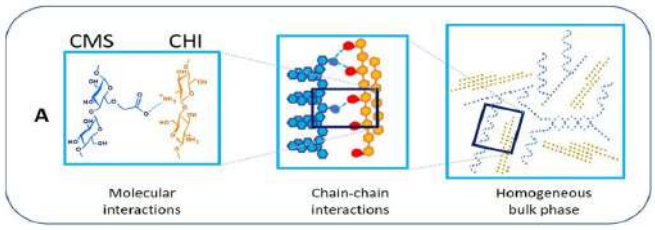

Figure 5A: Schematic presentation of CMS and CHI self-assembly established by electrostatic interactions between anionic carboxylic groups and cationic amino groups.

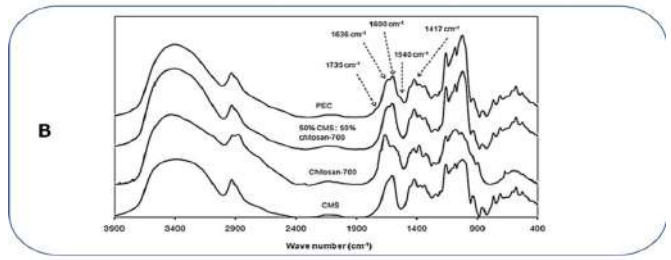

Figure 5B: FTIR spectra of CMS, CHI, CMS-CHI, CMS-CHI (50:50) blend and PEC in KBr disks [42].

We will consider the example of the CarboxyMethylStarch (CMS) to illustrate the impact of the anionic charges on starch functionality. Even at very low degree of substitution (few carboxymethyl CM groups grafted on starch chains (Degree of Substitution DS 0.029) [43] the polymer solubility becomes pH dependent exhibiting low solubility in gastric medium (pH 1.2) but dissolving in the intestine at neutral pH. From pharmaceutical perspective, this dependency was useful for oral dosage forms requiring gastro-protection. CMS have shown excellent features for oral formulation of bacteria [44], vaccines [45], therapeutic enzymes [46,47], etc. The mechanism of gastro-protection offered by CMS in media simulating stomach acidity can be explained by self-assembly of carboxylic groups. In acidic media they are protonated (Figure 4A) and, due to their tendency to create dimers the polymeric chains become very close and stabilize between themselves. These chain-chain interactions via carboxylic groups will generate *in-situ* an outer gel layer which will act as a pH-protecting coating at the surface of the tablet keeping the core untouched by acidity (Figure 4A). In Simulated Intestinal Fluid (SIF) the CM groups will be ionized and their repulsive electrostatic interactions as well as presence of water and salts in the media will favor a rapid hydration of chains and consequently tablet swelling, erosion and disintegration (Figure 4B).

This pH-dependency of CMS associated with its self-assembling capacity was applied to delay the release of some drugs (i.e., sodium diclofenac) for 4h or 8 h and respectively 12 h (Figure 4C) with a chronodelivery patterns [40]. Similar associative phenomena were observed also in proteins which are able to self-stabilize by weak forces when exposed to SGF. Formulation of therapeutic enzymes could be problematic considering that the application of an enteric coating could alter enzyme activity. For such challenging formulations it was found that a very simple process of dry mixing of enzyme powder with a minimum amount of CMS can generate gastro-resistant tablets [41]. The

external layer (brown color - Figure 4D) formed at the surface of such tablet obtained by direct compression of pancrelipase with a minimum amount of CMS (less than 10%) is acting like a protective coating able to preserve the enzymatic activity of pancrelipase inside the tablet core (light color).

Polyelectrolyte complexation: CM-Starch and Chitosan intelligent tandem-excipients

Generally, the presence of charges on the polymeric chain implies also counterions and, compared to non-charged polymers, the polyelectrolytes are more soluble in water due to electrostatic repulsions among and along polymeric chains and more sensitive to salts.

The usefulness of self-assembled structures can be illustrated by the preparation of Polyelectrolyte Complexes (PEC) when one of anionic polysaccharides (i.e., carboxymethyl starch, gellan, xanthan, alginate) was used in combination with chitosan [42,48,49]. When synthetic or semi-synthetic polymers are used, depending on preparation method, the distribution of the two polymers could be very different and may generate various types of products from nano fibers [50], beads [48], nano/microparticles [51] to cryogels and multilayer films [52] which can serve to adapt the dosage form to specific requirements [53].

In case of PEC obtained by self-assembling of CMS (carrying anionic COO^- groups) and Chitosan (CHI) (positively charged with NH_3^+ groups) (Figure 5A) it is interesting to note that the processing has a significant impact on properties of PEC. When CMS and CHI (80% deacetylated) were mixed as dry powders and compressed together their blend generated matrices able to control the drug release for up to 6-8h [42,54]. If the same individual polymers, respectively the anionic CMS and cationic CHI are co-processed together, the properties of the obtained complex may be improved in terms of stability and homogeneity. The mixture of the polymers in solution, upon drying, will present particles with size similar to the raw powders but each of them will contain small regions of both polymers. These small regions will allow closer neighboring of the cationic and anionic polymers than in the dry mixture. This will result in formation of stronger gel able to contain various molecules i.e., the liberation of aspirin was extended to more than 24h, compared to 6-8h for the mixed powders [42].

The structural analysis by microscopy have showed that the two components were co-precipitated. FTIR data have showed some chemical interactions between CMS and CHI. When PEC spectrum was compared with those of CMS and CHI blend, equivalent peaks were found, except for the weak shoulders around 1735 cm^{-1} and 1540 cm^{-1} for PEC at pH 5. They could be attributed to -COOH and - NH_3^+ groups and seems to be related to weak interactions established between the two ionic groups (Figure 5B). The amine and amide bands of chitosan are known to shift upon complexation or be influenced by the environment in regards of the type of polymer used for the association [55,56]. Further studies could emphasize the FTIR band shifting in relation to the PEC ratios or with different polymers used in associative compounds.

Self-assembled nanostructures in drug delivery hydrogels, via physical interactions between polymer-polymer and polymer-drug, require accurately controlled macro- or small molecular architecture and a comprehensive knowledge of the physicochemical properties of the therapeutics. A variety of nanostructures within hydrogels provide useful routes to stabilize the encapsulated drug and control its release kinetics such as micelles, layer-by-layer constructs, supramolecular inclusion complexes, polyelectrolyte complexes and crystalline structures [57-59].

Key Points

- Starch is a very versatile polymer able to generate by self-assembly a vast range of excipients useful for pharmaceutical and biomedical applications
- Minor modifications at molecular level will be translated in new self-organized structures and new features of the polymer
- Starch morphology plays a crucial role on its functionality and distinguishes starch from many other excipients

Drug - Drug Self-Assembly

Differently from existing approaches which explore mainly the drug-excipient association in order to improve drug solubility or stability, a new alternative: drug-drug self-assembling - using two different active molecules, was also explored recently [60-64]. Mesalamine (5-aminosalicylic acid, MES) known as a drug for inflammatory bowel disease seems be frequently associated with side effects when administrated orally [65,66]. Sucralfate (SUC) is a non-systemic local protector prescribed in the treatment of gastric ulceration. The anti-inflammatory action of MES in association with bioadhesiveness and mucosal healing properties of SUC were envisaged as a possible treatment of ulcerative colitis. It was found that via self-assembling of the two drug molecules, a new and stable entity can be generated [60].

The structural data (X-Ray, FTIR, SEM, DSC and ^{1}H-NMR) have shown that MES and SUC can interact leading to complexes with properties differing from those of each separate active agent and from their physical blends. ^{1}H-NMR results indicated that complexation occurred in aqueous suspension of mixed drugs, prior to drying suggesting that the drug-drug self-assembling was the driving mechanism in the formation of the new entity. Based on the structural data, a hypothetical structure of the complex was proposed (Figure 6) where ionic interactions

(between amino groups NH_2 and aluminum ions) as well as hydrogen bonds (established between HO- groups of carboxylic function of mesalamine and hydroxyl of the aluminum of sucralfate molecule) will contribute to stabilization of self-assembled entity. It was observed that when the two drug molecules are in aqueous medium a thixotropic paste is formed. Furthermore, *in vitro* dissolution studies monitoring mesalamine release from oral solid dosage forms based on MES-SUC complexes showed a very linear, controlled release [60].

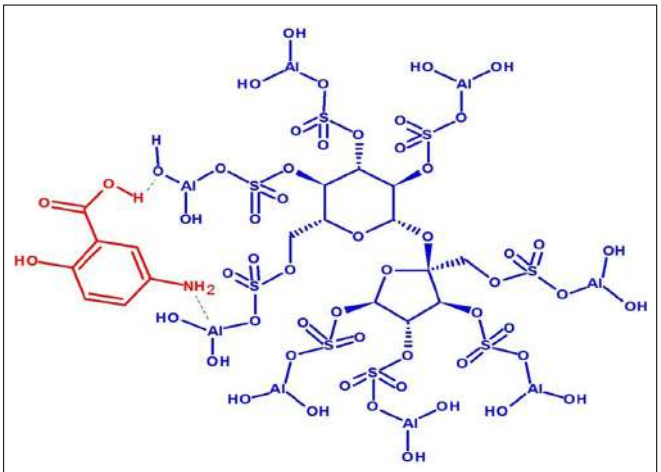

Figure 6: Hypothetical structure of self-assembled Mesalamine - Sucralfate complex.

Drug-Drug Delivery Systems (DDDSs) start to prove their better efficacy mainly in cancer therapy. Zang and co-researchers have shown that a supramolecular DDDS composed of pure drugs provides a hopeful approach for cancer treatment. The proposed drug-drug delivery system was obtained via coassembly of Gefitinib (GEF) and tripeptide tyroservatide (YSV), two chemotherapeutic pharmaceuticals used for non-small-cell lung cancer. Various techniques (transmission electron microscopy and dynamic light scattering) have shown that GEF and YSV self-assembled into nanoparticles with regular morphology and uniform size, results in more efficient entering into cancer cells and inhibition of the proliferation of cancer cells compared with single GEF, YSV, or GEF/YSV drug mixture. *In vivo* experiments showed that the DDDS can selectively accumulate in tumor tissue, resulting in much better drug efficacy without evident side effects provides thus a promising route for enhanced anticancer therapy in nanomedicine [63].

Conclusion

From the discussed examples it becomes evident that Nature can assemble various building blocks to form more complex polysaccharide structures. This principle is also found in many synthetic or semi-synthetic self-assembled biomaterials such as cyclodextrins and triblock copolymers with Polyethylene Oxide (PEO) forming supramolecular structures like polyrotoxanes [67-69] or metallo-organic antifreeze proteins able to inhibit ice-grow based on a model find in nature [70]. Combinations of different categories of substances (i.e., polymers with lipids, peptides or proteins) used as excipients in the design of new drug delivery systems can be prepared based on the same principles of weak interactions, hydrophilic-hydrophobic balance and presence of ionic charges that can be used to tune a specific structure of a self-assembled system.

Transition from natural structures to synthetic ones and the similarity in how these systems can stabilize themselves may open a multitude of roads to build desired supramolecular structures for specific purposes in various fields related to nanotechnology.

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