Chapter 11

An Overview of Chitosan-Xanthan Gum Matrices as Controlled Release Drug Carriers

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Additional information is available at the end of the chapter

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Abstract

Naturally occurring polysaccharides and/or their chemically modified derivatives have been widely investigated in relation to their use as components of controlled release systems for drug delivery. The aforementioned is due, in part, to their distinct properties such as abundant availability and biocompatibility as well as environmental and economic advantages. Chitosan (CS) and xanthan gum (XG) based matrices have received growing scientific/pharmaceutical interest as oral controlled release drug carriers. Herein, recent advances spanning the last two decades in CS-XG based drug delivery systems are reviewed with the emphasis being on oral tablet formulations, due to their versatility as pharmaceutical dosage forms. The mechanism of interaction between CS and XG, by means of computational and experimental approaches, is scrutinized. Results obtained from the literature establish the possibility of fabricating a controlled release drug delivery system based on CS and XG matrices. This can be achieved by monitoring and manipulating the physiochemical properties of the two polymers as well as the experimental variables affecting their drug retardation efficiency, without the need to employ special equipment or sophisticated experimental techniques/methodologies.

Keywords: drug delivery, controlled release, polymeric matrices, natural polysaccharides, xanthan gum, chitosan, polyelectrolyte complexes, molecular dynamics simulation

1. Introduction

The ultimate goal in drug design and development is to optimize a carrier that ensures the delivery of the active pharmaceutical ingredient(s) (APIs) to the systemic circulation in a safe

and stable manner [1]. Patient compliance is a key aspect to consider when designing a new pharmaceutical dosage form [2]. Therefore, the way the drug will be introduced to the body should be optimized to ensure the availability of the drug at its site of action, at levels within the range of its therapeutic window (**Figure 1**).

Despite emerging advances in drug delivery, the oral route remains the predominant route of drug administration. It is the simplest route, non-invasive and provides ~200 m^2 of readily available surface area for drug absorption [3]. Conventional oral dosage forms usually release drugs immediately in the body, via first order release kinetics for both absorption and elimination processes [4]. Since the efficacy of the administered drug is limited to its residence time in plasma, frequent administration is required for APIs which exhibit a short biological half-life. As a result, low patient compliance and high fluctuation of drug levels in plasma is expected [5, 6]. In order to counter the foregoing drawbacks of conventional dosage forms, a new term in drug delivery was introduced; modified release dosage forms [7].

The United States Pharmacopeia defines modified release tablets as "coated or uncoated tablets that contain special excipients or are prepared by special procedures, or both, designed to modify the rate, the place or the time at which the active substance(s) are released". Modified release delivery systems can be divided into delayed release systems and prolonged/extended release systems. Extended release delivery systems can further be subdivided into sustained and controlled release delivery systems, which differ in the rate at which they deliver APIs to the human blood circulation. Sustained release formulations function by continuously releasing APIs for a prolonged period of time. On the other hand, controlled release (CR) delivery systems do not only retard the release of the drug, but they deliver the drug to the body at a predetermined release rate or location [8]. Consequently, constant drug levels can be achieved (**Figure 2**).

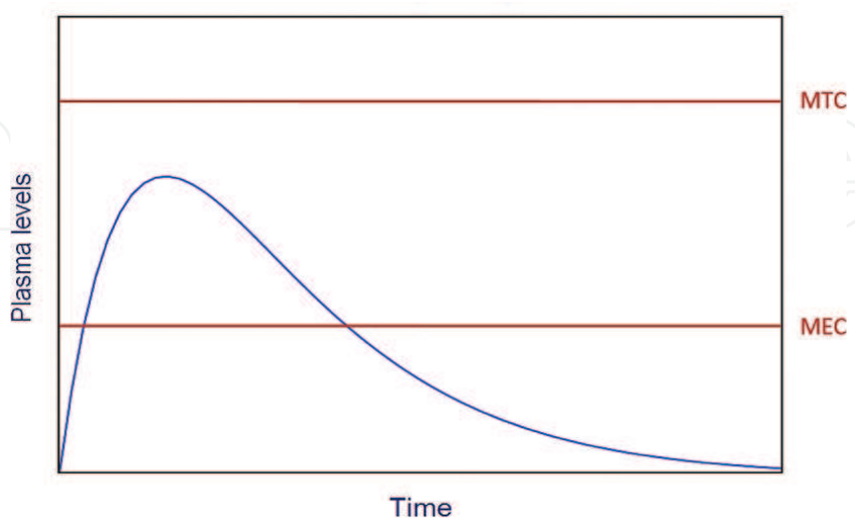

Figure 1. Plasma levels and therapeutic range of a drug following an oral administration of a single dose. MTC: minimum toxic concentration, and MEC: minimum effective concentration.

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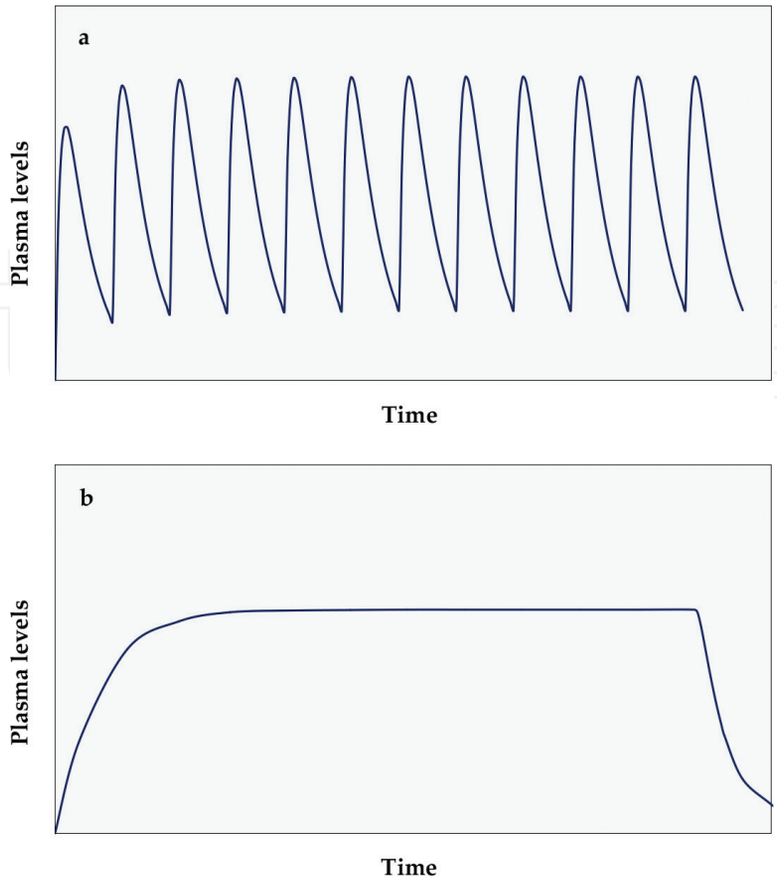

Figure 2. Comparison of plasma concentration-time profiles of drug release following multiple dosing from: (a) conventional, and (b) controlled-release dosage forms.

2. Controlled drug delivery

CR systems are composed of inactive pharmaceutical ingredient(s) that entrap the API(s) and release it/them at a time different from the immediate release form [4]. Researchers in the field of drug delivery have, and are currently still trying to acquire a better understanding of CR by attempting to integrate pharmaceutical technology with the relevant pharmacokinetic parameters associated with different drugs [9]. The rational underpinning controlled drug release includes, but are not limited to: masking the undesired side effects of drugs, attaining a constant drug release profile with minimal drug level fluctuations, and enhancing patient convenience by reducing administration frequency [10]. CR dosage forms are not only capable of extending the time over which drugs are released and providing constant drug levels but also with the potential of protecting therapeutic biomolecules such as peptides and proteins from enzymatic degradation in the gastrointestinal tract (GIT) [11]. CR systems can also be formulated to target the delivery of APIs to the desired site of action [12, 13].

Aside from the substantial need for CR formulations in drug delivery and the potential advantages they offer, the reproducibility and cost of equipment and techniques needed for the preparation of CR dosage forms on a large scale present a major obstacle towards the

widespread production of CR delivery systems in pharmaceutical manufacturing. **Figure 3** summarizes the key factors which require to be taken into account when optimizing a new CR dosage form.

2.1. Design of CR systems

2.1.1. APIs

There are several criteria and properties that should be taken into consideration in the proposed use of an API when designing a controlled release formulation [14, 15].

- The elimination half-life of the drug should be short. Drugs with long half-lives, greater than 8 h, provide a sustained release profile without the need to be formulated in a controlled release system.
- Drugs with a wide therapeutic window are better candidates since higher doses need to be incorporated in CR formulations and dose dumping could occur.
- The absorption rate of a candidate drug should be high to make sure that the release of drug from the CR delivery system is the rate determining step, not the absorption rate.
- Drugs which exhibit high protein binding are retained in the plasma for a long time; thus, they do not require a CR delivery system.
- Drugs that undergo extensive first pass metabolism are poor candidates for CR, since releasing the drug at lower rates will decrease its bioavailability. APIs with a bioavailability index higher than 75% are preferable.

Figure 3. Key factors to be considered when developing a new dosage form in the pharmaceutical industry.

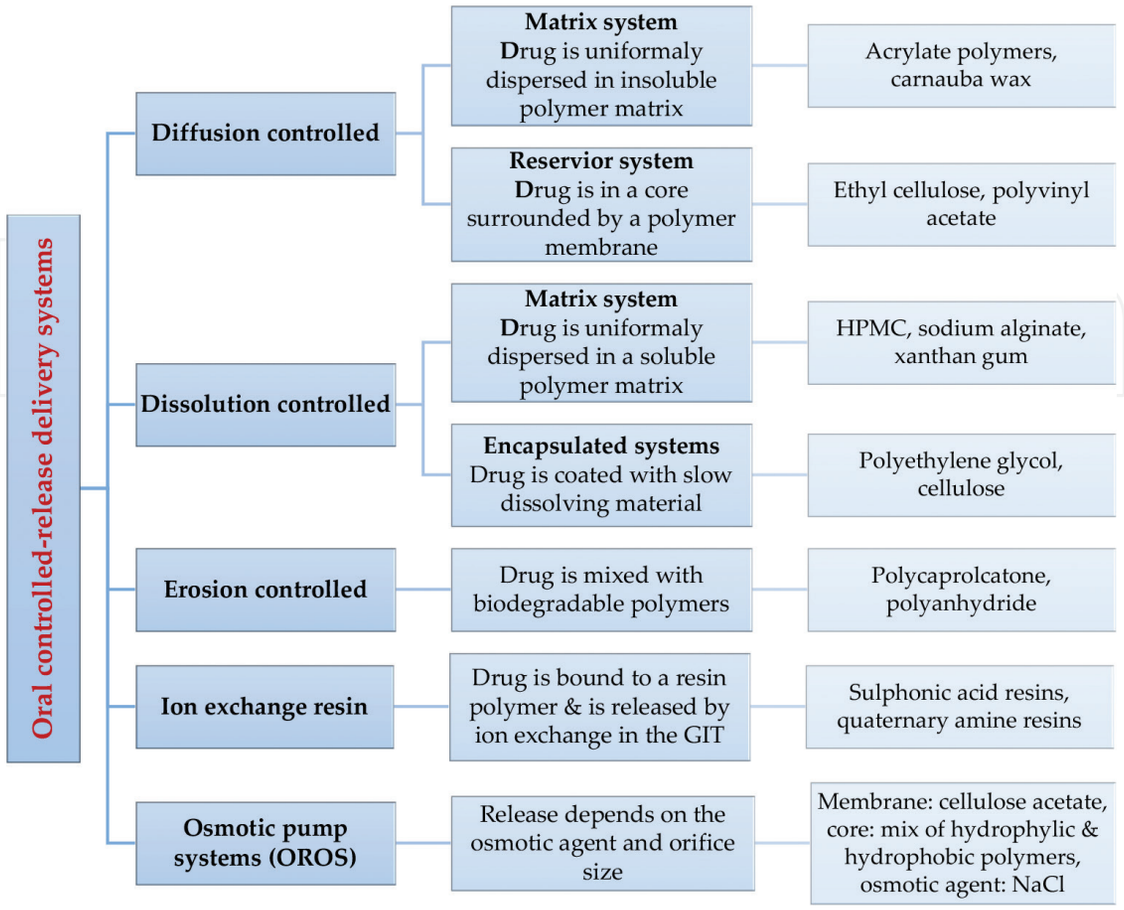

Figure 4. Classification of controlled release drug delivery systems combined with the main mechanisms involved in drug release and examples of inactive ingredients used to achieve CR.

Model	Equation	Mechanism of release
Zero order	$Q_t = Q_0 + K_0 t$	Release is independent of drug concentration within the matrix or device
First order	$\text{Ln}\, Q_t = \text{Ln}\, Q_0 + Kt$	Release is dependent on drug concentration within the matrix or device
Higuchi	$Q_t = K_H t^{1/2}$	Drug released via diffusion through an insoluble polymeric matrix
Hixon-Crowel	$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$	Drug release is dependent on drug dissolution rate in the media
Korsmeyer-Peppas	$Q_t/Q = K t^n$	This model is used when several mechanisms are involved in drug release from the system

*Where Q_0 is the initial amount of drug in the dissolution media, Q_t is the fraction released at time t, K is the rate release constant, and n is the release exponent.

Table 1. Mathematical models of drug release kinetics from CR formulations*.

2.1.2. Carriers and mechanism of drug release

Controlled drug release can be achieved by utilizing special techniques and devices. As the release of a drug from the delivery system is the rate limiting step in controlled release formulations, CR systems are classified according to the mechanism involved in drug release [3, 16].

In some preparations, more than one mechanism can be involved in the release of the API(s) from the CR systems (**Figure 4**).

2.1.3. In-vitro drug release kinetics

Since the objective of utilizing CR systems is to deliver a drug, or drugs, over a known time interval, several mathematical models (**Table 1**) have been suggested to describe drug release from the systems as a function of time.

3. Natural polysaccharides

Polymers are the most used materials to control the release of APIs. They can be classified as synthetic (silicons, polyesters and cellulose derivatives) and natural polymers (proteins and polysaccharides). Many naturally occurring polymers are inert, biodegradable, and cost-effective in relation to their industrial use [17]. In addition, their chemical structure can usually be easily modified to achieve the desired properties for a specific purpose [18]. Hence, the utilization of natural polymers as components of drug vehicles is gaining extensive attention [3]. The most used polymers are saccharides (carrageenan, cellulose) or proteins (collagen, gelatin) [19].

Natural polysaccharides are hydrophilic polymers consisting of repeating monosaccharide units linked via glycosidic bonds [20]. They are obtained from various sources, mainly vegetal (cellulose, starch), microbes (xanthan gum, dextran), crustaceans (chitin) and algae (alginate, carrageenan) [21, 22]. Depending on the identity of the constituent monomer(s), polysaccharides can be divided into homo-polysaccharides which are composed of the same repeating unit, such as cellulose, or hetero-polysaccharides which are built up from different saccharide units e.g., CS and XG [23, 24]. They can also be classified according to their ionic charge: non-polyelectrolyte (starch, cellulose), and polyelectrolyte polysaccharides. Polyelectrolytes are further sub-divided into negatively charged polymers; such as alginate and XG, or positively charged polymers, which are few in number, such as CS [25, 26].

The unique physicochemical characteristics of each polysaccharide are related to the type of monosaccharide building unit, position of the glycosidic bond, chain substitution and the overall molecular weight [25, 27]. Due to the presence of various functional groups attached to the polymer backbone (carboxyl ─COOH, amine ─NH2 and hydroxyl groups ─OH), polysaccharides have the ability to form non-covalent bonds with a wide range of synthetic and biological molecules [28, 29]. Moreover, they can attach to body tissues and mucus layers and sustain the release of encapsulated active ingredients [13]. The aforementioned properties have attracted attention towards the usage of polysaccharides in major industries including food, agronomy, cosmetics, biochemical engineering and pharmaceutical manufacturing [30, 31].

3.1. Chitosan (CS)

CS is a linear polysaccharide produced by the *N*-deacetylation of chitin [32]. Chitin is found mainly in the exoskeleton of marine crustaceans as well as insects and fungi [33]. Glucosamine and *N*-acetyl glucosamine are the building units of CS. They are linked via β(1-4)glycosidic bonds (**Figure 5a**). The degree of acetylation and distribution of acetyl groups along the polymer

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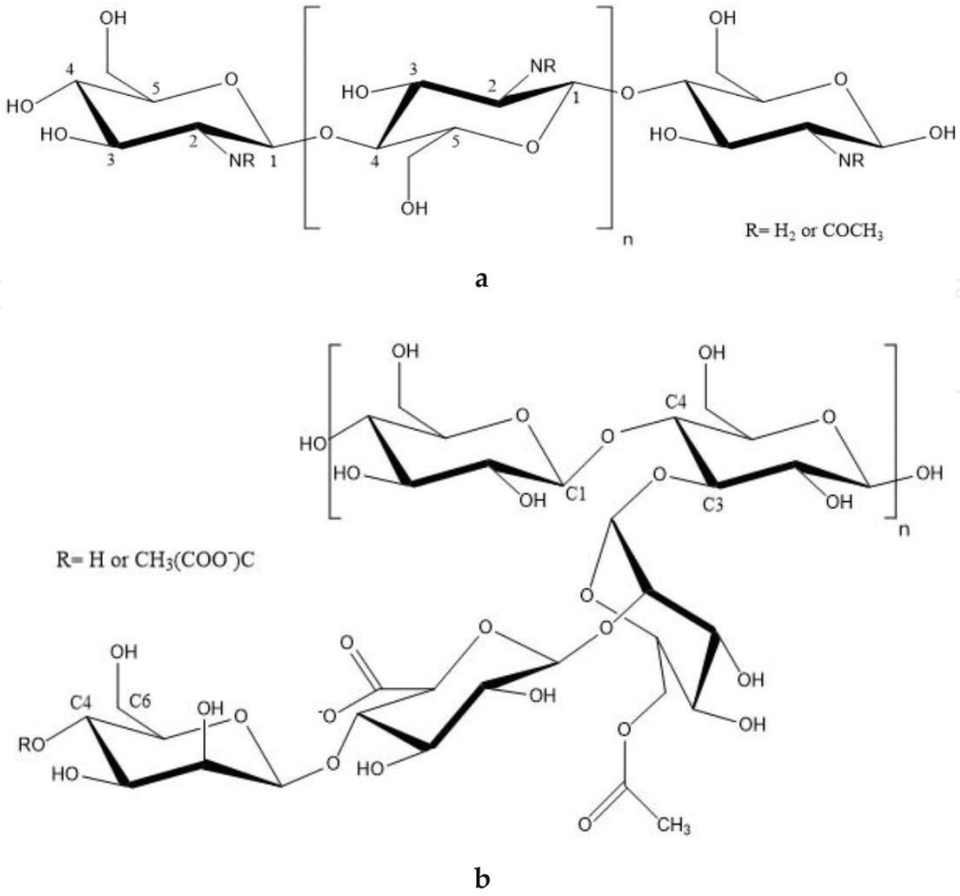

Figure 5. Schematic chemical structures of the building units of: (a) CS and (b) XG.

chain (either block or random distribution) are dependent on the duration of the deacetylation process and preparation method for CS [34, 35]. Following deacetylation of chitin, CS is (unlike chitin) soluble in acidic media. Moreover, the presence of primary amine groups leads to the unique properties of CS over all other natural polysaccharides [36]. It is the only saccharide possessing a high density positive net charge, which allows it to interact with a wide range of anionic polymers and biological molecules [32]. In addition, CS shows high mucoadhesion in the GIT which increases the residence time and enhances the permeation of active molecules [30]. Hence, CS is used commonly in the food industry, for pharmaceutical drug delivery and tissue engineering [37, 38].

3.2. Xanthan gum (XG)

XG is a branched, hetero-polysaccharide produced via microbial fermentation of the microorganism *Xanthomonas campestris* [39]. The primary unit of XG (**Figure 5b**) consists of a cellulosic backbone composed of two D-glucose units (1-4) β-linked to a side-chain of D-mannose and D-glucuronic acid units at a ratio of 2:1, respectively [40]. D-Mannose, which is connected to the main backbone, is attached to an acetyl group at O6, while approximately half of the terminal D-mannose forms a pyruvic acid group between carbons C4 and C6. This side-chain is found at the O3 atom of each alternate glucose unit on the backbone. Due to the presence of carboxylic groups in its structure, XG exhibits a net negative charge and can form complexes

with cationic polymers [41]. In the last decade, the demand for XG, in industry, has been increasing at about 5–10% per annum [42]. It is used in a broad variety of industries, including cosmetics, agriculture, food, textiles and oil [43, 44]. This is due to its safety (non-toxic), desirable rheological properties, high stability over a wide range of pH and temperature, together with its high resistance against enzymatic degradation [45, 46].

4. CS and XG matrices as controlled release drug delivery systems

4.1. Advances and applications

Matrix systems, based on polyelectrolyte polysaccharides, used to retard the release of APIs have been reported in the literature and some of them have been commercialized [29, 47]. The long term instability of their corresponding preparations due to the existence of charged groups limits their application in pharmaceutical manufacturing [48]. Introducing a cross-linker, such as tripolyphosphate or glutaraldehyde, to neutralize the polymeric matrix is a necessary approach to confront such a shortcoming. Though, substituting the cross-linker with an oppositely charged copolymer aids and abbets the synergistic effect of drug release retardation. XG proved to be a potential CR drug carrier. In aqueous solutions, XG shows high viscosity and water uptake capacity encapsulating the drug inside a thick gel-like layer which hinders the release of the incorporated drug. XG has been used alone and with other polymers such as HPMC, karaya gum, guar gum, and polyvinylpyrrolidone (PVP), or ethyl cellulose [49–53]. Formulated matrices were able to sustain the release of caffeine, azithromycin, ibuprofen and propranolol HCl. XG demonstrates a high capability of generating a near zero drug release profile.

Being the only known positively charged natural polymer in aqueous solutions, CS has been extensively investigated as a potential drug vehicle. CS has the ability to preserve the stability of active biomolecules, namely insulin, and enhance their absorption from the GIT [54–56]. CS was mixed with various polymers with the aim of modifying the release of active ingredients, protect genes and therapeutic peptides in the GIT and improve their permeation across the intestinal epithelium and to immobilize antibodies [57–59]. Alginate, carrageenan, pectin, hyaluronic acid and XG are amongst the many natural polymers to be used with CS [47, 60, 61].

The combination of CS and XG was first used in the form of a polyelectrolyte complex (PEC) hydrogel [62]. The hydrogels formed displayed pH dependent swelling behavior and addressed the possibility of developing a gastrointestinal drug delivery system. PECs are formed due to the attractive ionic forces between the positively charged amino groups in CS and the negatively charged carboxyl groups in XG [63]. Therefore, features of the PECs produced can be controlled by manipulating the physicochemical properties of each polymer [64]. Molecular weight, degree of acetylation (DA) of CS, and pyruvic acid content in XG are amongst the most crucial factors to be addressed [47, 65, 66]. Complexation conditions (including concentration of each polymer, mixing ratios, and pH) have a significant influence on the behavior and stability of the resulting PEC [67]. The combination of CS and XG has been extensively studied as a platform for CR drug delivery, resulting in many patents and the publication of research articles.

4.1.1. Patents on CS-XG based controlled release drug delivery system

CS-XG hydrogels have been studied in order to immobilize biological materials. This is due to their insolubility and high stability in acidic medium allowing the system to preserve biological activity and release the materials at neutral pH. CS-XG hydrogels served as a promising candidate for sustained release dosage forms [68]. CS-XG hydrogels were capable of stabilizing and controlling the release of highly sensitive active ingredients such as vitamins, amino acids, nucleic acids and polypeptides when applied topically or orally as dietary supplements [69]. Moreover, the prepared hydrogels were shown to play a role in regulating the dissolution rate of poorly water-soluble drugs as disclosed by the patent WO 2002003962 where fenofibrate, ursodeoxycholic acid, nifedipine and indomethacin were used as models of poorly water-soluble APIs [70].

Tablets comprising CS and XG as a hydrophilic matrix for oral controlled release were first presented by Badwan et al. [71]. A wide range of basic drugs were tested (e.g. ambroxol, salbutamol, metoclopramide, anti-infective, non-steroidal and anti-inflammatory agents (NSAIDs)). Tablets formulated using CS and XG have been used to deliver basic APIs in a controlled release pattern. The drug to polymer ratio used was 1:3, respectively and the preferred XG to CS ratio was 1:1. When the system was studied in-vivo on human volunteers, it produced constant serum levels of ambroxol over a period of 24 h. This study paved the way for further research on approaches and mechanisms involving tablet formulations based on the foregoing combination. A tablet dosage form based on CS-XG for the treatment of hypercholesterolemia was prepared [72]. A combination of lycopene and *Monascus purpureus* were used as active ingredients. When testing the preparation on human volunteers, a significant decrease in the plasma levels of cholesterol, LDL and triglycerides was reported. Moreover, HDL values were reported to be increased.

4.1.2. Research articles on CS-XG based controlled release drug delivery system

The applicability of CS-XG combinations to a wide range of dosage forms with different routes of administration has been investigated. Examples of the preparations reported in the literature together with a brief description of preparation methods, application and examples of incorporated APIs are summarized in **Table 2**.

4.2. Ionic interaction between XG and CS

In spite of the significant amount of research work conducted on XG and CS based matrices, a lack of understanding of the nature of the interaction between the two polymers and their behavior at the molecular level still exists. It was suggested that physico-chemical conditions in the stomach are an ideal environment for the formation of insoluble gels between the two polymers, which retards the release of APIs resulting in a sustained drug release profile [87]. Moreover, in vitro residence time evaluation on porcine mucin and in vivo studies using sheep models have addressed the bioadhesive nature of CS-XG matrices [88].

In order to acquire an understanding of the interaction between XG and CS and factors governing it, a molecular dynamics simulation (MDs) study was conducted by Dadou et al. [89]. The contribution of the DA of CS and protonation was evaluated. The resulting trajectories

Dosage form	Preparation method	Application	Incorporated ingredient
Hydrogels	Solution mixing under heat	Drug delivery, tissue engineering, immobilization of biological active materials	Probiotics [73], enzymes [64]
Films	Solution casting	Drug delivery, tissue engineering, food industry	Wound healing [74], amoxicillin [75], scaffolds [76]
Capsules	Complex coacervation, encapsulation of physically mixed powder	Drug delivery	Theophylline [77], ciprofloxacin HCl [78]
Beads	Extrusion-dripping technique, complex coacervation mechanism	Drug delivery, immobilization of biological active materials	Probiotics [79], glipizide [80], antibodies [59]
Microspheres	Spray drying, ionotropic gelation method	Drug delivery	Meclizine HCl [81]
Micro-emulsions	Homogenization with oil phase	Drug delivery	Progesterone [82]
Liposomes (chitosomes)	Thin film hydration method, spray drying	Drug delivery	Rifampicin [83]
Cryogel	Freeze-drying	Immobilization of biological active materials	Enzymes [84]
Tablets	Direct compression, granulation, hot melt extrusion	Drug delivery	Metformin HCl [85], terbutaline sulfate [48], propranolol [86]

Table 2. Main applications of CS-XG based matrices.

and binding free energy calculations revealed that electrostatic forces (polar interactions, ΔE_{ele}) are the driving force for the interaction, and that the interaction occurs regardless of the DA and state of protonation of CS (free energy values are negative for all complexes). Protonation of CS molecules increases their penetration between the branched chains of XG and produces more stable complexes with lower free binding energy (**Table 3**). Intermolecular interactions (Van der Waals) showed a positive contribution to the formation of CS-XG PECs. This can be explained by the presence of a large number of hydroxyl groups along the chains of the polymers which can induce an instantaneous dipole attraction with the surrounding atoms. High positive solvation free energy (ΔG_{solv}) values justify the resultant insoluble PECs upon complexation between CS and XG in the laboratory. ΔG_{solv} increases with protonation, reaching a maximum value when CS is fully protonated, indicating a higher extent of interaction with XG.

4.2.1. Mixing ratio

Since the interaction between CS and XG is electrostatically driven, the properties of the resultant PECs can be modified by controlling the net charge density. This can be achieved either by altering the mixing ratios or the initial concentrations of the polymeric solutions. Films of CS and XG were prepared and examined by scanning electron microscope (SEM) for additional information relating to the behavior and the interaction between the two polymers in

CS	ΔE_{ele}	ΔE_{vdW}	ΔG_{sol}	ΔG
0% P*, 0% DA	−21.290	−14.03	21.890	−13.43
50% P, 0% DA	−227.53	−24.47	222.77	−29.22
100% P, 0% DA	−419.95	−23.27	412.57	−30.65
0% P, 50% DA	−25.080	−21.12	28.460	−17.74
50% P, 50% DA	−232.68	−23.96	227.36	−29.28
0% P, 100% DA	−25.070	−25.79	30.150	−20.71

Values presented are in kcal/mol.*P represents state of protonation.

Table 3. Binding free energy calculations for XG-CS complexes.

aqueous solutions at different mixing ratios [90]. SEM images (**Figure 6**) show the rough surface of CS, whilst XG films produce a smooth surface. Combining the two polymers resulted in a pronounced alteration in the surface morphology of the films. The resulting PECs form irregular and fibrous surfaces with a porous structure. PECs at a mixing ratio of 1:1 (w/v %) showed a dramatic change in the surface structure and it is suggested that they represent the maximum interaction between the two polymers.

4.2.2. Initial concentration of XG

Argin-Soysal et al., studied the effect of polymer solution concentration on the formation of stable capsules and their subsequent swelling behavior [67]. The initial concentration of the XG solution was found to be the determining factor in relation to complexation density, more than CS. This is due its high molecular weight and the highly viscous hydrogels it forms when in contact with water [91]. The physical cross-linking between XG and CS was complete when the concentration of XG was 1.5%, regardless of other experimental conditions. Consequently, the degree of swelling was shown to be dictated by the initial aqueous concentration of XG.

4.2.3. pH and initial concentration of CS solutions

Dumitri et al., found that the pH of CS solutions has a moderate effect on the extent of interaction between XG and CS [65]. PECs where readily obtained within a wide range of pH (3.6–8.0). At lower pH values, the carboxyl groups of XG become protonated (uncharged) while the amine groups in CS are fully charged; hence, the interaction between CS and XG is

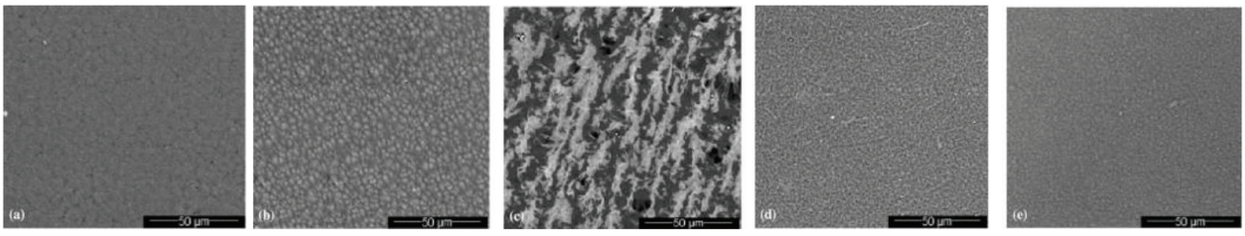

Figure 6. SEM images at magnification power of x2000 of: (a) CS, (b) CS-XG (2:1), (c) CS-XG (1:1), (d) CS-XG (1:2) and (e) XG films, from Eftaiha et al. [90].

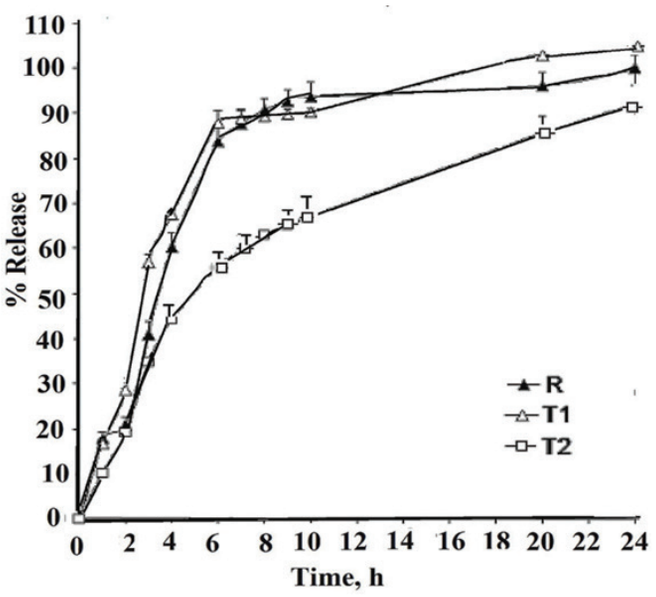

Figure 7. In-vitro release of ambroxol HCl from: (R) reference product, prepared tablets at a P:D of (T1) 1:1, and (T2) 3:1, as reported by Al Remawi et al. [94].

impeded and reduced drug retardation occurs. The effect of pH was more pronounced when preparing low concentration solutions of CS. A considerable increase in the degree of swelling with the pH of solutions at CS concentrations of 0.65–0.7% (w/v) occurs.

4.2.4. Molecular weight (Mw) of CS

The swelling capacity of CS-XG based PECs were found to be influenced by the Mw of CS [68]. Lower water retention capacity was achieved by using a higher Mw of CS. The absorption of water increased noticeably with around 1000% weight gain at lower Mw of CS. The increase in water absorption causes the formation of more PEC layers which results in potentially more drug retardation. The aforementioned claim was supported by the slow release of diclofenac sodium from low molecular weight CS tablets (13 and 30 kDa) [92]. AlAkayleh et al., found that the release rate of terbutaline sulfate from XG-low molecular weight CS tablets (viscosity 38 mPa s) was slower than XG-high molecular weight CS (70 mPa s) [48].

4.2.5. DA of CS

The PEC between XG and CS is formed due to the electrostatic attraction between oppositely charged groups. Increasing the DA content decreases the number of available free amine groups that are readily protonated. In addition, the rigidity of CS chains increased with DA owing to strong intramolecular hydrogen bonds dictated by amide groups [93]. As a consequence, the extent of interaction between the polymers is reduced. Release of propranolol HCl from an CS-XG matrix was studied as a function of the degree of deacetylation (DDA) of CS [86]. Release of drug from the matrix was faster from the acetylated form of CS. This result is in accord with the outcomes of the molecular dynamics simulation study (**Table 3**) [89].

4.2.6. Ionic strength of solution

Adding ionic species to the solution resulted in a large decrease in water uptake of CS-XG PECs. Competition takes place between free ions and water molecules for the hydroxyl groups of the polymers and reduces the hydration of CS and XG chains. Thus, the degree of swelling is lower which, in turn, will have an effect on the drug retardation capability of the system [63].

4.2.7. Concentration of incorporated API

Hydrophilic matrices need to be used at high polymer to drug ratios in order to exert their effect in sustaining the release of APIs [27]. Thus, their application is restricted to low strength drugs, as addressed by Badwan et al. [71]. Al Remawi et al. studied the effect of polymer to drug ratio (P:D) on the release of ambroxol HCl from CS-XG based tablets [94]. The release rate of ambroxol was highly dependent on the P:D ratio. Greater retardation of drug release was attained at higher polymer ratios (**Figure 7**).

5. Tablets comprising CS-XG

Oral solid dosage forms remain the most favorable choice to deliver APIs. The main reason is that they preserve the physicochemical stability of chemical entities more than liquid forms [95]. Additionally, tablets offer advantages for both manufacturers and patients which include ease of handling, low production cost, dose precision and self-administration capability [96].

Utilization of CS as an efficient excipient in tablet formulation is gradually increasing. CS powder exhibits a high surface area and porosity [93]. It produces tablets with high tensile strength that form a network-like structure when examined by microscopy [97]. The aim of using a combination of polymers, as tablet excipients, is to enhance compressibility and flowability properties. Furthermore, a polymeric mixture can increase the overall retardation performance of the system. CS-XG based tablets were formulated by compression of one layer and multi-layers; they were used solely or with other polymers such as galactomannan, seed gum or β-cyclodextrin [48, 85, 86, 98]. Moreover, they were used in immediate release, floating mucoadhesive and buccal tablets [99, 100]. According to Badwan et al., combining XG with CS has the advantage of improving the mechanical properties of both polymers [93].

5.1. Tablet preparation methods

5.1.1. Direct compression

Direct compression is a technique for formulating tablets which limits the use of solvents, temperature and equipment. It is the first choice whenever the API and inactive materials are suitable for direct compression and are stable at high pressure [101]. Powders of both active and inactive ingredients are mixed homogeneously, then sieved to the desired particle size. Finally, the prepared blend is compressed using a tablet press machine at a predetermined

pressure [102]. CS-XG based tablets prepared via direct compression, showed a high potential towards sustaining the release of terbutaline sulfate and ambroxol [48, 103].

5.1.2. Dry granulation

Dry granulation is utilized to improve compaction properties of ingredients. It can influence flowability, stability, content uniformity of the powders and enhance the bioavailability of the API. This is attained by increasing the particle size of powder materials via aggregation of particles by either roller compaction or slugging and then milling to produce granules with the desired size [104].

5.1.3. Wet granulation

Wet granulation of tablet components is usually achieved using water, ethanol or a mixture of both. Following drying at an appropriate temperature, granules are mixed with other excipients if needed, passed through a sieve and finally compressed using a press machine at a predefined pressure [105]. Wet granulation is used to produce dust free granules, enhance flowability and cohesion. Eftaiha et al., investigated the ability of CS-XG tablets prepared by wet granulation using an aqueous solution of XG 1% (w/v) to modify the release of metronidazole [87]. The preparation was able to sustain the release of metronidazole, both in-vitro and in-vivo. A mucoadhesive behavior was observed when applying the tablets on sheep duodenum.

5.1.4. Hot melt extrusion (HME)

In HME the powdered API, functional polymers and any other excipients are blended in a mortar and pestle then fed into the hopper of a single or double screw extruder. Fukuda et al., prepared CS-XG tablets using HME to study the release of chlorpheniramine maleate [106]. The processing temperature was 90°C (zone 1), 95°C (zone 2), 105°C (zone 3) and 110°C (die) with a screw speed of 15 rpm. The processing time needed for powders inside the barrel of the extruder is usually ~3–4 min. The extruded materials were then manually cut into tablets of the desired weights. Chlorpheniramine release from the prepared CS-XG tablets occurred in a sustained manner and was independent of the pH and ionic strength of the dissolution media. HME offers the advantage of continuous processing and process analytical technology (PAT) which enables quality control testing throughout the process [107].

5.2. Mechanism of drug release

Drug release from CS-XG matrices is suggested to be governed by the dissolution rate of the drug and the polymers in the media as well as the diffusion of the drug from the matrices and erosion of the polymers. The data in **Figure 8** illustrates the processes of drug release from a tablet composed of CS and XG. When the tablet is first exposed to aqueous media, an insoluble gel layer forms on the top surface of the tablet, as a result of polyelectrolyte complexation between the two charged polymers [108]. Water molecules start to penetrate this layer towards the matrix owing to the high water uptake capability of XG. [91]. Accordingly, both polymers and drug are dissolved and a rubbery hydrated region is formed (white area) [27].

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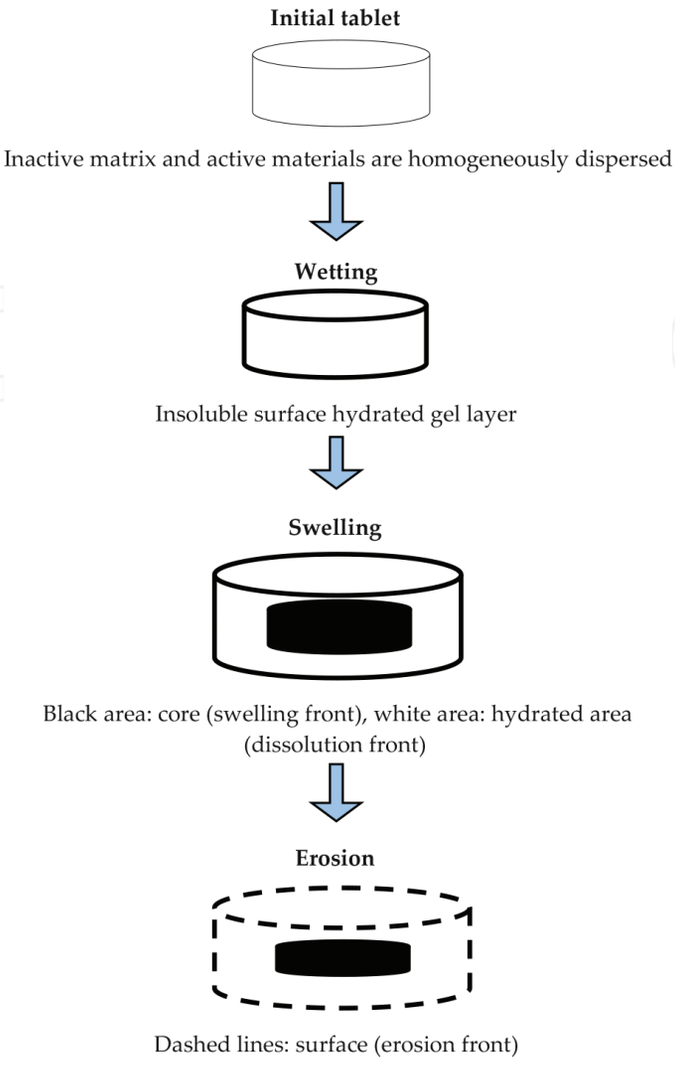

Figure 8. Schematic representation of the behavior of CS-XG tablets in an aqueous medium.

On the other hand, a non-hydrated glassy area is formed at the core of the tablet, where no water molecules reach the system (black area) [109]. As time lapses, further penetration of water molecules into the tablet occurs resulting in the polymers chains being solvated. Consequently, swelling of the matrix occurs [110]. At this stage, water molecules enter between the polymer chains, the radius of gyration of the polymers increases and the end-to-end distance of the polymer backbones also increases [111]. This phenomenon of polymer relaxation is referred to as "swelling of the matrix" [91]. As more water molecules pass into the matrix, the polymer concentration on the outer surface of the tablet decreases, losing its integrity, and starts to dissolve in the medium. This phenomenon is termed "polymer erosion" [112].

The rate of drug release from such a matrix could occur as a function of diffusion of the water molecules into the matrix, dissolution of both polymers and drug, polymer relaxation and erosion [91, 113]; this depends on the previously mentioned factors (Section 4.2) [111, 114].

6. Conclusions

Controlling the release of active ingredients is one of the fastest growing applications of CS-XG based matrices. Various drug delivery systems and newly emerging technologies have been developed in order to optimize the foregoing mixture. XG-CS matrices show a high potential towards controlling the release of a wide range of active biomolecules. The efficiency of CS-XG matrices to control the release of drugs can be reinforced by manipulating the physicochemical properties of CS and XG and the experimental conditions used. Thus, incorporation/use of expensive devices and the method of preparation can be kept to a minimum. With further optimization and the utilization of newly emerging computational and quality by design tools, relatively simple and straightforward CS-XG based matrices can be formulated as potentially universal carriers to control the release of APIs.

Conflict of interest

The authors declare no competing financial interests.

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