Chapter 15
Synthesis, Structural Modification and Physiochemical Response of Chitosan Built Nanohydrogel for Control Drug Delivery Applications

Faheem Ullah, Fatima Javed, and Hazizan Md. Akil

Abstract The present chapter explains the progressive synthesis, structural modification and physicochemical response of chitosan built hydrogel for controlled drug delivery applications. The name chitosan built referred to the hydrogel where chitosan can be used as the main component in addition to other monomers. An overview of hydrogel classification, processing, drug loading and release mechanism is highly stressed to discover the production of in-situ gelling system and their functionalization with induced sensitivity (hydrophilicity, hydrophobicity, glucose sensing and self-assembling) for the controlled release of versatile hydrophilic and hydrophobic drugs. The detailed chemistry of various stimuli-responsive hydrogel in biomedical and pharmaceutical applications has been clarified to state of the art of physicochemical responses at physiological conditions. Particular attention is paid to stimuli, including glucose, pH, temperature, ionic strength and urea-responsive hydrogel at physiological conditions. The use of chitosan built hydrogel as a controlled drug delivery system is not only limited to structure–property–relationship but needs a fundamental understanding in terms of chemical, thermal, morphological, optical and interfacial properties. These areas are addressed in terms of synthesis of chitosan built hydrogel, the respective functionalization with induced moieties along with detailed characterization and physicochemical responses for controlled drug delivery applications.

Keywords Nanohydrogel · Chitosan · Structural modification · Physicochemical · Controlled drug delivery

F. Ullah · F. Javed · H. Md. Akil (✉)
School of Materials and Mineral Resources Engineering, Engineering Campus, Universiti Sains Malaysia, Seri Ampangan, 14300 Nibong Tebal, Pulau Pinang, Malaysia
e-mail: hazizan@usm.my

F. Ullah
Institute of Chemical Sciences, University of Peshawar, Peshawar 25120, KPK, Pakistan

F. Javed
Department of Chemistry, Shaheed Benazir Bhutto Women University, Charssada Road, Peshawar 25000, Larama, Pakistan

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1 Chitosan Built Hydrogel

A three-dimensional network of polymers made of natural (chitosan)and synthetic materials, possessing a high degree of flexibility due to large water content is called hydrogel. Under physiological conditions, they are able to retain a large amount of water or biological fluids and are characterized by a soft rubbery consistency similar to living tissues, making them an ideal substance for a variety of applications. Hydrogel with characteristic properties such as desired functionality, reversibility, sterilizability and biocompatibility meets both material and biological requirements to treat or replace tissues, organs, function of living tissues as well as to interact with the biological system [8, 19, 29]. Hydrogels have been found in nature since life on earth. Bacterial biofilms, which are hydrated extracellular matrix components and plant structures are universal water swollen motifs in nature. Gelatine and agar were also known and used for various applications early in human history, but the modern history of hydrogel as a class of materials designed for biomedical applications can be accurately traced.

From chemistry point of view, hydrogel is a mixture with characteristic solid and liquid properties. The crosslinked network structures of hydrogel from randomly crosslinked macromolecules consist of polymeric solid phase, interstitial fluid phase and ionic phase. Polymeric chains create a three-dimensional matrix with interstitial spaces (filled up with water or biological fluids), formed by van der Waals interactions, hydrogen bonding, electrostatic interactions and physical entanglements as well as by covalent bonding [14]. The fluid phase comprises the pores which make the hydrogel wet and impart elastic properties. Due to these properties, structures of hydrogel resemble living tissue. The ionic phase consists of the ionizable groups that are bound to the polymeric counter-ions and co-ions. These phases exist normally due to the presence of electrolytic solvent. Recently, many attempts have been made to develop chitosan-based drug delivery systems, such as anticancer drug carriers, peptide carriers, antibiotic agents or steroid carriers [43]. The biodegradable polymer such as chitosan, a pH-dependent polycation, where the significant chains are able to interact with oppositely charged molecules through electrostatic interactions is highly recommended for drug delivery, wound dressing, tissue engineering and biotechnology applications due to its biocompatible and biodegradable nature. Due to its antibacterial, biofriendly, nontoxic and mucoadhesive properties, it is used to increase the time of intact for drug penetration [21]. Chitosan is known to protect the drug from hostile and antagonistic environment. Chitosan is only soluble in water at a pH below 6.5 ($\approx$pKa value of chitosan), where the protonation of the amine group will help to create positive charge cloud and the resultant electrostatic repulsion of these pendant group assists in solubilization and swelling of hydrogel matrices. Another important aspect of selecting chitosan for the proposed system is its efficient removal through renal filtration and enzymatic degradation [7, 12]. Fundamental physicochemical and electrokinetic investigations are of utmost importance in order to understand the responses of selective stimuli including glucose, pH, temperature, ionic strength, urea and drug sensitivity of the chitosan built hydrogel.

These responses govern the internal and external interaction of hydrogel entities with the biomolecules (drug, glucose, enzymes, proteins, DNA and dyes). So how and why the changes occur in the hydrogel system with the environment (glucose, pH, ionic strength, temperature, drug) depends upon the physical and chemical properties of the system. Several researchers reported the chitosan built hydrogel for drug delivery focusing on the macroscopic- and microscopic films, microspheres, effect of crosslinker and the reaction conditions, but still the effect of internal and external parameters needs to be addressed. This chapter reveals the desirable properties by inducing glucose sensitivity, self-assembling and hydrophilicity into such hydrogel, which enhanced the internal and external properties significantly. The investigation of physicochemical, electrokinetic parameters with several model drug loading versus release profiles are striking to evaluate the potential of chitosan built hydrogel for controlled drug delivery applications.

To date, there is no report of a boronic acid-based glucose sensor that fulfills all the criteria of biocompatibility, biodegradability, multi-responsiveness (toward pH, temperature, ionic strength, urea) and in vitro evaluation of loading and release profiles of model drugs at physiological conditions [38]. For a glucose sensor to be useful in a device, the sensing components must be free to allow instantaneous nursing. For in vivo practice, the device must function at physiological conditions with biocompatible and biodegradable characterizations. There is a need to address and replace unhealthy moieties containing glucose oxidase-based glucose sensors, which present random sensitivity, instability, immobilization, where the application is restricted by intrinsic nature of enzymes present in the body [23, 36]. Hence, a simple, enzyme-free glucose sensor with low cost, reproducibility, selectivity and reliably fast determination seems to be an attractive system that is free from the abovementioned drawbacks. Among the significant glucose sensors [42], the chitosan-based hydrogel is considered as the most proficient and accessible sensors with updated 3-aminophenylboronic acid (3-APBA) moieties to detect glucose in terms of simplicity, movability, controlled response, high sensitivity and selectivity at physiological conditions [6].

More than 40% new chemical entities developed in the pharmaceutical industry are hydrophobic which are practically insoluble in water [32]. So, hydrophobic drug carriers must be designed in such a way to improve the selectivity, effectiveness and safety of hydrophobic drug administration (loading and release). One class of drug delivery vehicle that has received widespread attention is micelles, formed by self-assembly of amphiphilic hydrogel in aqueous solution [15]. Chitosan is a hydrophobic biomaterial with promising features for biomedical and pharmaceutical applications due to significant swelling and mucoadhesive properties. The hydrophobic nature of chitosan can be controlled by copolymerizing with a hydrophilic entity to create a hydrophobic/hydrophilic balance regarding the administration of hydrophobic drugs. Further, chitosan built hydrogel as micelles is specified for drug delivery applications for a number of reasons. First of all, hydrophobic drugs can be physically entrapped in the core of such polymeric micelles and transported at concentration that can exceed their intrinsic water solubility. Second, the hydrophilic blocks, which are often composed of poly(ethylene glycol) PEG, have

the superior ability of hydrogen bonding with the aqueous environment and form a tight shell around the micellar core. Hydrogel as micelles with a PEG corona resists protein adsorption and cellular adhesion due to the highly hydrophilic nature of PEG which is resistant to hydrophobic surfaces of protein and mucosal layers. Thus, the PEG corona easily assembles in between aqueous and cellular spaces and protects the drug from deactivation at the cellular level and contents of hydrophobic core are effectively protected against hydrolysis, deactivation and enzymatic degradation. In addition, the PEG corona prevents recognition by the endothelial system and therefore avoids the preliminary elimination of the micelles from the bloodstream. The PEG corona results in increased blood circulation and allows the drug to be administered over a prolonged period of time. A final feature that makes amphiphilic micellar block copolymer attractive for drug delivery application is the molecular weight, block length ratio and hydrophilic monomer which controls the size, morphology and association of the micelles [18, 34]. Considering the previous reports, the literature poorly characterizes chitosan in terms of various molecular weights and their effect on critical micelle concentration (CMC) and thermokinetic parameters of drug administration. Further, lack of studies associating the chitosan built hydrogel to function as self-assembled micelles and the distinct attainment methods to allow its use in hydrophobic drug delivery. The effects of varying molecular weight of chitosan on properties, particularly sol–gel transition, surface, electrokinetic and physicochemical characterization of the overall system are systematically explored. Also, the effects of pH, temperature, urea and ionic strength on physicochemical and electrokinetic parameters in terms of swelling, zeta potential, conductance and electrophoric mobility are explored in this study for hydrophobic drug delivery applications [37].

Regarding internal interactions, the carboxylate moieties present in alginic acid (AA) units interact with the protonated amines present in chitosan (CS) to form a three-dimensional interpenetrating network (IPNs) due to strong electrostatic interactions [2]. Thus, capability to modify the physicochemical properties of chitosan and alginic acid hydrogel is to control the degree of association between AA and CS moieties. Accordingly, controlling the association in such molecules requires a comprehensive understanding of the structure and introducing highly hydrophilic moieties to extend the external interactions with the surrounding environment (blood, aqueous solution, drug and cellular organelles). The tuneable properties of such a system with selective ligands to ensure the extended interactions is a very new concept for further consideration which are systematically described in this chapter [35]. Gibas et al. [10] reported that swelling of hydrogel is a complex process comprising of a number of steps. In the first step, the polar hydrophilic groups of the hydrogel matrix are hydrated by water, which appears in the form of primary bound water. In the second step, the hydrophobic pendant groups present in the polymeric hydrogel interpenetrating networks (IPNs) are also hydrated by water (due to short range Vander Wall's forces and hydrogen bonding) and thus appear in the form of secondary bound water. The primary bound water and the secondary bound water both form the total bound water. In the third step, the osmotic driving force of network toward infinite dilution is resisted by the physical or chemical crosslinks, so additional water is absorbed. The water absorbed at equilibrium swelling is called the bulk water or

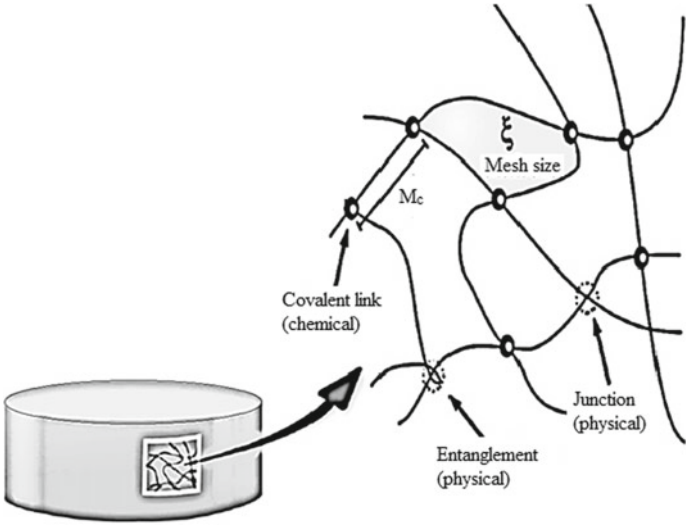

Fig. 1 Structural chemistry of hydrogel [10]

the free water, which fills the spaces between the network or chains and the centre of the larger pores. The amount of water absorbed by a hydrogel depends on the temperature and specific interaction between the water molecules and the polymer chains, which can be explained by the Flory–Huggins theory [9]. The solid portion of the hydrogel is a network of crosslinked polymer chains, a 3D network, usually referred as a mesh as shown in Fig. 1, with the spaces filled up with a fluid, normally water.

The meshes hold the fluid and impart an elastic force that can be completed by the expansion and contraction of the hydrogel and therefore are responsible for the solidity of the hydrogel. The ionic phase of hydrogel usually consists of ionizable groups bound onto the polymer chains and a number of mobile ions, including counter-ions and co-ions due to the presence of the electrolytic solvent, which surrounds the hydrogel.

2 Classification of Hydrogel

The classification of hydrogel depends on physical properties, nature of swelling, method of preparation, origin, ionic charges, sources, rate of biodegradation and observed nature of crosslinking [26]. It is clear from Fig. 2 that classification details for each type are beyond the scope of this chapter, but some of the prominent hydrogels are discussed.

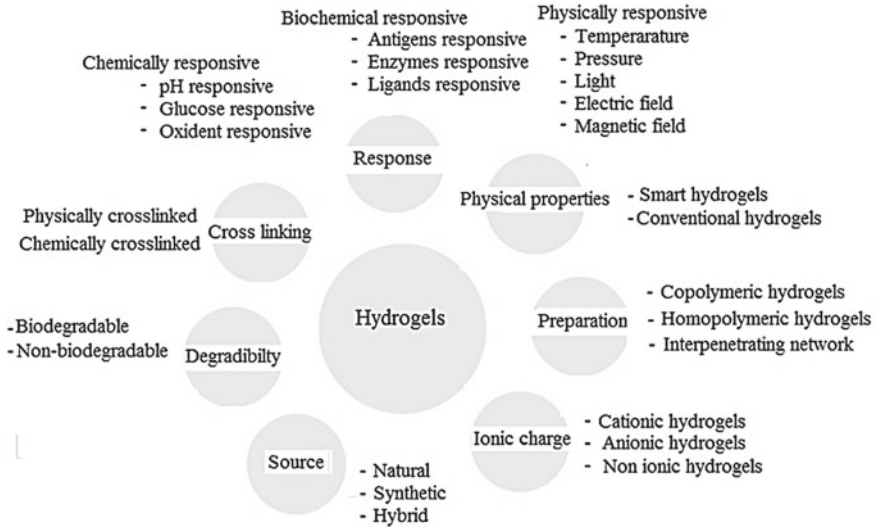

Fig. 2 Classification of hydrogel on the basis of crosslinking, responses, preparation and nature of hydrogel

3 Synthetic Strategies in Chitosan Built Hydrogel

Polymeric hydrogel is normally produced by one of two well-established schemes

- Polymerization of hydrophobic/hydrophilic monomers;
- Modification or functionalization of existing polymers (natural or synthetic).

The unique sources of hydrogel comprise of two main classes, i.e., natural, containing two main groups based on polypeptides (proteins) and polysaccharides (chitosan), and another is synthetic (petrochemical-based). Natural hydrogels are usually prepared through the addition of some synthetic parts to natural substrate, e.g., copolymerization of vinyl monomers with polysaccharides. When the term "hydrogel" is used without specifying its type, it truly means the conventional type of hydrogel [1]. The synthetic route for the production of most synthetic hydrogel is the free radical polymerization of multifunctional vinyl monomers. Each monomer contains a carbon double bond where an active centre may propagate to produce polymer chains but generating active centers also depends on solvent, reaction conditions and particular monomers which can be initiated by heat (thermal-initiators), light (photo-initiators), enzymes (bio-initiators) or electron beams [30] as shown in Fig. 3. Usually, water-soluble natural or synthetic polymers are crosslinked to form hydrogels in a number of ways, such as (1) linking polymer chains via chemical reaction, (2) using ionizing radiation to generate main chain-free radicals, which can recombine as crosslink joints and (3) interacting physically such as electrostatics,

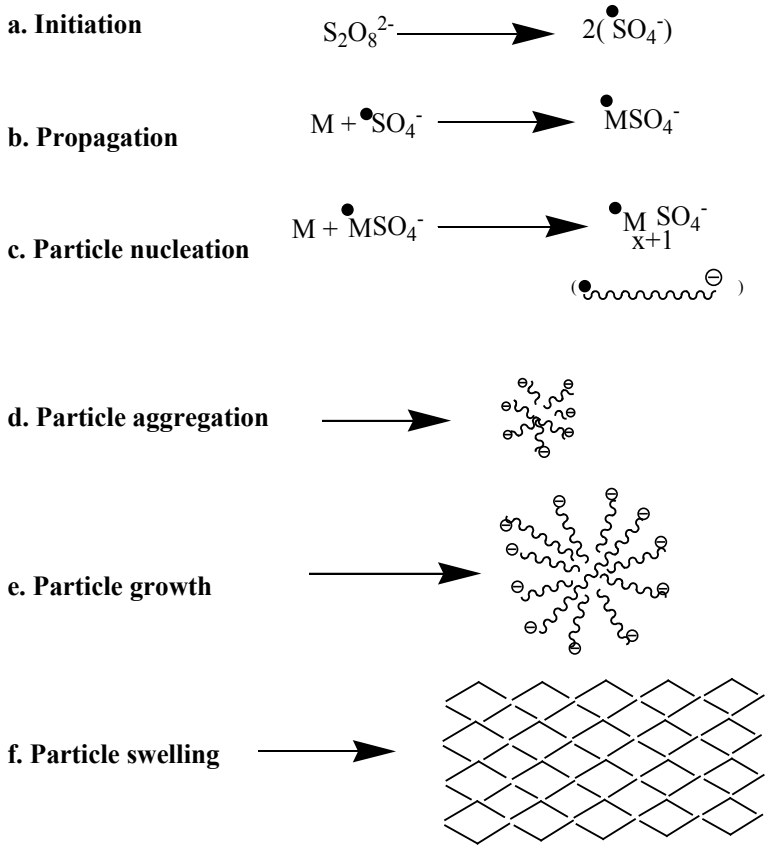

Fig. 3 Synthesis of hydrogel by free radical polymerization [40]

entanglements and crystallite interactions. Any of the various polymerization techniques can be used to form hydrogel, including bulk, solution and suspension polymerizations. The three main components of hydrogel are monomers, initiators and crosslinkers, which can be diluted in water or any solvent to control the heat of polymerization. However, its disadvantage appears in the form of impurities left from the preparation process containing unreacted monomers, initiators, crosslinkers and side products. Hydrogel is commonly prepared from monomers of both natural and synthetic origins by free radical polymerization in aqueous medium.

4 Physical and Chemical Cross-linking in Hydrogel

The reported methods to synthesize chitosan built hydrogel include physical crosslinking, chemical crosslinking and interpenetrating polymeric networks (IPNs)

formation [5]. Physical crosslinking of chitosan occurs due to physical interactions like polyelectrolyte complexation, interpolymer complexation, ionic complexation and hydrophobic associations. The physically crosslinked hydrogel is produced without using any toxic chemical crosslinker, but at the same time, weak mechanical features, inconsistent in vivo behavior and shorter lifetime at physiological conditions, are considered as the key barriers in pharmaceutical applications. Consequently, physical crosslinked chitosan built hydrogels are not strong enough to establish permanent junctions in the molecular network and also lack the ability to promote the water residency in the polymeric chains [3]. Therefore, chemically crosslinked hydrogel is more favorable for pharmaceutical and biomedical applications which fulfill the above-stated features. The toxic crosslinkers are non-favorable for pharmaceutical applications, and thus, the targeted applications need biocompatible, biodegradable and non-toxic crosslinker for practical use. One of the bio-friendly crosslinker is known as methylenebisacrylamide (MBA) with reported biocompatibility and biodegradability, which is used to produce the crosslinking points by Schiff base formation where C=O double bond (from *N*-acetyl glucoseamine units) is replaced by a –C–N bond between chitosan and secondary polymer chains [11]. The advantages assigned to chemical crosslinking in chitosan built hydrogel in comparison to physical crosslinking highlighted as

- Hydrogel is obtainable below 80 °C.
- Hydrogel can stabilize the encapsulated drug.
- The pendant groups must respond to the external stimuli.
- The physicochemical properties can be improved by surface modification.
- The pendant groups are accessible to communicate with drug and cell surface.

5 Synthesis of Chitosan-co-Alginic Acid Hydrogel

The synthetic and functionalization mechanisms of chitosan built hydrogel are shown in Fig. 4. The copolymerization of chitosan (Cs) and alginic acid (AA) can be initiated by using a thermal initiator system at 75 °C to produce active radicals in both polymers as chemical crosslinking junctions points. As per reported literature, 700 mg of Cs was softened in 90 mL acidified DDH_2O (1.2% v/v) under constant magnetic stirring for 20 h at 25 °C. Further, 400 mg of AA was added to the reaction mixture and the reaction temperature was increased up to 75 °C at the rate of 3 °C/min. Exactly after 1 h of achieving the desired temperature (75 °C), 10 mL of 0.5 M APS was added drop-wise and allowed to react with the mixture for 30 min in order to produce free radicals in both the polymers, followed by the addition of 10 mL of 0.5 M MBA under constant stirring and N_2 purging. During the reaction, 0.2 mg of sodium dodecyl sulfates (SDS) was added as a surfactant in order to achieve uniform particles and particle size distribution due to the surface active properties of SDS in aqueous solution. After some time, the system became progressively thicker and was observed until it could not be stirred. The resultant hydrogel were then purified by centrifugation, decantation followed by frequently washing with DDH_2O. Finally,

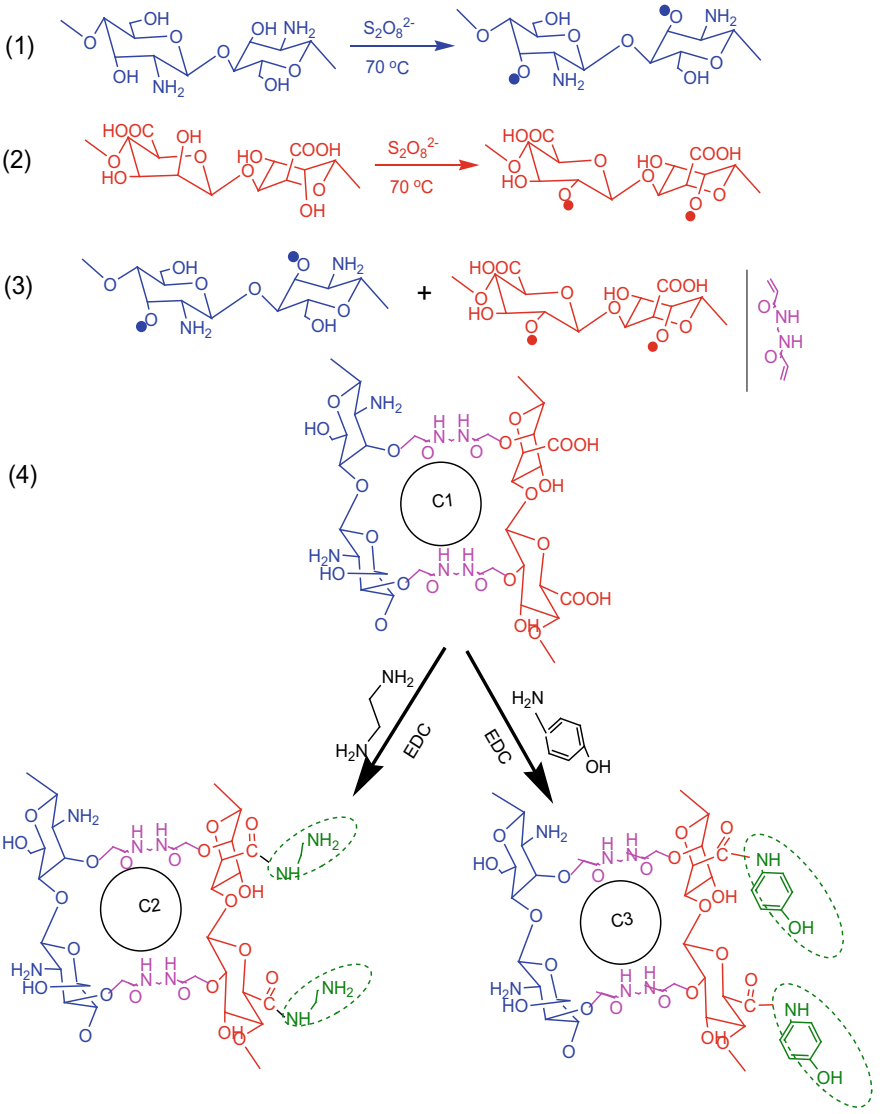

Fig. 4 Synthetic routes of native (C1) hydrogel and their functionalization with soft (C2), and hard (C3), ligands for extended interactions

the hydrogel was purified by dialysis for 07 days in membrane tubing (Spectrum laboratories, Inc., Rancho Dominguez, CA, USA; MW cutoff 12,000–14,000). The product was de-watered using ethanol for 02 h, grounded sieved and dried again at 80 °C for 72 h. The feed composition is shown in Table 1.

Table 1 Feed composition of C1, C2 and C3 hydrogel

Sample code	(Composition)[a] (mg)	SDS (mg)	APS (M)	EDA (mg)	AP (mg)	EDC (mg)	Curing time (h)	Curing temp. (°C)
C1	700:400:0.5	02	0.5	–	–	–	23	75
C2	700:400:0.5	02	0.5	150	–	150	15	25
C3	700:400:0.5	02	0.5	–	150	150	15	25

[a]Composition = (Chitosan: Alginate: MBA)

6 Functionalization CS-co-AA Hydrogel

The functionalization of CS-co-AA hydrogel termed as C1 by the respective ligand N-Ethylenediamine (EDA) and 4-Aminophenol (AP) via carbodimide (EDC) coupling was carried out as follows: stoichiometric amount of EDA (150 mL) and EDC (150 mg) was solubilized in 55 mL DDH_2O under constant stirring for 5 h. The solution was then placed in an ice bath followed by the addition of 200 mg dialyzed C1 hydrogel for 10 h to confirm the effective functionalization via EDC catalyzed coupling of EDA by replacing -OH groups in AA units**.** The functionalized hydrogel was declared as C2 and again purified by dialysis to ensure the complete removal of unlinked moieties. A similar scheme was followed for the effective functionalization of (C1) hydrogel via EDC catalyzed coupling of AP to replace -OH groups in AA units and was declared as C3 as shown in Fig. 4.

7 Choice for Controlled Drug Delivery Applications

Starting from the most classical drug delivery system, where the drug is naturally administrated by the oral, intravenous, intramuscular routes and drug distribution are governed by blood plasma. The drug is free and unable to reach the targeted site, so need several directions to show a therapeutic effect. A fast drug release also produces high plasma levels, causing adverse effects and compromising patient compliance [20]. Therefore to overcome the limitations of classical drug delivery, controlled drug delivery systems (CDDSs) have been introduced with desired characteristics at physiological conditions. Initially, many liposomes based drug delivery systems have been investigated with reported microparticles, nanoparticles, films and hydrogel formulations to substitute the classical drug delivery systems [17, 22]. Many biomaterial and synthetic strategies were applied to achieve the drug delivery system which function at physiological conditions. Thus, chitosan built hydrogel was introduced as a striking candidate with pharmacokinetics parallel to the cell activity without any side effects for targeted and controlled drug delivery applications. Chitosan built hydrogel is characterized with significant features to deliver drug to the targeted site per required level of dosage in a self-controlled manner with enhanced circulation

Table 2 Chitosan-based drug delivery system prepared by different methods

Form	Preparation method
Gel	Crosslinking
Films	Solution casting
Beads	Precipitation
Nanoparticles	Precipitation
Capsules	Emulsion/precipitation
Microspheres	Spray drying/ionic gelation
Tablets	Matrix coat

time. As many drugs and proteins are deactivated after oral and intravenous doses, thus to improve the solubility of hydrophobic drugs (e.g., paclitaxel, tamoxifen, etc.), chitosan built hydrogel is reported with odd results [31]. Nowadays, chitosan built hydrogel is under investigations to formulate the marketed drugs into new pharmaceutical arrangements. Chitosan-based hydrogel can be used in a variety of ways as controlled drug delivery system as shown in Table 2. Such hydrogel is characterized with effective role in terms of bioavailability, biodegradation, biodistribution and controlled drug administration at physiological conditions.

From physiochemical point of view, the chitosan built hydrogel has been characterized with the ability to swell and shrink in response to the external stimuli, especially pH, glucose concentration and ionic strength. Therefore, a substantial volume of research is focused on the synthesis of chitosan built hydrogel for controlled drug delivery applications as a variety of pH exist in the body. The pH sensitivity of hydrogel confirms the delivery of specified drugs to the gastrointestinal tract, stomach and colon. By controlling the physicochemical properties, chitosan built hydrogel can cover the epidermal, rectal, subcutaneous and oral drug administration without any side effects at physiological conditions. The drug administration for any polymeric hydrogel depends upon many factors like the chemical structure, hydrophilicity, hydrophobicity, reactivity, molecular weight, toxicity, nature of pendant groups and biocompatibility of polymers. Unfortunately, the natural polymers fulfilling the abovementioned properties are very few like chitosan, alginate and cellulose, so there is an urgent need to copolymerize these natural polymers with synthetic polymers in the form of interpenetrating networks (IPNs), to fabricate standard hydrogel for controlled drug delivery applications. Similarly, hydrogel with different functionalities can be prepared with effective functionalization with induced moieties to fulfill different pharmaceutical applications along with thermodynamic and thermokinetic of drug loading and release profiles. Several routes of hydrogel-based drug delivery system are presented in Fig. 5.

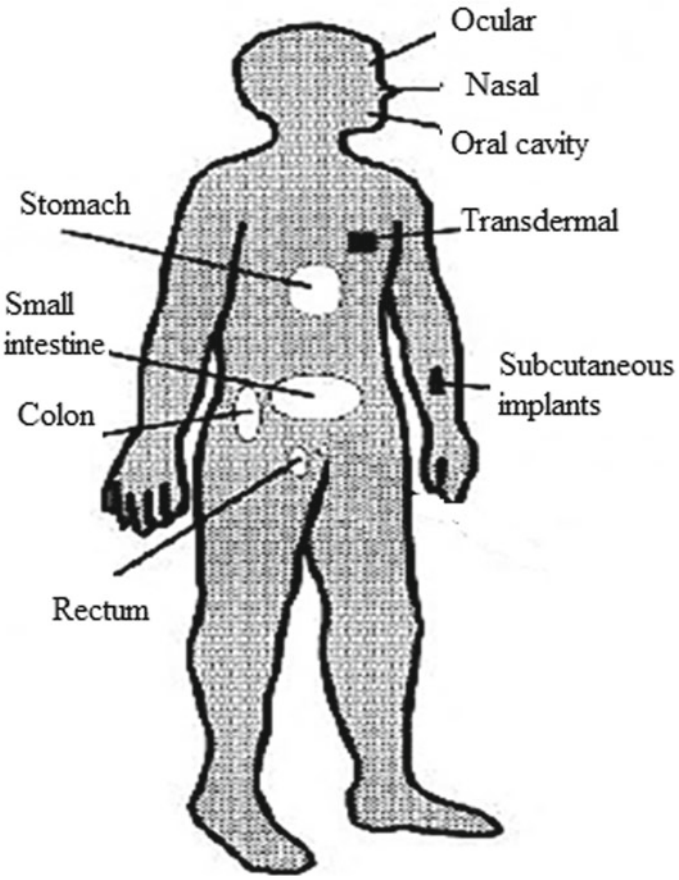

Fig. 5 Tissue locations applicable for hydrogel-based drug delivery system

8 Drug Loading Mechanismin Chitosan Built Hydrogel

There are three methods of drug loading to hydrogel matrices, namely diffusion, entrapment and tethering as shown in Fig. 6. For larger drug molecules, the drug loading is achieved by tethering of drug during the hydrogel synthesis, where a crosslinker is used to chemically attach the drug to the hydrogel. Tethering process is characterized to avoid the loss of therapeutic during administration but the main problem with tethering method is that drug is only available to tissue when the molecular tether breaks or the hydrogel degrade which mean that bioavailability of drug is negligible at the targeted site [4]. Another reported method of drug loading is entrapment, where the drug molecules are entrapped during the gelation process in hydrogel without using any crosslinker. The hydrogel work effectively in the course of entrapment, but due to free motion of drug from hydrogel matrices, initial

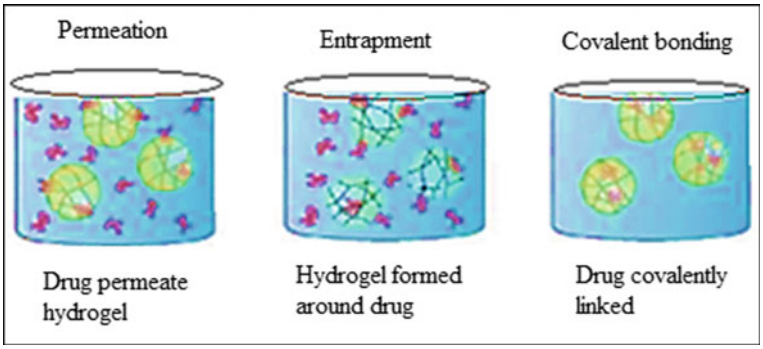

Fig. 6 Three different loading strategies in chitosan built hydrogel [4]

burst release is observed which is undesirable in controlled drug delivery system. In diffusion method, the hydrogel is allowed to interact with the saturated solution of drug, where the drug slowly diffuses into hydrogel matrices. After diffusion of drug into hydrogel, the drug-loaded hydrogel is dried for clinical use. Here the effect of hydrogel porosity, molecular weight, chemical structure and dimension of drug and hydrogel are considered as key parameters for drug administration (loading and release profiles). Diffusion of drug into hydrogel is applicable for smaller therapeutics, but larger drug molecules cannot be diffused into hydrogel matrices [39]. In overall investigations, diffusion is considered as the simplest and effective way of drug loading into hydrogel matrices. The attraction of chitosan must be addressed which is vigorously used in the synthesis of smart hydrogel for controlled drug delivery applications due to its bioavailability, biocompatibility, biodegradability and environmental (pH, temperature and ionic strength) sensitivity at physiological conditions [4, 33].

9 Drug Release Mechanism from Chitosan Built Hydrogel

In this section, a very clear picture of drug release from the hydrogel is presented. Drug release from a hydrogel is possible due to absorption of water and desorption of drug through a process known as swelling controlled mechanism [27]. As drug-loaded hydrogel particle comes in contact with water or thermodynamically stable fluid, the respective solvent penetrates into the available free spaces present on the surface of hydrogel. At this stage, the hydrodynamic radius and end-to-end distance of polymeric chains increase due to the stress produced by solvent, and this phenomena is so-called swelling [16]. Due to swelling, the water molecules penetrate into the hydrogel matrices and due to electrostatic repulsion of pendant groups, the charged entities move far away from each other and result in expulsion of entrapped drug from the hydrogel matrices to the external environment. Along with swelling, drug can

also be release from the hydrogel matrices through diffusion and chemical reactions. Diffusion is the most common method for drug release from hydrogel matrices. Diffusion is defined as movement of molecules according to concentration gradient [9]. A controlled drug delivery system must fulfill the following conditions according to Higuchi steady-state assumptions [41]:

- The initial concentration of drug must be higher than solubility of drug.
- The size of drug must be smaller than pore size of drug delivery vehicle.
- The drug diffusivity should be constant with the time and position.
- Perfect sink conditions are maintained in the system.

Peppas and coworkers developed empirical equation (Eq. 1) which assumes a time-dependent power law function [25]

$$\frac{M_t}{M_O} = k \cdot t^n \tag{1}$$

where M_t/M_O is fractional release, k is structural/geometric constant, and n is known as release exponent representing the releases mechanism. Consequently, for spherical hydrogel particles, if $0.43 < n < 0.85$, refer to controlled diffusion. It is important here to mention that if drug release occurs due to polymer degradation, it is known as surface erosion, otherwise if drug release occurs through controlled diffusion, it is known as bulk erosion. According to Heller and Baker model, controlled diffusion of drug follow first order kinetic [13].

Although, hydrogel is characterized with superior controlled drug delivery applications, there are some intrinsic pharmacological limitations of hydrogel like poor mechanical strength, difficulties in processing, dissolution prior to targeted site, unpredictable homogeneity, rapid release, larger pore size and high water contents. Several strategies have been explored to minimize the burst release of drug, enhance the hydrogel-drug interactions and increase the diffusion barrier for drug release from the hydrogel matrices. The author contribution in this regard is the functionalizion of hydrogel with specified ligands which can release the drug only in response to the particular stimulus like glucose, pH, ionic strength, urea and temperature at physiological condition.

10 Photoluminescence Analysis of Drug Loading/Release from Chitosan Built Hydrogel

Fluorescein, rhodamine with diol and diamine architectures (comparative to insulin) were selected to study the drug loading and release profiles of chitosan-based hydrogel. Bromocresol green (model anionic drug) was also used as sparingly soluble drug to state the hydrogel drug loading and release trials. Fluorescein with standard absorbance of 390 nm was used as a hydrophobic model drug to study the loading and release trials of micellar hydrogel by using UV–vis spectrophotometer [35, 37, 38].

A fixed amount of dried hydrogel was allowed to mix with an aqueous solution of the drug with pre-determined concentration. Drug loading and release profiles were obtained from the hydrogel in a shaker incubator at 75 rpm at 37 °C. Each time, 4 mL of each solution was analyzed for the drug concentration/20 min delay by using a UV-Vis spectrophotometer. An equal volume of the same solution medium was added back to maintain a constant volume. The drug release study was investigated in a sophisticated dissolution apparatus by immersing 0.45 g of drug-loaded dried hydrogel beads in 250 mL of pH 6.85 solutions. After mixing, the mixture was centrifuged at 75 rpm at 37 °C. 04 mL of the solution was taken for analysis with continuously replacing by fresh buffer solution to maintain a steady volume. Thus, the concentration of the released drug was investigated in term of absorbance. The in vitro release tests of all samples were conducted in triplicate at specified time intervals [28].

11 Swelling and Degradation Analysis

Phosphate buffer solutions PBS pH = 7.45, with added NaCl (0.05 M ≈ physiological ionic strength) was used in order to state the art of hydrogel swelling gravimetrically at 37 °C. The known amount of hydrogel was immersed in DDH_2O (150 mL) and allowed to soak for several h at 37 °C. The immersion of hydrogel in the aqueous solution followed by spreading on the filter paper, and then non-stop weighing was performed for all the samples in triplicate. The swelling capacity (SC) at time t and the equilibrium swelling ratio (S_{eq}) were calculated using Eqs. 2 and 3 [24].

$$\text{Swelling ratio } (\%) = \frac{(W_t - W_d)}{W_d} \times 100 \tag{2}$$

$$S_{eq}\,(\%) = \frac{(W_e - W_d)}{W_d} \times 100 \tag{3}$$

where W_d (initial weight of the dry hydrogel), W_t (weight of the hydrogel at time t) and W_e (equilibrium weight during the swelling process).

Similarly, the introduced degradation test reflects the physiological stomach and intestinal conditions used as a guideline to explore further regarding the in vitro degradation of these biocompatible hydrogel at physiological conditions. Such tests were accomplished in phosphate buffer solution PBS pH ≈ 7.4 (simulated intestinal fluid) and pH ≈ 1.5 (simulated gastric fluid) with added 0.05 M each NaCl, NaOH, $CaCl_2$, acetic acid without any added enzymes. At specific time intervals, the loss in wet mass of hydrogel matrices was calculated by using Eq. 4.

$$\text{Wet mass change } (\%) = \left(\frac{W_t}{W_e}\right) \times 100 \tag{4}$$

where W_e (hydrogel mass in equilibrium swollen state) and W_t (hydrogel mass in at time t) in the test solutions.

12 Summary

The present chapter summarizes the literature related to hydrogel in the past 10 years, which describe the classification of hydrogel based on the different physical and chemical properties with emphasis on stimuli-responsive hydrogel for controlled drug delivery applications. The method of preparing hydrogel and the designing process influences the production of hydrogel by different techniques where a high degree of sensitivity is highlighted. The path of the research in this chapter indicates that the combination of polymers, which respond to different stimuli (physical, chemical and biochemical) must be identified and future generation of hydrogel that undergoes spontaneous swelling when in contact with the drug, cellular organelle and infected cells should be investigated. The chitosan built hydrogel is recognized with particular consideration as innovative materials that swell rapidly to a large size regardless of their original size. The materials tend to absorb much water or aqueous fluids in a relatively short period. This innovative category will receive serious attention of academic and industrial research with selective surface modification for controlled drug delivery applications. In this age of nanofabrication, there is a need for miniaturization of the hydrogel with enhanced durability, hydrophilicity, biocompatibility, mechanical and thermal properties for advanced applications. Therefore, realizing the clinical requirements and simultaneously limiting the complexity of hydrogel formulation will be the main goal for the coming decades. The role of chitosan built hydrogel is studied, especially for controlled drug delivery applications. Finally, an inclusive description of drug loading and release mechanism is provided.

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