EXPERT OPINION

Chitosan-based gastroretentive floating drug delivery technology: an updated review

Rakesh Pahwa, Nidhi Saini, Vipin Kumar† & Kanchan Kohli
†*Kurukshetra University, Institute of Pharmaceutical Sciences, Kurukshetra, India*

Introduction: Gastroretentive floating drug delivery systems have emerged as efficient approaches for enhancing the bioavailability and controlled delivery of various therapeutic agents. Significant advancements exploiting chitosan have been made worldwide, in order to investigate these systems according to patient requirements, both in terms of therapeutic efficacy as well as patient compliance. Such systems precisely control the release rate of the target drug to a specific site, which facilitates an enormous impact on health care.

Areas covered: Different novel strategies have been undertaken for the development of various gastric floating dosage forms utilizing chitosan as a promising excipient. The present paper is an earnest attempt to provide new insights on various physicochemical and biological characteristics of chitosan, along with its potential applications in a wide array of biomedical approaches. Numerous and significant research findings in the vistas of chitosan-based gastroretentive floating drug delivery technology are also discussed.

Expert opinion: Chitosan has been considered as a unique and efficacious agent possessing a myriad spectrum of desired characteristics. It is emphasized that recent scientific advancements in the use of this excipient as a carrier will yield new generation gastroretentive drug delivery systems, with better pharmacotherapeutic interventions. Further studies are required to unveil the hidden beneficial properties of chitosan and its derivatives, to obtain newer delivery systems which may hold tremendous prospects in the near future.

Keywords: bioavailability, chitosan, floating drug delivery systems, gastroretentive technology

Expert Opin. Drug Deliv. (2012) 9(5):525-539

1. Introduction

In recent years, various scientific and technological advancements have been carried out in the vistas of several drug delivery approaches. Different types of controlled drug delivery systems have been speculated for several routes of administration, as they require less frequent drug administration, provide more efficient therapeutic profile, reduce the incidence of adverse effects, etc. [1]. Despite significant developments and innovations, oral delivery of drugs is by far the most preferred route of drug delivery owing to ease of administration, patient compliance, and flexibility in formulation [2]. Oral controlled release dosage forms have been extensively used to enhance therapy with better bioavailability. However, the developmental process is precluded by several physiological adversities such as an inability to restrain and localize the delivery system within desired region of gastrointestinal tract (GIT), fluctuation in the gastric emptying process, etc. [3]. This variability may lead to an unpredictable bioavailability of an orally administered dosage form. Furthermore, the relatively brief gastric emptying time in humans normally averages 2 – 3 h through the major absorption zone (stomach or upper part of the intestine) can

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10.1517/17425247.2012.673581 © 2012 Informa UK, Ltd. ISSN 1742-5247

result in an incomplete drug release from the dosage form leading to diminished efficacy of administered dose [4]. Thus, control over placement of drug delivery system in a specific region of GIT offers numerous advantages, especially for drugs exhibiting an absorption window in the GIT or drugs with a stability problem. Overall, the intimate contact of drug delivery system with an absorbing membrane has potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities [5,6].

To increase the gastric retention time of drugs, various attempts have been made for the development of controlled release gastroretentive dosage forms which remain in the gastric region for several hours. Prolonged residence time in the stomach is highly desirable for drugs that are locally active in the stomach, or are unstable in the intestinal or colonic environment, and/or have low solubility at higher pH values [7]. Furthermore, drugs which are primarily absorbed in the stomach or have narrow absorption window are also potential candidates for the development of controlled release gastroretentive dosage forms [8]. The main approaches for gastric retention that have been examined thus far include floating system, mucoadhesion or bioadhesion system, high-density system, magnetic system, superporous hydrogels, raft-forming system, low-density system and floating ion exchange resins, unfoldable, extendable or expandable systems [9,10]. Among the various approaches employed to increase the retention of an oral dosage form, floating drug delivery system (FDDS) is considerably acceptable and logical approach in the development of gastroretentive dosage forms [11].

Floating dosage forms, also referred to as low-density systems, remain buoyant in the gastric fluid for an extended period of time [12,13]. While the system is floating over the gastric contents, the drug is released slowly at the desired rate from the system. This results in an increased gastric retention time and better control of fluctuations in plasma drug concentration [2]. Incorporation of the drug in floating dosage form also provides a mean to utilize all the pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms [14]. It is imperative to gain a deeper insight into drug release mechanisms, in order to design a more systematic and intellectual floating system [15]. Several approaches have been utilized in the design of various floating dosage forms such as single- and multiple-unit dosage forms. Single unit floating dosage forms which includes floating tablets, floating capsules, etc. are designed to prolong the stay of dosage forms in the GIT and aid in enhancing the absorption. Floating multiparticulates can be developed in various forms such as granules, pellets, beads, microspheres, etc. These dosage forms are designed with the purpose to develop a reliable formulation with all advantages of single unit floating dosage forms and also devoid of the disadvantages of single unit formulations. With floating multiple unit dosage forms, it is considered that majority of particles will remain above the stomach contents for an extended period of time. This approach reduces the intersubject variability in absorption. Moreover, it lowers the probability of dose dumping and bursting associated with the single unit systems. It has also been described that multiple unit floating dosage forms distribute more uniformly within the gastric content, resulting in long-lasting effects [16,17].

Significant research endeavors have been done in the development of floating drug delivery systems such as floating tablets [18-21], floating beads [22-25], floating pellets [26-28], floating capsules [29-31], floating microspheres [32-34], etc. These floating dosage forms have been evaluated by various studies such as determination of floating behavior, *in vitro* dissolution studies, stability studies, hardness, weight variation, drug content and friability in case of tablets. In case of multiparticulate drug delivery systems, differential scanning calorimetry, particle size analysis, flow properties, surface morphology, and mechanical properties are also performed [17]. *In vivo* gastric retention of floating dosage form is usually determined by gamma-scintigraphy technique. This is a well established radionuclide imaging technique which is valuable for evaluating dosage forms in different regions of the GIT and various other body organs [35-37]. Various other methods have also been utilized such as magnetic resonance imaging, radiography, endoscopy, radiotelemetry, and magnetic-marker monitoring in order to study the parameters affecting the process of gastric emptying. Furthermore, indirect information on gastric emptying could be gained by comparing the pharmacokinetics of drugs administered in oral dosage forms of different size [38-40].

1.1 Advantages

FDDS approach is gaining popularity due to numerous advantages and patient compliance benefits. Some significant benefits of this system are summarized in the following text [11,16,41]:

- Enhancement of the bioavailability and therapeutic efficacy of drugs with narrow absorption window in the upper part of GIT.
- Maximum utilization of the drug with minimum adverse effects.
- Avoidance of gastric irritation because of sustained release profile.
- Site specificity.
- Low dosing frequency, thus improved patient comfort and compliance.
- Uniform drug release with no risk of dose dumping.
- Reduced inter- and intra-subject variability.
- Controlled drug release behavior offering the advantages of uniform and consistent blood level of medication.
- Increased gastric retention time because of buoyancy principle, circumventing the invariable and inadequate absorption of drugs.

- Fluctuations in drug concentration are minimized. Therefore, concentration-dependent adverse effects can be reduced.
- Flexibility in the dosage form design.
- Extended patent protection, globalize product, and provide new business opportunities.

2. Chitosan – a versatile excipient

Considerable use of polymeric materials to deliver bioactive agents has attracted attention of various investigators throughout the scientific community. Polymer chemists, chemical engineers along with pharmaceutical scientists are highly engaged in bringing out the design and development of various gastroretentive controlled drug delivery systems [42]. Polymers are generally employed in FDDS so as to target the delivery of drug to a specific region in the GIT, i.e. stomach [43]. Numerous synthetic and natural polymers have been studied extensively in the design of these drug delivery systems [44]. In spite of the advent of many synthetic polymers, use of natural polymeric materials has gained lot of importance during the last two decades in drug delivery arena. Incorporation of natural polymers may prove to be the active avenue of research and development in drug delivery due to various pivotal benefits such as biocompatibility, inexpensive, readily availability, etc. [42]. In addition to the above benefits, natural polymers are also safe, non-toxic, biodegradable, and capable of chemical modification along with gel-forming nature. In this context, large number of natural polymers has been explored due to their promising potential in the novel drug delivery approaches [45]. Extensive applications along with exciting physicochemical characteristics of natural polymeric material such as chitosan fascinate the scientific community worldwide in avenue of sophisticated pharmaceutical and biomedical approaches.

The history of chitosan dates back from 19th century, when the deacetylated forms of the parent chitin, a natural polymer was discussed by Rouget in 1859 [46]. During the past 20 years, a substantial amount of work has been reported on chitosan and its potential use in various bioapplications [47]. Chitosan is a versatile polymer which is prepared by the alkaline deacetylation of chitin. It has various favorable biological properties such as non-toxicity, biocompatibility, and biodegradability [48-50]. Such beneficial properties of chitosan make it a suitable candidate for the development of various conventional as well as novel dosage forms [51-53]. Chitosan is comprised of a rigid crystalline structure with inter- and intra-molecular hydrogen bonding. Chitin is the second most abundant polysaccharides occurring in nature. It may be found in the exoskeleton of the crustaceans, insects, and cell walls of some fungi [54]. The main commercial sources of the chitin include lobster, krill, shrimp, and crab [55,56]. Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine. The degree of deacetylation necessary to obtain a soluble product must be greater than 80 – 85% [57,58]. The treatment of the sample chitin with an aqueous NaOH solution (40 – 45% w/v) at temperature ranging from 90 to 120°C for 4 – 5 h results in N-deacetylation of chitin. The product or the crude sample of chitosan is obtained as an insoluble precipitate which is washed with water. The condition followed for deacetylation procedure of the chitin determines the molecular weight of the polymer and the degree of deacetylation. After that, the resulting crude sample is dissolved in the aqueous (2% w/v) solution of acetic acid and the insoluble material is removed, yielding a clear supernatant solution which is neutralized with NaOH solution resulting in separation of the chitosan as a white precipitate [59]. Chitin and chitosan are now commonly and commercially produced in India, Poland, Japan, USA, Norway, Australia, etc. Considerable amount of research is in progress on chitin/chitosan worldover, including India, to tailor and impart the required functionalities to maximize its utility [51].

2.1 Structural aspects

Chitin (**Figure 1**) is the second most ubiquitous natural polysaccharide after cellulose on earth and is composed of β(1–4)-linked 2-acetamido-2-deoxy-β-D-glucose (N-acetylglucosamine) [60].

Chitosan is a hydrophilic biopolymer and linear polysaccharide composed of β(1–4)-linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glucopyranose [61]. The sugar backbone of chitosan (**Figure 2**) is comprised of β-1,4-linked D-glucosamine with a high degree of N-acetylation, a structure similar to cellulose, except that the acetylamino group replaces the hydroxyl group on the C-2 position. Hence, chitosan is a poly(N-acetyl-2-amino-2-deoxy-D-glucopyranose), where N-acetyl-2-amino-2-deoxy-D-glucopyranose units are linked with the help of (1–4)-β-glycosidic bonds [62]. The various synonyms for chitosan are 2-amino-2-deoxy-(1,4)-β-D-glucopyranan, deacetylated chitin, deacetylchitin, β-1,4-poly-D-glucosamine, poly-D-glucosamine, and poly-(1,4-β-D-glucopyranosamine) [57].

2.2 Physicochemical and biological properties

Chitosan occurs as odorless, white or creamy-white powder or as flakes. It is commercially available in several types and grades that vary in molecular weight ranging between 10,000 and 1,000,000, and vary in degree of deacetylation and viscosity. It is sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above 6.5. Chitosan is readily soluble in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acid). Solubility is greatly influenced by the addition of salt to the solution [57].

Chitosan is a weak base having pKa value of about 6.2 – 7.0 for the D-glucosamine residue, and therefore it is insoluble at neutral as well as alkaline pH values. Chitosan

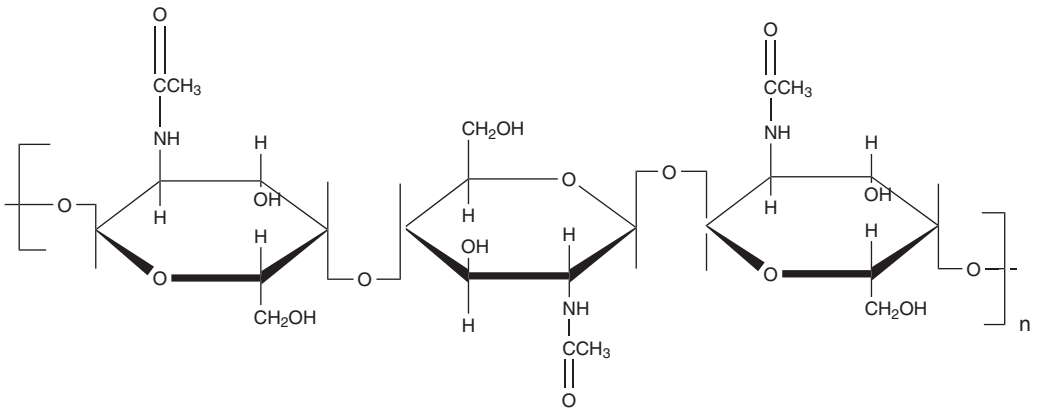

Figure 1. Structure of chitin.

readily makes the salt with inorganic and organic acids, e.g. acetic acid, lactic acid, etc. In acidic environment, amine groups are protonated which results in soluble, positively charged polysaccharide that has a high degree of charge density [63-67]. Chitosan with low degree of deacetylation, i.e. ≤ 40%, are soluble up to the pH range of 9, whereas highly deacetylated chitosan, i.e. ≥ 85%, are soluble only up to the range of 6.5 [68]. Moreover, chitosan is a well-accepted choice for its ability to chelate metal ions [69].

The active primary amino groups on the molecule are reactive and thus provide sites for a variety of side group attachments employing mild reaction conditions [70] as shown in **Figure 3**.

Chitosan have different types of conformations in an aqueous solution. This biopolymer depicts extended conformation with a more flexible chain when it is highly deacetylated, because of the charge repulsion present in the molecule. However, the chitosan molecule has a rod-like or coiled shape at low degree of deacetylation due to the low charge density in polymer chain [60]. The viscosity of chitosan solution is also affected by factors such as concentration and temperature. As the chitosan concentration increases and the temperature decreases, the viscosity increases [71].

The quality of chitosan is affected by the factors including the choice of chitin and its isolation process in a significant way [72]. Depending on the origin of the polymer and its treatment during the extraction process, chitosan shows crystallinity and polymorphism. Crystallinity is maximum for chitin (0% deacetylated) and fully deacetylated chitosan (100% deacetylated) [73]. **Table 1** summarizes the important physicochemical attributes of chitosan.

Chitosan in solution exists in the form of quasiglobular conformation stabilized by extensive intra- and intermolecular hydrogen bonding. The hydrogen bonding in chitosan chains due to the presence of amine and hydroxyl groups causes the high viscosity of chitosan solutions. Chitosans with lower degree of deacetylation have lower number of amino groups in the polymer chains [74].

Because chitosan has favorable biological properties such as biodegradability and biocompatibility, it has gained lot of attention in the pharmaceutical and medical fields. Chitosan has oral toxicity with an LD_{50} of 16 g/kg in rats [75]. Toxicity of chitosan may depend on a number of different factors including degree of deacetylation, purity, molecular weight, and route of administration [52]. Several authors have reported that chitosan shows properties such as analgesic [76-78], antitumor [79-81], hemostatic [82-84], anticholesterolemic [85-87], antimicrobial [88-90], antioxidative [91-93], and permeation enhancing effect [94-97].

3. Salient applications

Owing to its various favorable characteristics such as biocompatibility, biodegradability, mucoadhesion, non-toxicity, safety profile, etc., chitosan has been widely employed in several drug delivery systems, implantable systems such as orthopedic and periodontal composites, wound healing management and as scaffolds for tissue regeneration advancements. Chitosan is found to have an acceleratory effect on the tissue engineering process [98-101] due to its polycationic nature which enhances the cells attraction to this polymer [51,102,103] along with different biomedical applications [104]. The tissue engineering approach is considered significant for repair or regeneration of damaged tissue through replacement with the engineered tissue, in the hope that it will facilitate restoring of the functions during the process of regeneration and subsequent integration with the host tissue [105,106]. It is a promising candidate for wound healing/wound dressing process and also suitable for burn treatment as it forms tough, water absorbent, biocompatible films [51]. Non-toxic and non-allergenic with antimicrobial properties, chitosan has also the ability to rapidly clot blood [107]. Chitosan polysaccharide structurally similar to glycosamino glycans can be considered for developing substratum for skin replacement as well [108,109]. Chitosan membranes have also been proposed as artificial kidney

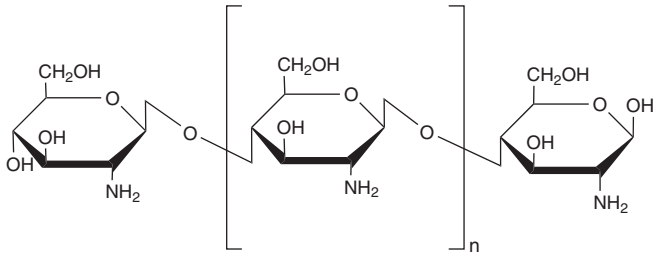

Figure 2. Structure of chitosan.

membranes because of their suitable permeability and high tensile strength [110]. It has remarkable contribution to medical-related textile sutures, threads, and fibers [111]. Chitosan possesses all the characteristics required for an ideal contact lens, i.e. optical clarity, mechanical stability, sufficient optical correction, gas permeability, partially toward oxygen, wettability, and immunologically compatibility [112]. It has also an excellent property of mucoadhesion and depicts significant potential in controlled drug delivery approaches and thus employed for various systems including oral drug delivery systems [113-117], parenteral drug delivery systems [118,119], ocular delivery systems [120-124], transdermal drug delivery systems [125-128], nasal delivery systems [129-132], etc. for various therapeutic moieties. Promising observations were also reported in the formation of complexes between chitosan and DNA for gene delivery [133,134].

Due to its inimitable physicochemical and biological properties, chitosan is commonly used in the vast array of different products and applications, ranging from cosmetics [51] to water treatment [135,136], nanostructured surface adhesion [137] and plant protection. Regenerated chitin, chitosan and other chitinous membranes could be widely used for processes as osmosis, reverse osmosis, micro-filtration, desalination, dialysis, and hemodialysis. Beds of flaked chitosan can be used for purification of potable water. Use of chitosan in food industry is well known because of its non-toxicity [51]. It acts as solid support for the entrapment of whole microbial, enzyme or cell immobilization [138,139]. It also offers a wide range of unique applications in the food industry [140,141] as well, including preservation of foods from microbial deterioration, formation of biodegradable films, and recovery of material from food processing discards [142,143]. Moreover, it can act as a dietary fiber and as a functional food ingredient [73]. These multiform aspects of chitosan make it a promising and versatile excipient in various biomedical, food, biocatalysis, waste water treatment avenues, etc.

4. Chitosan-based gastroretentive technology

Owing to its good safety profile along with assorted physicochemical and biological attributes makes chitosan a unique candidate in various modern pharmaceutical avenues. In drug delivery, the selection of an ideal type of chitosan with certain suitable characteristics is useful for developing sustained drug delivery systems, prolonging the duration of drug activity, site-specificity, improving therapeutic interventions, reducing adverse effects, etc. Extensive efforts have also been undertaken worldwide in the vistas of gastroretentive floating drug delivery technology. Several approaches have been utilized by large number of investigators in the development of various single and multiparticulate gastric floating dosage forms employing chitosan. Some significant research endeavors are discussed in the following section.

Different novel strategies have been investigated for the development of gastroretentive floating microspheres with enhanced therapeutic interventions. These dosage forms can be retained in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. These multiple unit system retains their structure in GIT and each unit acts as an individual entity. Moreover, multiple unit systems may perform better *in vivo* than monolithic ones, as they distribute more uniformly within the gastric content causing less irritation, enjoy a slower transit through the GIT and provide more reproducible as well as consistent drug release. These systems also reduce the intersubject variability in absorption and minimize the probability of dose dumping resulting in long-lasting effects. Coupling of bio/mucoadhesive, swelling and other versatile characteristics of chitosan to multiple unit systems has further additional advantages, such as efficient absorption and enhanced bioavailability of therapeutic molecules due to high surface to volume ratio, more intimate contact with the mucus layer and specific targeting of drugs to the absorption site. In addition, breakage and instant release from individual entity of multiple unit systems will have considerably lower effect as compared to the breakage of one monolithic system. In view of these facts, Sarojini *et al.* fabricated and evaluated albumin chitosan floating microspheres of clarithromycin as a model drug. Morphology of microspheres was examined by scanning electron microscopy (SEM) and from *in vitro* floating test; it was found that most of the microspheres remained floated for around 12 h [144]. In another study, Sultana *et al.* prepared gastroretentive microspheres of lacidipine using chitosan polymer and glutaraldehyde as a cross-linking agent. Central composite design was employed to study the effect of independent variables on dependent variables. It was observed

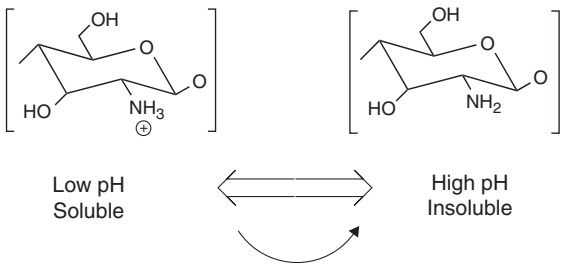

Figure 3. Schematic representation of chitosan's versatility. At pH less than 6, the amine groups of chitosan are protonated conferring polycationic behavior to chitosan. At pH above 6.5, its amine groups are deprotonated and thus reactive.

that polymer concentration and glutaraldehyde volume had a more significant effect on dependent variables. The selected formulation showed controlled release for more than 6 h and *in vitro* release studies followed Higuchi kinetics via Fickian diffusion [145].

Wide range of developmental techniques has been utilized by large number of investigators globally for the preparation of gastroretentive floating microspheres. During the preparation of floating controlled release microspheres, the choice of an optimal method has utmost relevance for the efficient entrapment of active constituents. In this context, Senthilkumar *et al.* prepared and evaluated floating microspheres using rabeprazole sodium as a model drug for prolongation of gastric retention time. Microspheres were prepared by solvent evaporation method using different polymers like hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose, and chitosan. The average diameter and surface morphology of prepared microspheres were characterized by optical microscope and SEM methods, respectively. *In vitro* drug release studies were performed and drug release kinetics was evaluated using linear regression method. The microspheres were also investigated for buoyancy profile and incorporation efficiency [146]. Ma *et al.* also formulated floating alginate microspheres of diltiazem hydrochloride by ionotropic gelation method with calcium carbonate being used as a gas-forming agent. Attempts were made to enhance the drug encapsulation efficiency and delay the drug release by adding chitosan into the gelation medium and by coating with eudragit, respectively. Gastrointestinal transit of optimized floating sustained release microspheres was compared with that of the non-floating system manufactured from the same material using the technique of gamma scintigraphy in healthy human volunteers [147]. Furthermore, Patel *et al.* formulated and evaluated floating chitosan microspheres containing propranolol hydrochloride. Microspheres were prepared by chemical denaturation using glutaraldehyde as a cross-linking agent. A 3^2 full factorial design was employed to study the effect of independent variables, i.e. polymer to drug ratio and volume of cross-linking agent on dependent variables, i.e. drug entrapment efficiency, t_{80}, floating lag time, mean particle size and similarity factor. *In vivo* study also demonstrated significant antihypertensive effect of floating microspheres of propranolol hydrochloride over a 12 h period [148].

Gastroretentive dosage forms have been developed in the form of beads using different drugs which represents the promising avenue for successful delivery of molecules in a more efficient manner. Chitosan has been evaluated for stomach-specific drug delivery system as gastroretentive floating beads. Eldeen *et al.* prepared gastroretentive beads of verapamil using chitosan as polymer and glutaraldehyde as a cross-linking agent. Internal structure of dried beads showed that verapamil is incorporated within the cores of the beads. It was found that beads prepared using medium molecular weight chitosan showed good floating characteristics and floating lag time was found to be 5 min with total duration of buoyancy more than 6 h. In order to determine the release kinetic model and mechanism, the dissolution data of microspheres were also analyzed [149]. Srinatha *et al.* studied the effect of additives on ciprofloxacin release from multiple unit floating alginate system. Floating beads were fabricated by simultaneous external and internal gelation method and studied the effect of blending of alginate with gellan, HPMC, starch, and chitosan polymer. *In vitro* release of ciprofloxacin from the alginate matrix in simulated gastric fluid was influenced significantly by the properties and concentration of additives [150]. Similarly, Murata *et al.* prepared two types of floating alginate gel beads of metronidazole using vegetable oil and chitosan. They concluded that both were applicable not only for sustained release of drug but also for targeting the gastric mucosa [151]. Anal *et al.* developed single and multilayer beads employing ionotropic gelation for controlled delivery of ampicillin. Various combinations of chitosan and Ca^{2+} as cationic components and alginate and polyphosphate as anions were utilized. Beads prepared with high concentration of chitosan entrapped more ampicillin. During incubation in simulated gastric fluid, the beads swelled and floated but did not show any sign of erosion. It was concluded that chitosan alginate multilayered beads cross-linked with polyphosphate offer an opportunity for controlled gastrointestinal passage with low molecular weight compounds like ampicillin [152]. Jiang and co-workers prepared calcium alginate-chitosan intragastric floating beads of naringenin combining with the solid dispersion method and investigated the *in vitro* floating characteristics, entrapment efficiency and

Table 1. Important physicochemical attributes [51,52].

Linear polyamine
Reactive hydroxyl groups
Reactive amino groups
Chelates certain transitional metal ions
Cationic
Insoluble at high pH
High charge density at pH < 6.5
Forms gels with polyanions
Viscosity, high to low
Amiable to chemical modification
Adheres to negatively charged surface

drug release property of the beads. More than 70% of beads kept floating in artificial gastric juice for 9 h and the release ratio of drug was 65 – 70% and entrapment efficiency was observed to be about 70 – 80% [153].

Chitosan-based gastroretentive floating beads of different drugs have also been employed for the treatment of gastric diseases. *H. pylori* infection is a very contagion to the GIT. The bacterium is directly related to development of ulcers in stomach and duodenum, and it is believed that the infection may be related to cancers involving the stomach [154]. So in the hope of getting better profile by using chitosan, Rajinikanth *et al.* prepared and characterized gellan-based floating beads of acetohydroxamic acid for eradication of *H. pylori*. Floating beads were prepared by ionotropic gelation method using gellan gum and chitosan polymers. It was found that chitosan coating increased encapsulation efficiency of beads and reduced the initial burst release of drug from beads. Kinetic treatment of drug release data revealed a matrix diffusion mechanism. Prepared floating beads exhibited good antimicrobial activity as potent urease inhibitors [155]. Working on similar grounds, Ishak and co-workers prepared stomach-specific metronidazole-loaded alginate beads as local anti-*Helicobacter pylori* therapy. Floating beads were prepared by ionotropic gelation method. A ($3 \times 2 \times 2$) factorial design experiment was used in which three viscosity imparting polymers namely: methyl cellulose, carbopol 934 P and κ-carrageenan, two concentrations of chitosan as encapsulating polymer and two concentrations of low-density magnesium stearate as a floating aid were tested. Histopathological examination showed that groups receiving metronidazole in the form of floating alginate beads at doses of 5, 10, 15 and 20 mg/kg were better than corresponding suspension form, regarding eradication of *H. pylori* infection [156]. Furthermore, Sahasathian *et al.* designed mucoadhesive and floating chitosan-coated alginate beads as a gastroretentive delivery vehicle for amoxicillin, toward the effective eradication of *H. pylori*, the major cause of peptic ulcers. Alginate was used as beads core polymer and chitosan as mucoadhesive polymer coating. This resulted in the dosage form which could be retained in the GIT for an extended period of time [157].

Concerted research efforts have also been carried out utilizing chitosan-based stomach-specific floating microspheres and hydrogels against *H. pylori* infection. Stomach-specific tetracycline-loaded chitosan microspheres have been formulated and evaluated by Hejazi *et al.* against *H. pylori* infection. Chitosan microspheres were prepared by ionic cross-linking and precipitation method. Cumulative amount of tetracycline that was released from chitosan microspheres and the stability of drug were examined in different pH medium at 37°C [158]. Torre *et al.* also formulated poly(acrylic acid) chitosan interpolymer complexes of amoxicillin for stomach-controlled antibiotic delivery. Preliminary results from this study suggest that amoxicillin polyionic complexes have potential for improving local antibiotic therapy against *H. pylori* [159]. Torrado *et al.* designed chitosan-poly(acrylic) acid-based controlled drug release system for gastric antibiotic delivery. Different mixtures of amoxicillin, chitosan, and poly (acrylic) acid were employed to obtain these polyionic complexes. Gastric emptying rate study was performed by means of the [^{13}C]octanoic acid breath test. The gastric emptying rates of two different formulations (conventional and gastric retentive system) were studied. Swelling studies indicated that the extent of swelling was greater in the polyionic complexes than in the single chitosan formulations. The amoxicillin diffusion from the hydrogels was controlled by the polymer/drug interactions. Results suggested that these polyionic complexes are good systems for specific gastric drug delivery [160].

Gastroretentive floating chitosan microcapsules and micropellets have also been explored for buoyancy profile. To investigate this attribute, El-Gibaly developed novel floating chitosan microcapsules by the ionic gelation method. Characteristics of the floating microcapsules generated were compared with the conventional non-floating microcapsules. Dissolution profile of most of the microcapsules showed near zero order kinetics in simulated gastric fluid. Novel floating chitosan microcapsules of melatonin by ionic interaction of chitosan with a negatively charged surfactant, sodium dioctyl sulfosuccinate were developed. Chitosan concentration and drug/polymer ratio had a remarkable effect on drug entrapment in microcapsules. Most of the hollow microcapsules tended to float over simulated biofluids for more than 12 h. Data obtained suggest that the developed floating hollow microcapsules represent an interesting gastroretentive controlled release delivery system for drugs [161]. In the proceeding year, El-Gibaly and his co-workers also prepared buoyant melatonin-loaded chitosan microcapsules with favorable sustained release characteristics in comparison with non-buoyant chitosan particles. Buoyant microcapsules were prepared by ionotropic gelation method using sodium lauryl sulfate for coagulation. The characteristics of microcapsule were affected by initial drug and sodium lauryl sulfate concentration as well as the presence of sodium dioctyl sulfosuccinate or pectin with sodium lauryl sulfate in external phase. The best sustained release profiles were observed with high theoretical payload microcapsules prepared with both sodium lauryl sulfate and dioctyl sulfosuccinate in a 1:2 ratio [162]. In an attempt to overcome the drawback of the short gastric

release time of drug in stomach, Muthusamy *et al.* designed sustained release floating micropellets of lansoprazole by emulsion solvent diffusion technique using drug to carrier ratio of 1:1, 1:2, 1:3. HPMC, methyl cellulose, and chitosan were used as carriers. The yield of micropellets was up to 82%. Drug to chitosan ratio of 1:1 showed good incorporation efficiency and high percentage *in vitro* release of lansoprazole from micropellets. The range of particle size was between 327 and 431 µm [163].

Mucoadhesive systems are designed to adhere to the mucosal surface of the stomach and other biological tissues. Adhesion of the drug delivery system in the stomach offers several diverse applications. Hence, by employing mucoadhesion feature of chitosan, numerous systems have been explored by scientific investigators for site-specific drug delivery. Dhaliwal *et al.* reported gastroretentive mucoadhesive microspheres of acyclovir as a model drug. Microsphere formulations were prepared using emulsion chemical cross-linking technique using chitosan, methocel 15M and carbopol 71G and evaluated *in vitro*, *ex vivo* and *in vivo*. All microsphere formulations were spherical in shape and possessed smooth surface as visualized under SEM [164]. Patel and his co-workers prepared stomach-specific amoxicillin-loaded chitosan mucoadhesive microspheres by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. A 3^2 full factorial design was employed to study the effect of independent variables, polymer to drug ratio and stirring speed on dependent variables such as percentage mucoadhesion, t_{80}, drug entrapment efficiency, particle size and swelling index [165]. Working on similar grounds, another group also developed stomach-specific drug delivery system of ranitidine hydrochloride superporous hydrogel composites containing chitosan, material to improve characteristics of superporous hydrogel to prepare a drug system. The base monomers selected included acrylic and acrylamide due to their high water affinity and fast copolymerization velocity, whereas chitosan is used for its biocompatibility. *In-vitro* release profile of drug from superporous hydrogel composites was explained using the Korsmeyer–Peppas model. The superporous hydrogel composites – drug delivery systems – were found to be stable for a period of 3 months at 40°C/75% RH [166].

Tablets have also gained considerable attention of researchers globally owing to their various therapeutic advantages such as ease of administration, better patient compliance, flexibility in formulation, etc. In addition, tablets may offer greatest precision with least drug content variability as compared to other dosage forms resulting in improved efficacy of drug molecules. Therefore, investigators have designed these dosage forms as gastroretentive floating drug delivery systems (GRFDDS). Moreover, the principle of buoyant tablet preparations offer a simple and practical approach to achieve increased gastric residence time and sustained drug release profile. Numerous types of tablets have been shown to reveal floatable and gastric retentive characteristics. Significant number of polymeric materials including chitosan has been extensively studied for the design and fabrication of floating tablets. In an attempt to overcome the drawbacks of conventional dosage forms, Gnanaprakash *et al.* prepared floating tablets of famotidine with isolated chitosan, having desirable properties in order to achieve an extended retention in the upper gastrointestinal tract, which resulted in an enhanced absorption and thereby improved bioavailability. Floating tablets of famotidine showed better gastric cytoprotection when compared with conventional dosage forms [167]. Sahu *et al.* formulated and evaluated floating matrix tablets of chitosan and HPMC using furosemide as a model drug. Investigation of *in vitro* dissolution, floating capability, drug release kinetics and mechanism, and similarity factor analysis were performed along with differential scanning calorimetry to determine the physicochemical properties of the prepared tablets and the excipients. Effects of chitosan and HPMC concentrations on drug release kinetics and buoyancy were also determined. *In vitro* drug release of furosemide in all formulations followed typical mechanism of non-Fickian diffusion. By combining HPMC with chitosan in various blends, it was observed that formulations followed zero order kinetics with floatation period of more than 8 h and was found to be suitable for oral control release of furosemide [168]. Inouye *et al.* developed sustained release intragastric floating granules of prednisolone using chitosan of different degrees of deacetylation in granular form or in laminated preparations. They concluded that the release properties were controlled by regulating the chitosan L content of the granules, or the chitosan L membrane thickness of the laminate [169]. In another research endeavor, Chinta *et al.* prepared and evaluated a novel spray-dried tableting excipient using a mixture of chitosan and lactose. The study utilized three different grades of chitosan. Propranolol hydrochloride was used as a model drug. Specific amount of chitosan was dissolved in an aqueous solution of citric acid and later mixed with aqueous solution of lactose and propanolol. Resultant solution was sprayed using a laboratory spray drier. Granules were evaluated for bulk density, tap density, Carr's index, particle size distribution, surface morphology, thermal properties, and tableting properties. Floating tablets prepared by direct compression of these granules with sodium bicarbonate showed 50% drug release between 30 and 35 min. It was concluded that spray-dried granules prepared with chitosan and lactose showed excellent flow properties and were suitable for tableting [170].

Hydrodynamically balanced systems (HBS) have also been designed using chitosan to prolong the stay of dosage form in the stomach and aid in enhancing the absorption. Dorozynski and his co-workers carried out the evaluation of macromolecular polymers used as excipients for the preparation of HBS. Hard gelatin capsules were filled with polymeric substances belonging to various chemical groups like chitosan, sodium alginate, hydroxypropyl methycellulose. Properties such as density, hydration, erosion, and floating force of

HBS were investigated. Each polymer demonstrated different hydration/erosion abilities and floating properties. The floating properties of dosage forms were reliant on type of polymer and the medium-fasted state-simulated gastric fluid or fed state-simulated gastric fluid. Moreover, the size of the HBS influenced the floating force value. The authors also observed that the mechanisms of erosion and swelling of polymeric matrices play a dominant role in flotation of the dosage forms [171]. In an attempt for obtaining suitable floating lyophilized formulations, Caro and Veiga developed chitosan lyophilized formulations for gastric drug delivery of acyclovir. No changes in the acyclovir crystallinity were observed during X-ray diffraction powder studies as a consequence of the manufacturing process. Swelling behavior of floating lyophilized formulations was dependent on chitosan and acyclovir proportions within lyophilized formulations and on medium nature due to pH-dependent chitosan solubility. Furthermore, *in vitro* dissolution of acyclovir from lyophilized formulations was influenced by swelling behavior. Results demonstrated that the freeze drying process achieved effective floating systems capable of remaining within stomach while the total amount of acyclovir is released from lyophilized formulations [172].

Several scientific advancements utilizing this polymeric material have been carried out globally which reflects its successful and effective use in the development of different stomach-specific drug delivery systems. Recent innovations in better and proper utilization of this polymer as carrier have been significantly explored which reflect numerous exciting opportunities in the avenue of chitosan-based gastric floating dosage forms. These emerging drug delivery strategies at the interface of chitosan's chemistry and sophisticated pharmaceutical technologies have also quicken the realization of full potential of GRFDDS.

5. Conclusion

Owing to indomitable potential of chitosan, continuous developments have been made in the vast array of biomedical and pharmaceutical sciences. It is a versatile candidate which provides exciting opportunities in the fascinating arena of applied polymer science and current drug delivery technology. Considerable research efforts have been directed globally toward the development of chitosan-based efficient GRFDDS.

6. Expert opinion

Gastroretentive technology represents one of the leading avenues of modern pharmaceutical sciences involving multidisciplinary, innovative, and technological approaches. Numerous drug delivery systems such as high-density systems, bio/mucoadhesive systems, expandable/swellable systems, floating systems, magnetic systems, raft-forming systems, superporous hydrogels, etc. have been proposed over the years for gastric retention abilities. While most of the proposed approaches illustrated promising drug release profile and *in vitro* retentive behavior, however, only some of them have revealed acceptable *in vivo* gastric retention characteristics. Some other systems suffer from one or another drawback and therefore only a very few commercial preparations are presently available in the healthcare scenario. It is imperative to perceive that for good gastroretentive performance, the floating dosage forms may be preferred over others as these systems have been found to possess considerable gastric retention ability for several hours without interfering with the normal gastric functioning and ensuring maximal absorption of therapeutic molecules for desired period of time. Prolongation of the gastrointestinal residence time may be utilized to extend the absorption profile which may be advantageous for the drugs with narrow absorption window. These systems are expected to provide the clinicians with a new choice of more bioavailable formulation for the effective management of diverse diseases. In this context, large numbers of research and development centers are actively engaged worldwide to explore this attractive option with excellent expertise in the fabrication of tailored site-specific formulations.

Recent scientific literature reveals that due to assorted potential of chitosan, it has attracted significant attention of researchers all over the world. Owing to various beneficial properties of chitosan such as high biocompatibility, biodegradability, mucoadhesive characteristics, non-toxicity, swellable nature, etc., significant developments have been made globally exploiting this preferential biopolymer in the avenue of drug delivery. Also, chitosan base is soluble in mild acids, such as acetic acid, citric acid, and glutamic acid, while chitosan salt is soluble in water, which can be advantageous in diverse pharmaceutical processing for encapsulation of several therapeutic moieties. Moreover, the presence of reactive amine groups in chitosan also provides easier ligand attachment for targeted drug delivery. Therefore, numerous unique and versatile characteristics make chitosan as a favored biomaterial for various site-specific drug delivery applications. The polymer has also been investigated as potential adjuvant for diverse swellable controlled drug delivery systems. Good safety profile along with favorable characteristics makes chitosan an exciting and pivotal moiety in modern pharmaceutical and other biomedical approaches. Chitosan-based gastroretentive floating formulations have shown promising benefits as compared to other floating dosage forms prepared by employing different polymeric materials. Drug release from chitosan-based formulations can be controlled/governed by utilizing swelling and biodegrading characteristics of biomaterial. Chitosan gastroretentive formulations have also revealed superior buoyancy profile along with enhanced encapsulation efficiency. These formulations also offer an opportunity for controlled gastrointestinal passage with site-specific targeting of gastric mucosa, which subsequently improved the therapeutic interventions. Chitosan-mediated gastric floating drug delivery systems designed on the basis of delayed gastric

emptying and buoyancy principles appear to be an effective and rational approach for the modulation of controlled oral drug delivery.

Despite remarkable achievements in gastroretentive technologies, this area still has promising potential for future research and innovations. New medical and pharmaceutical developments are imperative to be conducted in close collaboration with gastroenterologists for advanced expansion of research and commercialization of gastroretentive floating technique. Moreover, advancements in this area are still required to accurately control the drug input rate into the specific site of the GIT for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents.

It is anticipated that various new drug delivery strategies at the interface of modern polymer chemistry and current pharmaceutical technologies will accelerate the realization of full potential of chitosan. Likewise, design and synthesis of novel derivatizable groups of this polymer will further expand the scope of site-specific drug delivery systems in the near future. Flexibility for usage with different therapeutic molecules will also provide opportunities to focus on developing novel and improved technologies so as to enhance performance during pharmaceutical characterization. Investigational research can also be persuaded with different newer grades of excipients for formulating them into single or multi-unit floating dosage forms. Furthermore, increased sophistication of this technology will certainly ensure the successful delivery of molecules to a specific site in a more efficient and controlled manner, thus extending the frontier of futuristic pharmaceutical development.

Acknowledgements

Lt. Gen. DDS Sandhu, Vice Chancellor, Kurukshetra University, Kurukshetra-136119, India, is duly acknowledged for providing necessary facilities. The authors also thank PC Sharma, Assistant Professor, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, India, for his valuable suggestions.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Rakesh Pahwa[1], Nidhi Saini[2], Vipin Kumar[†3] & Kanchan Kohli[4]
[†]Author for correspondence
[1]Assistant Professor,
Kurukshetra University,
Institute of Pharmaceutical Sciences,
Kurukshetra-136119, India
[2]Post Graduate Research Scholar (Pharmaceutics),
Kurukshetra University,
Institute of Pharmaceutical Sciences,
Kurukshetra-136119, India
[3]Associate Professor,
Kurukshetra University,
Institute of Pharmaceutical Sciences,
Kurukshetra-136119, India
Tel: +91 9416391274;
E-mail: vipbhardwaj@rediffmail.com
[4]Associate Professor,
Hamdard University,
Faculty of Pharmacy,
Department of Pharmaceutics,
Jamia Hamdard,
New Delhi-110062, India