science, engineering and health studies

Review Article

Science, Engineering and Health Studies
https://li01.tci-thaijo.org/index.php/sehs
ISSN (Online): 2630-0087

Chitosan as floating-mucoadhesive polymers in gastroretentive drug delivery

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Received: *14 June 2023*
Revised: *21 August 2023*
Accepted: *20 September 2023*
Published: *31 December 2023*

Citation:
Ainurofiq, A., Sari, A. P. F., Mardhiyah, A., Nisa, F. S., Azka, R. L., Putri, S. K., and Saputri, V. L. (2023). Chitosan as floating-mucoadhesive polymers in gastroretentive drug delivery. Science, Engineering and Health Studies, 17, 23010002.

ABSTRACT

Oral drug delivery is limited by incomplete absorption in the digestive tract. The absorption of oral drugs in the stomach is affected by several factors, including gastric residence time, which causes the drug to be unable to be retained in the stomach for a long time, causing suboptimal drug absorption. One of the drug delivery systems that can prolong contact duration within the stomach is gastroretentive drug delivery system (GRDDS). GRDDS has various advantages, notably in improving the bioavailability of drugs. Several systems are involved in the GRDDS, including the floating and mucoadhesive systems. The floating system makes the drug float so it can be retained longer in the stomach. There are two mechanisms in the floating system: the effervescent and non-effervescent mechanisms. The mucoadhesive system works by adhering to the mucus or epithelial cells of the stomach. The mechanisms of mucoadhesive systems involves two stages: the contact and consolidation stages. The combination of the floating and mucoadhesive systems is aimed to improve the efficiency and effectiveness of a preparation for prolonged retention in the stomach. The choice of polymer is one of the crucial factors affecting this system. Chitosan is a natural polymer that has been evaluated for its potential in a gastroretentive floating beads delivery system. It has various advantageous properties, such as non-toxicity, biocompatibility, and biodegradability.

Keywords: gastric residence time; gastroretentive drug delivery system; floating system; mucoadhesive system; chitosan; polymers

1. INTRODUCTION

Oral drug delivery system is highly favored due to its ease of administration, high patient acceptability, and formulation flexibility (Khan, 2013). Oral drug absorption, especially in the stomach, is affected by several factors, including the gastric residence time (GRT). The longer retention of the drug is in the stomach, enhances absorption, thereby improving its bioavailability. However, short GRT results in inadequate drug retention in the stomach, leading to suboptimal drug absorption. Thus, a drug delivery system that can prolong the duration of a drug in the gastrointestinal system (the stomach), such as the gastroretentive drug delivery system (GRDDS), is needed (Gupta et al., 2018).

GRDDS can enhance an absorption window of a controlled drug delivery system by continuously releasing the drug for up to 24 h before reaching its absorption site (Pawar et al., 2011). The GRDDS is beneficial in several ways, that is, improving a drug's bioavailability, primarily for drugs that are easily damaged or lose solubility in high pH environments (e.g., weak base drugs, such as domperidone and papaverine); localizing the therapeutic effect of the drug in the stomach, enabling dose reduction; controlling the therapy level to reduce fluctuation; and improving the efficiency of therapy (Jassal et al., 2015). Various systems of gastroretentive preparations have been developed, such as floating drug delivery system, superporous hydrogel system, expandable system,

bio/mucoadhesive system, high-density system, and a combination system (Prinderre et al., 2011).

Combination systems, such as floating-mucoadhesive systems, have shown improved gastroretentive capacity in various studies. Floating systems are low-density systems with sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. Mucoadhesive systems, also known as bioadhesive systems, incorporate a delivery system with bio/mucoadhesive agents, allowing the device to stick to the stomach (or other gastrointestinal) walls, hindering gastric emptying. The combination is expected to overcome the limitation of each system when used independently. In the case of floating system, it is a risk that the delivery system may advance to the pylorus and be expelled from the stomach during periods of low gastric juice. Meanwhile, the weakness of the mucoadhesive system involves the potential detachment from the mucosa triggered by gastric peristalsis. Several formulation technologies, including microspheres, tablets, beads, films, and ring capsules, have this combination characteristic (Das et al., 2021; Pawar et al., 2011; Singh et al., 2011). In this case, excipients with certain characteristics are needed to combine the two systems (Blynskaya et al., 2022).

Excipients, especially polymers, are important for controlling drug release in various GRDDS preparations (Tripathi et al., 2019). Different polymers can produce a different drug release mechanism. Polymers are generally classified as natural, semi-synthetic, and synthetic. Natural polymers, which are safe, non-toxic, biodegradable, and can be modified chemically, have the potential to be employed in a drug delivery system owing to their inherent advantages. One of the natural polymers that is commonly used in the formulations of GRDDS is chitosan (Pahwa et al., 2012).

Chitosan is a highly beneficial hydrophilic biopolymer made from the deacetylation of alkaline chitin, and it has various advantageous properties, such as non-toxicity, biocompatibility, and biodegradability (Prabaharan and Mano, 2004). Chitosan is a polysaccharide derived from glucosamine copolymers and N-acetyl glucosamine (Rowe et al., 2006). Chitosan is composed of (β1→4)-linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glucopyranose. It is employed as a matrix-forming ingredient and a film-forming substance, and it can provide mucoadhesive abilities in floating delivery systems. Because of its ionic nature, chitosan is frequently utilized to create microcapsules through emulsion cross-linking and ionotropic gelation (Das et al., 2021; Lopes et al., 2016; Vrettos et al., 2021).

Chitosan has a favorable safety profile, making it a distinctive candidate in the pharmaceutical field. In drug delivery, choosing an ideal chitosan type with specific characteristics is useful for developing a sustainable drug delivery system, prolonging the duration of drug activity, improving therapeutic effects, and reducing adverse effects. Several approaches have been conducted, using chitosan as a natural polymer of the floating-mucoadhesive system in gastroretentive preparations (Pahwa et al., 2012).

Chitosan microspheres have high potential for the development of effective GRDDS due to their combined mucoadhesion and floating abilities. This is particularly advantageous for drugs that are readily soluble in acidic media but poorly soluble in intestinal medium, such as verapamil (Yassin et al., 2006). Svirskis et al. (2014) developed mucoadhesive floating hollow chitosan beads based on chitosan using a solvent-free, ionotropic gelation method. The results obtained from that system could increase acyclovir's oral bioavailability and reduce the required administration frequency.

Based on the above explanation, this article will discuss the utilization of chitosan in the floating-mucoadhesive system in gastroretentive preparations.

2. GASTROINTESTINAL SYSTEMS

2.1 Stomach anatomy

The stomach is a J-shaped cavity that forms like a pocket between the esophagus and the small intestine (in the epigastric, umbilical, and left hypochondriac regions). The stomach is across from left to right in the upper abdomen, just below the diaphragm. The stomach has two surfaces, i.e., the facies anterior (facies superior) and facies posterior (facies inferior), and it has four main regions, i.e., the cardia, fundus, corpus, and pars pylorica. Based on structure and function, the stomach is divided into three parts: the fundus, corpus, and antrum. The fundus is a part of the stomach located above the esophageal orifice. It is shaped like a dome and is located on the left of the cardia, extending superior above the height of the gastroesophageal junction. The corpus is the middle and the primary part of the stomach. It is also known as the stomach body because it comprises 2/3 of the stomach. The antrum is a thicker muscle layer on the bottom part of the stomach (Sherwood, 2011).

The cardia surrounds the esophageal opening to the stomach. A superior angle formed when the esophagus enters the stomach is called incisura cardiaca. The fundus is the round part above and on the left of the cardia. The inferior part of the fundus comprises the larger central part of the stomach, known as the *corpus*. The most distal part of pars pylorica is the pylorus. It is marked on the organ surface by pyloric constriction and consists of a thickened circular muscle ring of the stomach, the M. sphincter pylorica. It covers the distal end of the stomach, which is the orificum pylorica. The pylorus is connected to the duodenum. When the stomach is empty, the mucosa will form a large fold known as rugae (plica) ventriculi. The pylorus is connected to the duodenum through a smooth muscle sphincter known as the M. sphincter pylorica. A contracted sphincter pylorica prevents the backflow of intestinal contents into the stomach. The concave medial side of the stomach is called *curvatura minor*, and the convex lateral side is called *curvatura major*. A curve in the *curvatura minor* is called *incisura angularis* (Tortora and Nieslen, 2017). The anatomy of the stomach is depicted in Figure 1.

The stomach and duodenum are innervated by the parasympathetic nervous system. This nervous system is supplied and transmitted by the nerves in the esophagus. All blood supply in the stomach derives from the celiac artery or the celiac trunk, which branches to the curvatura major and minor (Altschuler et al., 1993). Damage to the stomach mucosa is affected by internal glands in the stomach. The pyloric and cardiac glands secrete mucus. The corpus and fundus contain several parietal cells that act in secreting HCl and chief cells, also known as zymogen cells or peptic cells, which act in secreting pepsinogen. The mucus is secreted by mucous cells on the epithelial surface.

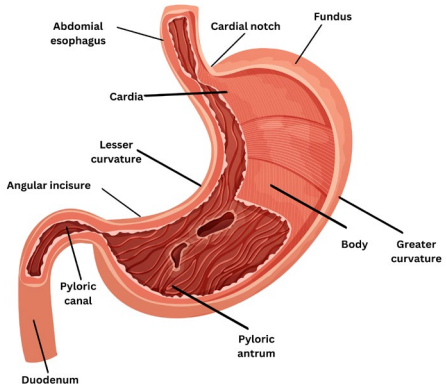

Figure 1. Stomach anatomy

Mucus membranes (mucosae) are the moist surfaces lining the walls of various body cavities, such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer. The epithelia may be single-layered (e.g., the stomach, small and large intestines, and bronchi). The former contains goblet cells, which secrete mucus directly onto the epithelial surfaces, and the latter contains or is adjacent to tissues containing specialized glands, such as salivary glands, that secrete mucus onto the epithelial surface. The mucus is present either as a gel layer adhering to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts, and water, and water for more than 95% of their weight, making them highly hydrated. The major functions of the mucus are protection and lubrication (Boddupalli et al., 2010).

2.2 Stomach physiology

The main function of the digestive system is to deliver nutrients, water, and electrolytes from the foods we eat into the body's internal environment. This system carries out four basic digestive processes, i.e., motility, secretion, digestion, and absorption (Guyton and Hall, 2014).

The stomach has motoric, digestive, and secretory functions. The motoric function of the stomach consists of a reservoir that temporarily stores foods from the esophagus through the cardiac orifice and slowly digests them into smaller particles. The foods, which have been turned into smaller particles, will move to the next digestive tract. Then, the foods in the stomach are mixed with gastric juice by muscle contractions surrounding the stomach. Protein digestion is a digestive process by pepsin and hydrochloric acid (HCl), synthesis, and release of gastrin affected by the proteins consumed. The secretion function of the stomach involves bicarbonate secretion and mucus gel secretion, which acts as a barrier from HCl and pepsin (Trowers and Tischler, 2014). HCl has an important role in eliminating swallowed bacteria, aids in protein digestion, provides the required pH for pepsin to digest protein, and stimulates the flow of bile and pancreatic juice. HCl is secreted by parietal cells in the proximal part of the stomach. There is a physiological stimulation of the stomach to produce gastric acid when there is food. Three secretory phases of gastric acid are interconnected: the vagal or cephalic phase, gastric phase, and intestinal phase (Guyton and Hall, 2014).

The vagal phase indicates when the hypothalamus in the cortex receives the stimulation to release gastrin from antrum G cells so that the stomach produces gastric acid. The gastric phase involves the release of total gastric acid. This phase lasts for several hours to empty the stomach. After complete gastric emptying, the intestinal phase is the final gastric acid production phase. In this phase, if the chime is still in the proximal side of the small intestine, it will be carried out continuously. In the absent of food, the stomach mucosa forms large folds known as rugae, which is visible to the naked eye. When food is present, the rugae seamlessly flatten out, resembling the collapsing folds of an accordion. The stomach mucosa consists of three secretory cells: the chief, parietal, and mucous cells. The chief cells secrete the pepsinogen enzyme, the parietal cells secrete HCl that activates pepsinogen to pepsin, and the mucous cells secrete mucus to protect the stomach (Schubert, 2016).

The stomach functions by breaking down food particles into a solution known as chymus, which contains fragments of protein molecules, polysaccharides, particles of lipids, salt, water, and various small molecules introduced with ingested food. However, only water can pass through the gastric epithelium as absorption of nutrients primarily occurs in the small intestine.

3. FLOATING-MUCOADHESIVE SYSTEMS IN GASTRORETENTIVE DRUG DELIVERY

The oral route is considered the most ideal for drug delivery due to its advantages, such as formulation flexibility. Administration of a drug delivery system through oral route is particularly advantageous when the drug locally acts on the target in the GI tract and can maintain its concentration for a long time. However, the physicochemical properties of most drugs are weak, such as high solubility in acidic pH but poor solubility in basic pH, which leads to poor drug absorption in the intestine (Prinderre et al., 2011). Therefore, GRDDS presents additional advantages by improving the bioavailability compared to drugs designed for local action in the stomach. This improved bioavailability not only reduces the dose required but also minimizes gastrointestinal effects, thus improving patient compliance (Garg and Gupta, 2008).

One type of GRDDS is the floating-mucoadhesive system, commonly employed in gastroretentive preparations. The floating system relies on the principle of low density, where the density of the drug must be lower than that of the gastric fluid, which is <1.004 g/mL. This characteristic allows drugs to float and remain longer in the stomach (Annisa, 2021).

In recent decades, many publications have described formulations and the development of various dosage forms of mucoadhesive GRDDS designed for a specific interaction with the mucus membrane. Studies related to the floating-mucoadhesive system are now focused on improving gastroretention through the incorporation of floating or adhesive additives. Floating-mucoadhesive systems have been demonstrated to improve the delivery of local and systemic therapeutic substances. One study focused on the selection of polymers for developing the floating-mucoadhesive delivery system (Ainurofiq et al., 2023a).

Characteristics of polymers that are ideal for use in mucoadhesive systems are non-toxic, not absorbed by the gastrointestinal tract, do not irritate the gastric mucosa, form strong bonds with the epithelial cell mucin, do not become a barrier to drug release, are stable, or have a long shelf life. The most promising mucoadhesive polymers include chitosan, alginate, pectin, poly(acrylic acid), and carboxymethyl cellulose (Patil et al., 2016). Research on mucoadhesive polymers over the last decade has mostly shown that chitosan is the strongest and most promising candidate as a polymer of choice for mucoadhesive systems compared to other candidates, such as alginate and pectin, because it can increase stability, provide controlled release, reduce side effects, and increase bioavailability. In addition, most of the studies have proven the efficacy of chitosan for oral mucoadhesive administration in stomach cancer. This biodegradable material avoids the possibility of the drug dose remaining in the body because it will be directly degraded and broken down into molecules and excreted by the body (Kumar et al., 2022).

3.1 Mechanisms of the floating-mucoadhesive system

3.1.1 Floating system

The floating system enables drugs to float, and retain longer in gastric fluid (Tripathi et al., 2019). The controlled release of drugs in gastric fluid can lead to the reduction of variability in the plasma concentration. Generally, floating system does not cause gastrointestinal side effects (More et al., 2018). This system can be divided into two mechanisms: effervescent and non-effervescent.

3.1.1.1 Effervescent system

The effervescent system uses gaseous agents derived from the production of CO_2 or the evaporation of organic solvents. When the volume increase surpasses the mass increase, the system density decreases, causing it to float in the gastric fluid. The drug release rate and floating duration depend on added polymers and other excipients (More et al., 2018). The effervescent system comprises two systems: gas-generating and volatile liquid-containing systems.

a. Gas-generating system

This system has two layers: an inner layer of an effervescent, containing materials that produce gas, such as sodium bicarbonate, citric acid, or tartaric acid, and an outer layer, a hydrophilic polymer membrane. The main mechanism of this system is the production of CO_2 through an effervescent reaction with the stomach content (Tripathi et al., 2019). The gas-generating system can be divided into monolayer, bilayer, multilayer, and ion-exchange resin systems. In the monolayer system, the gas-generating system and drugs are contained in a tablet matrix. The CO_2 generated during the effervescent reaction is trapped inside a hydrophilic matrix, resulting in floating of the delivery system. The bilayer system consists of an immediate release layer (drug) and a sustained release layer (drug, polymer, and CO_2). Increased polymer hydration and surface area for drug diffusion increases the GRT and slows the drug release rate from the matrix in the presence of CO_2 (Jassal et al., 2015; More et al., 2018). The multilayer system involves sustained-release tablets covered with multilayers (inner and outer layers). The inner layer consists of an effervescent substance, and the outer layer is a polymer membrane. The tablet expands like a balloon and floats when the system melts at body temperature. The ion-exchange resin system consists of resin-containing drug complexes and bicarbonate ions. A hydrophobic polymer covers the resin. After contact with the stomach content, chloride ions will be exchanged with bicarbonate and drug ions. The produced CO_2 can be trapped in the polymer and float in the system (Jassal et al., 2015; More et al., 2018).

b. Volatile liquid-containing system

This system has two chambers—one containing the drug and the other a volatile liquid. Volatilization occurs when volatile liquids of organic solvents, such as ether or cyclopentane, are introduced into an inflatable chamber, followed by evaporation or gas formation at body temperature. This process leads to an increase in systemic space within the stomach (Lopes et al., 2016). The volatile system can be divided into three categories: gastric buoyancy, distention, and penetration. Buoyancy is considered one of the most promising approaches for gastro-retention of dosage forms. Floating drug delivery systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach, causing an increase in GRT. The buoyancy of these systems is attained with the aid of substances responsible for generating low density (Ishak, 2015; Pasumarthy et al., 2009). The floating intragastric system uses a vacuum or gas to insert drugs, packed in a microchamber, into the floating chamber. The inflatable system is made by filling an inflatable chamber with drugs and polymers enclosed in gelatin capsules. Following oral administration, the capsule dissolves, releasing the drugs along with the inflatable chamber. This chamber then automatically releases the drugs from the stomach into the gastric fluid (Jassal et al., 2015). The osmotic system has two compartments: the drug compartment and an active osmotic compartment. Upon contact with the gastric fluid, the inflatable capsule dissolves, releasing the drugs through osmosis (Pant et al., 2016).

Floating rafts have been used in the treatment of gastric esophageal reflux disease (GERD). The mechanism involved in raft formation includes the formation of a viscous cohesive gel upon contact with gastric fluids. Each portion of the liquid swells, forming a continuous layer called a raft. This raft floats on gastric fluids due to the low bulk density created by the generation of CO_2 (Yaswantrao et al., 2015).

3.1.1.2 Non-effervescent system

The non-effervescent system involves several components, including a single layer, microporous compartment, alginate beads, and hollow microsphere. In the single layer, usually a gelatin capsule, one or more hydrophilic polymers are mixed with drugs. The system inflates upon hydration, forming a gel layer that traps air around the core, allowing the system to float. The microporous compartment combines the formula from a gas-containing chamber into a microporous component, enabling the system to float. Alginate beads are floating multiunits made from lyophilized alginate calcium. Floating beads can extend the GRT to more than 5.5 h. The hollow microsphere contains the drug inside a polymer formulated using a simple solvent evaporation method or solvent diffusion, contributing to an increased GRT (Gupta et al., 2018; Lopes et al., 2016; More et al., 2018).

The floating system in the stomach can be made by creating a chamber filled with air or inert gas formed by the interaction between the gas-generating system and the gastric fluid. Inflatable polymers, including chitosan. can be used in the floating system. The floating mechanism with chitosan begins with the contact between the gastric fluid and a tablet, which causes the polymers to hydrate and form a gel layer that can hold CO_2 formed by the interaction between bicarbonate and citric acid. Consequently, the tablet expands and floats. Chitosan is a hydrocolloid hydrophilic polymer that can form a barrier gel with high viscosity, thereby slowing down the penetration rate of the gastric fluid. This results in fewer gas-generating agents encountering the gastric fluid, leading to an increases in the floating lag time of the tablet (Sharma et al., 2011).

3.2 Mucoadhesive system

3.2.1 Mucoadhesive polymer classification

3.2.1.1 Non-specific first-generation polymers

First-generation mucoadhesive polymers can be divided into three main subsets, as follows.

a. Anionic polymers

These polymers are characterized by carboxyl and sulfate functional groups, resulting in an overall negative charge at pH values exceeding the pKa of the polymer. They are most widely used for developing drug delivery systems due to their highly mucoadhesive functionality and low toxicity. Examples of anionic polymers are poly(acrylic acid) and its cross-linked derivatives, as well as sodium carboxymethylcellulose (Andrews et al., 2009; I. Singh and Rana, 2013).

b. Cationic polymers

Cationic polymers exhibit a net positive surface charge due to cationic groups within the structure. Because of this positive charge, the polymer displays strong ionic interactions with negatively charged mucin molecules, providing significant adhesive strength necessary for developing mucoadhesive drug delivery systems. Chitosan is the most extensively researched cationic polymer for its mucoadhesive properties. Its good biocompatibility, biodegradability, and low toxicological properties make chitosan a favorable candidate for drug delivery applications. Chitosan is commercially produced by the deacetylation of chitin, a natural polysaccharide found in the outer skeletons of crustaceans (crabs, shrimps, etc.) (Bansal et al., 2011; Singh and Rana, 2013).

c. Non-ionic polymers (Priya et al., 2013)

These polymers are also used for its mucoadhesive property. The example of non-ionic polymer are, hydroxyethylcelullose, hydroxypropylcelullose, polyvinylpyrrolidone, and polyethylenglycole 6000 (Masal and Shinde, 2022).

3.2.1.2 Novel second-generation polymers

The main drawback of first-generation polymers is their non-specific binding to the mucosal substrate. This issue has been addressed with the emergence of second-generation polymers that exhibit more specific (site-specific) binding, and these are more precisely referred to as 'cytoadhesives' (Priya et al., 2013; Singh and Rana, 2013). These polymers are less vulnerable to mucin turnover rates, providing an additional advantage for developing mucoadhesive drug delivery systems. Second-generation polymers can be developed through surface modifications of existing polymers, such as polymer modification/functionality with lectins, bacterial adhesins, and amino acid sequences. Chemical modification of polymers, for example, the introduction of thiol groups or thiolation, is another method currently being investigated to enhance the mucoadhesive properties of polymers (Singh and Rana, 2013).

However, the mucoadhesive system works by binding the epithelial surface of the stomach or mucus. The binding can prolong the GRT of drugs in the stomach because drugs have a longer contact duration with biological membranes (Kumar and Kaushik, 2018). Bioadhesive polymers can be divided into two groups: cytoadhesive and mucoadhesive polymers. Cytoadhesive polymers can bind to epithelial cell layers by interacting with a certain receptor cell. However, mucoadhesive polymers can bind the mucus layer. Common polymers used for this system are chitosan, tragacanth, sodium alginate, carbopol, hydroxypropyl methylcellulose (HPMC), glycol, and dextran (Lopes et al., 2016).

The mucoadhesive system binds with the epithelial surface of the stomach or mucin and prolongs the GRT by increasing the duration of contact between the dosage form and biological membrane. Mucoadhesive materials consist of natural or synthetic polymers that can bind to a biological membrane (bioadhesive polymer) or mucus layer of the gastrointestinal tract (mucoadhesive polymer) (Sharma et al., 2011). There are different theories of the binding mechanism of the preparation to the mucosal surface as follows (Nayak et al., 2010).

a. Wetting theory

The wetting theory is based on the ability of polymers to disperse and directly contact the mucosal layer.

b. Diffusion theory

The diffusion theory is based on the interpenetration of mucin strands into the polymer pore structure.

c. Absorption theory

The absorption theory is based on bioadhesion, which occurs because of a secondary force, such as van der Waals or hydrogen bonding.

d. Electron theory

This involves attractive electrostatic forces between mucin glycoprotein and bioadhesive materials.

The polymer used plays a role in the binding of the preparation with the mucosal membrane. Appropriate mucoadhesive polymers that can bind to the mucosal epithelial surface are typically divided into three classes of drug delivery system as follows (Kaurav et al., 2012):

a. Polymers that become sticky when placed in water,

b. Polymers that attach through a non-specific, non-covalent interaction mechanism, which is the primary electrostatic force in nature (although hydrogen and hydrophobic bonds might play a role), and

c. Polymers that bind to a specific receptor site on its surface.

Requirements for polymers in the mucoadhesive system include (Mihir et al., 2011; Sharma et al., 2011).

a. The polymer and its degradation products must be non-toxic and not absorbed into the digestive tract.

b. It does not irritate the mucosal membrane.

c. A non-covalent bond forms strongly between the polymer and the mucin or epithelial surfaces.

d. Drugs can penetrate easily into the polymer, and the polymer does not hinder drug release.

e. The polymer is not damaged during storage or as a finished drug product.

The bioadhesive system can consist of natural or synthetic polymers that can interact with biological substrates. When the substrate is mucus or mucosa, the system is called mucoadhesive. Chitosan has been a popular component of this system because it can form various interactions between the mucosa with many hydrogen bonds and electrostatic interactions as adhesion interactions of the preparation. Implementing the bioadhesive system involves several advantages for drug release in the stomach, including increased bioavailability, optimal pharmaceutical dosage form, and long GRT. GRDDS and mucus molecules must interact in the interface during the adhesion process. This interaction can occur through an ionic or covalent bond, van der Waals forces, hydrogen bonds, or hydrophobic interactions. Adhesion is marked by two main stages, the contact and consolidation stages, as shown in Figure 2 (de Souza et al., 2020).

In the mucus-polymer interface, due to the distribution of electric charges (electronic theory), a relationship can be established (adsorption theory). Then, the polymer and protein chains diffuse (diffusion theory) and become entangled, forming further bonds (electronic and adsorption theory) for longer adhesion. This mechanism can be categorized into the contact and consolidation stages shown in Figure 2. During the contact stage, wetting between the dosage form and the mucus surface will occur. During the consolidation stage, the plasticizing and adhesion activities of the polymer are activated by moisture, which promotes the formation of hydrogen bonds and van der Waals forces. Diffusion theory also explains the consolidation phase in which the slime layer glycoproteins and polymer molecules diffuse within each other and form secondary bonds. This will strengthen and extend the adhesion. Bioadhesion or mucoadhesion cannot be explained by one theory but is better explained by combining all or some of the mechanisms mentioned above (Chatterjee et al., 2017).

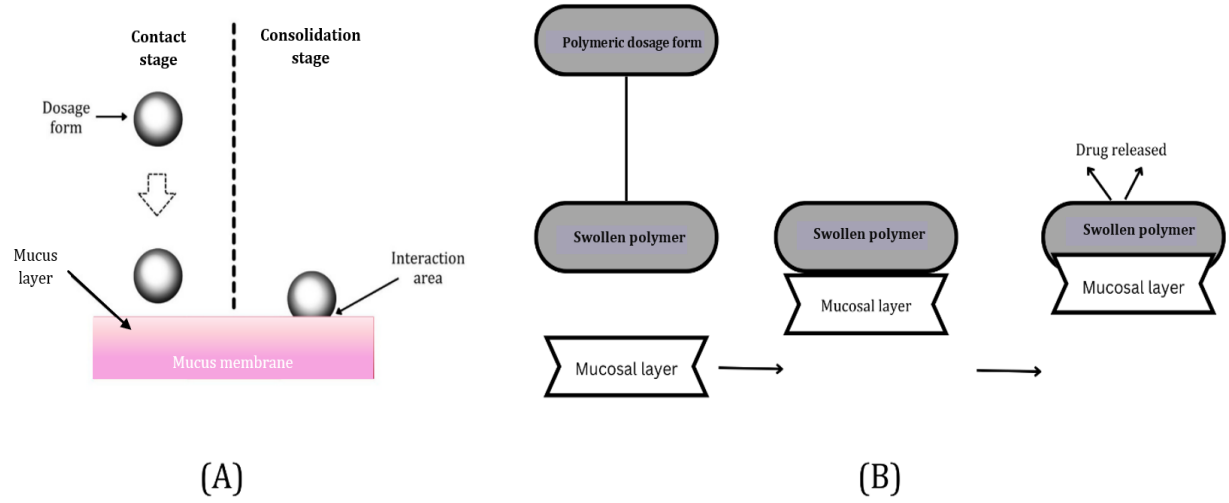

Figure 2. (A) Schematic representation of mucoadhesion stages (de Souza et al., 2020), (B) mucoadhesive mechanism (Chatterjee et al., 2017)

Stage I (contact stage) - Early contact between the pharmaceutical dosage form and the mucosal mucus begins with chain interpenetration in the mucosal mucus and adhesion to the surface. The polymer chain starts interacting with the medium and mucus in this stage. In cases where GRDDS is developed with chitosan, an acidic solution must act by protonating and hydrating the chitosan chain. This provides a more effective interaction between the mucosal mucus and pharmaceutical dosage form (de Souza et al., 2020).

Stage II (consolidation) - Adhesion consolidation of the pharmaceutical dosage form occurs because the polymer forms a mostly hydrated system. Protonated chitosan provides larger conformational freedom that can develop interactions with the mucus membranes. The main interactions in this stage are hydrogen bonds, van der Waal forces, and electrostatic interactions. Because of high conformational freedom from the polymer chain and close contact with the mucus, the chain diffuses through the mucosal layer and forms a stronger interaction. Another important contribution in this stage is the suction effect promoted between high-affinity polymers and water, which causes dehydration of the mucus during increasing system adhesion (de Souza et al., 2020).

4. ADVANTAGES AND DISADVANTAGES OF FLOATING-MUCOADHESIVE SYSTEMS

Advantages of the floating-mucoadhesive delivery system include the following (Sachan and Bhattacharya, 2009).

a. It has a longer transit duration in the GI tract. Gastric emptying and intestinal peristalsis influence the transit time in the digestive tract. The floating-mucoadhesive drug delivery system can inhibit gastric emptying so the drug remains in the stomach longer before entering the intestine. This allows the drug to interact with the mucosa longer and be absorbed before it is excreted from the body.

b. It can be used as a local action with proper delivery. The system, with its floatability and mucoadhesive properties, extends the drug's residence time in the application area. This extended duration allows a longer time for the drug to interact with target tissues or organs, increasing the chances of achieving the desired local effect.
c. Contact of the particle with the mucosa causes an increase in the drug's concentration gradient. Floating-mucoadhesive drug delivery systems can be designed to release a drug in stages. When the drug particles release the drug slowly, the concentration around the particles may become higher than in the ambient fluid. This creates a difference in drug concentration between the particle and the mucosa, increasing the drug concentration gradient and facilitating drug absorption through the mucosa.
d. Direct contact with the site of particle absorption occurs in the upper part of the intestinal cells. The floating-mucoadhesive system has mucoadhesive properties that allow drug particles to adhere to the mucosal surfaces of the digestive tract. Because the upper intestinal cells have a mucosal lining, drug particles can adhere to this mucosa and directly contact the upper intestinal cells.
e. It can release the drugs continuously for a long time. Floating-mucoadhesive drug delivery systems can be designed with a release control mechanism that allows gradual and continuous drug release. This could include using a polymeric matrix that slows drug diffusion, a coating or membrane that regulates the drug release rate, or a combination of other strategies. With proper release control mechanisms, drugs can be released gradually over a sufficiently long time.
f. It can be frequently used because it does not interfere gastrointestinal motility. The mucoadhesive properties in floating-mucoadhesive formulations can be fine-tuned to minimize their effect on gastrointestinal motility. Controlled mucoadhesion with controlled particle sizes and shapes and using low-density materials can provide sufficient contact time between drug particles and the digestive tract mucosa without disturbing normal peristalsis or food movement in the digestive tract (Patil et al., 2016).
g. It possesses the capability to attain an optimal an appropriate therapeutic concentration. It can retain a high concentration in the stomach region, improving the therapy's effectiveness (Dey et al., 2016).

The floating-mucoadhesive delivery system also has some limitations, including the following (Bernkop-Schnürch and Gilge, 2000).

a. The mucoadhesive system is relatively costly. Developing mucoadhesive systems involves intensive research and development to optimize the formulation, mucoadhesive characteristics, and drug performance. High research and development costs can affect the final price of the product.
b. It has the possibility of dose dumping, which is the rapid release of many drugs from the preparation. If the drug has physicochemical properties incompatible with mucoadhesive formulations, such as high solubility or poor stability, it can lead to rapid and uncontrolled drug release.
c. It can result in unpredicted *in vitro* and *in vivo* correlations. The interaction between the mucoadhesive system and the mucosa involves many factors, including the physical and chemical properties of the drug, adhesion to the mucosa, and drug release from the mucoadhesive system. Various factors, such as particle size, mucoadhesive properties, and mucosal conditions, can influence this interaction. These factors can affect the response *in vivo* without detection in *in vitro* testing.
d. Factors of physiological variables, such as the pH of the stomach and intestine, enzyme activity, gastric and small intestine residence times, food, and the disease level of the patient, can inhibit the achievement of drug action.
e. Not all active substances can be formulated as mucoadhesive preparations. Some active ingredients may be unstable in the environment the mucoadhesive system requires. The physicochemical properties of the mucoadhesive system, such as pH, humidity, and temperature, can affect the stability of the active substance. If the active substance is unstable under these conditions, using a mucoadhesive system for drug delivery may affect the integrity and effectiveness of the active substance.
f. The half-life of drugs that can be used as a general preparation guideline with a modified release of 2 to 6 h. Using a half-life longer than 2 to 6 h may increase the risk of side effects or drug accumulation in the body. Meanwhile, a shorter half-life may not achieve the desired therapeutic effect.

5. CHITOSAN

Chitosan is produced from chitin and has a chemical structure similar to chitin, a long molecular chain with a high molecular weight. The difference between chitin and chitosan is the presence of the acetyl group (CH_3-CO) in the second carbon atom of each ring of the chitin molecule. In contrast, chitosan has an amine group (-NH_2). Chitosan can be produced from chitin through deacetylation, which is a reaction with a high alkali concentration over a relatively long duration at high temperatures. Chitin and chitosan are polycationic linear polymers. The presence of hydroxyl and amino groups along the polymer chain makes chitosan highly effective in adsorbing heavy metal ion cations and organic cations (proteins and fat) (Kusumawati, 2009). Chitosan is a copolymer of D-glucosamine and N-acetyl-D-glucosamine with the β~(164) bond. It has the chemical name of poly(D-glucosamine ((β1→4)-linked 2-amino-2-deoxy-D-glucose) (Guyton and Hall, 2014). The structure of chitosan is depicted in Figure 3.

Chitosan can be obtained in many morphological shapes, including irregular, crystalline, or semi-crystalline structures. It can also exist as a white-colored amorphous solid with the crystal structure of pure chitin. Derived from fishery waste, such as shrimp shells and crabs, chitosan has special properties—being biocompatible, biodegradable, and non-toxic, making it an attractive biomaterial. It can serve as a drug carrier and is amenable to modification.

The capabilities of chitosan specified in various modern industries have encouraged the development of various research modifications of chitosan. The

modification can be carried out both physically and chemically. Physical modification of chitosan includes changing the size of the chitosan particles or granules to smaller than the size of nanoparticles (particles ranging from 10 to 1000 nm). If the particle size is made smaller, then the surface area of the particles will be larger, increasing the abilities of chitosan as an adsorbent, antifungal agent, antibacterial agent, and carrier in the body. A small particle size also increases the stability of the nanoparticles.

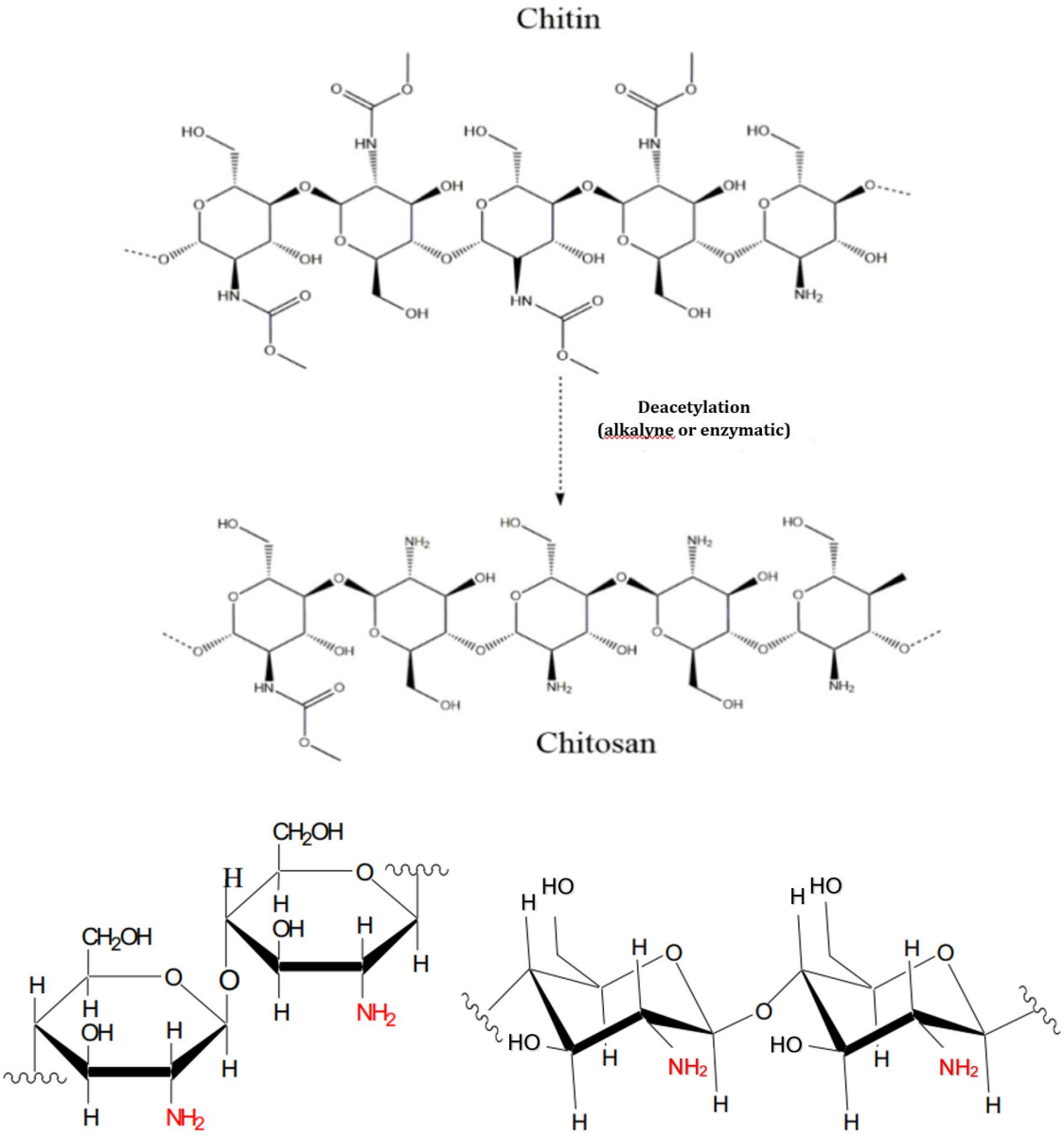

Figure 3. Deacetylation of chitin producing chitosan, and the chitosan structure

The application of nanochitosan in pharmaceuticals has various advantages, such as increasing the solubility of compounds, increasing absorption, and reducing drug doses (Ainurofiq et al., 2023b). In the pharmaceutical industry, nanochitosan is widely used as a drug delivery system (carrier), for substances like glycrrhizinte, retinol, dexamethasone, and estradiol. The method involves dispersing the substance into a chitosan solution in deionized water during sizing, resulting in nanoparticles with sizes ranging from 80–260 nm. This nanoform acts as a beneficial carrier, increasing the penetration of the active substance and providing controlled release.

5.1. Chitosan solubility

The solubility of additives and active substances is an important factor in the formulation of drug preparations (Ainurofiq et al., 2021). Chitosan has the highest solubility in a 2% acetic acid solution. The solubility of chitosan is affected by its molecular weight, degree of deacetylation, and specific rotation. This depends on the source and method of separation and transformation (Sugita, 2009).

The standard in determining chitin or chitosan polymer is based on the different contents in the amides. Chitosan contains 60% of amide groups, while chitin contains less than 60%. Chitosan is easily degradable, non-toxic, highly cationic, excellent flocculant and coagulant, readily forms membranes or films, and forms gels with divalent anions. Chitosan is not soluble in water above pH 6.5 or organic solvents, including alcohol, acetone, dimethylformamide, dimethylsulfoxide, and basic or mineral acid solvents. Chitosan is rapidly dissolved in organic acids such as formic, citric, and acetic acids.

Citric acid, in particular, can react with two or more amine groups, leading to the breakage the chitosan chain and the crosslinking of chitosan into a large structure. However, the solubility of chitosan is not increased by the number of carboxyl groups in citric acid due to its one carboxyl group, which acts as a proton donor. In contrast, acetic acid can dissolve chitosan without forming a large structure, as seen with citric acid (Szymańska and Winnicka, 2015). The properties of chitosan are affected by the bond between amino and hydroxyl groups. The high chemical reactivity with cations contributes to the polyelectrolyte property and serves as a substitute for amino groups.

6. CHITOSAN IN FLOATING-MUCOADHESIVE SYSTEM

The floating-mucoadhesive system manufacturing method using chitosan is a strategy that combines the advantageous properties of floating and mucoadhesion in drug delivery. The basic principle of this method is to use the ability of chitosan as a mucoadhesive polymer that can interact with the gastric mucosa by producing gas bubbles to keep the system afloat on the surface of the gastric fluid (de Souza et al., 2020). Chitosan was selected upon considering its molecular weight and degree of deacetylation (Pahwa et al., 2012). According to Shaikh et al. (2012), the preparation begins with hydrated chitosan in a weak acid solution, such as acetic acid, to form a chitosan solution. Additives and drugs are mixed in a chitosan solution. The next step is to form a floating-mucoadhesive system, for example, in tablet form. The chitosan mixture solution is then printed in tablet molds and dried to remove moisture. The result is a tablet containing chitosan as a mucoadhesive matrix and drug producer. According to Pahwa et al. (2010), its evaluation can include rigorous tests. A mucoadhesive test was performed to examine the interaction between chitosan in the system and the gastric mucosal lining. A buoyancy test was conducted by placing tablets in a simulated hull medium to measure their floating time. Release rate tests were carried out to understand the drug release profile from the system over time. In addition, the physicochemical characteristics of the tablets, including hardness, friability, and particle size, have been evaluated. Bioavailability tests can be performed to understand the extent to which these systems enhance drug absorption, and stability tests are important to examine the physical changes and performance of the system during long-term storage.

Chitosan can form a thick gel coating when in contact with gastric fluid, and can control the release of drugs through diffusion (Rowe et al., 2009). Chitosan has been evaluated as a stomach-specific drug delivery system as gastroretentive floating beads. Yassin et al. (2006) stated that gastroretentive beads prepared from verapamil used chitosan as the polymer and glutaraldehyde as the cross-linking agent. It was found that beads made from chitosan showed excellent floating characteristics, and the floating lag time was 5 min with a total buoyancy duration of over 6 h.

Pawar et al. (2013), who used a combination of HPMC polymer, ethyl cellulose, and chitosan, showed that chitosan coating on floating microballoons (FMB) provides an excellent mucoadhesion to the intestinal walls of mice, which was also supported by a mucin glycoprotein test. Dey et al. (2016) investigated the combination of sodium alginate polymer, HPMC, and chitosan and showed a good mucoadhesive power from 5.7±3.0 to 85.0±5.5%. Most studies have also indicated that chitosan and its derivatives have anticancer properties. This polymer shows low toxicity, thus reducing adverse effects and tumor size by inhibiting the proliferation of tumor cells, which leads to apoptosis (Adhikari and Yadav, 2018). Table 1 shows chitosan utilization in the floating-mucoadhesive system.

Different dosage forms, such as beads and microballoons, can affect the buoyancy of floating mucoadhesive systems. Microballoons are designed with a hollow core filled with gas, making them highly buoyant. The size and thickness of the shell and the gas content in the hollow core contribute to the buoyancy of the microballoons. The mucoadhesive properties of the outer surface of the microballoons may affect their interaction with the gastric mucosa. The drug release and floating properties primarily depend on the type of polymer and the solvents employed for the preparation. Microballoons are loaded with drugs in their outer polymer shell to create a hollow inner core, and they have been prepared by a novel solvent evaporation or solventdiffusion/evaporation method (Verma et al., 2022). The beads typically vary in size. The density affects buoyancy, which can be adjusted using low-density materials or incorporating gas-producing materials. The choice of polymer or material used to make the beads can affect their ability to float. Beads have been prepared using solvent evaporation and ionotropic gelation methods. A floating multiparticulate dosage form has been prepared by solvent diffusion and evaporation to create a hollow inner core. Ionotropic gelation is based on the ability of polyelectrolytes to crosslink in the presence of counter ions to form beads (Setia et al., 2018). In summary, both beads and microballoons affect the floating properties in floating-mucoadhesive systems due to their size, density, and structural characteristics. The larger size and lower density contribute to improved buoyancy. Microballoons have an inherent advantage in terms of buoyancy due to their hollow gas-filled structure, which helps them remain buoyant in gastric fluids (Negia et al., 2014). Beads can be formulated to have specific buoyant and mucoadhesive properties, enhancing their retention in the stomach. The choice between beads or microballoons would depend on the targeted application's specific drug delivery objectives and desired properties (Kumar et al., 2022)

Table 1. Utilization of chitosan in a floating-mucoadhesive system

Polymer	Objective	Methods	Results	References
HPMC 80–120 cps, ethyl cellulose 45 cps, chitosan	Increases the bioavailability of norfloxacin with the floating-mucoadhesive mechanism.	Floating microballoons (FMB) are made using non-water solvent evaporation using HPMC and ethyl cellulose to develop the core matrix. The chitosan layer is prepared using an ionotropic gelation method to increase the mucoadhesive property and the gastric retention time of the microballoons.	The microballoons exhibited a zero-order release in simulated gastric fluid, demonstrating drug release from 64.99±3.26 to 99.94±8.45% after 10 h through various formulations. The chitosan layer overlying the FMB provides excellent mucoadhesion to the intestinal wall of rats. A mucin glycoprotein test supported this result.	Pawar et al., 2013
Sodium alginate, HPMC, chitosan	Investigation of the entrapment design of amoxicillin trihydrate with sunflower oil and HPMC as the matrix polymer and chitosan as the layer polymer to localize antibiotics in the stomach against *Helicobacter pylori*	The beads were prepared using an ionotropic gelation technique, evaluated for their physicochemical properties *in vitro* and *in vivo.*	The formulated beads showed good mucoadhesive properties. The optimal result showed 100% growth inhibition of *Helicobacter pylori* within 15 h in an *in vitro* culture. Beads of all batches were floated for >24 h with a maximum lag time of 46.3±3.2 s. The prepared beads showed good mucoadhesiveness of 75.7±3.0 to 85.0±5.5%.	Dey et al., 2016
Chitosan, galactomannan, alginate	Formulation and evaluation of controlled release of floating bioadhesive gastroretentive chitosan-coated amoxicillin trihydrate (CCA)-loaded with *Caesalpinia pulcherrima* galactomannan (CPG)-alginate beads (A) to eradicate *H. pylori*	The beads of CCA-CPG-A were made by ionotropic gelation using 23 factorial designs with drug components by combining CPG with sodium alginate and calcium chloride concentration as the variable.	The developed beads showed 79–92% drug release, 65–89% entrapment efficiency, and 61–89% mucoadhesion. An *in vivo* mucoadhesion study showed more than 75% of mucoadhesion beads even after 7 h. The *in vitro-in vivo* growth inhibition study showed complete eradication of *H. pylori*.	Thombre and Gide, 2016
Chitosan, Pluronic F127	Development of a nanomicelle-loaded gastroretentive bead delivery system to improve the treatment of stomach disease and reduce systemic adverse effects	Emodin-loaded nanomicelles coated with chitosan were developed and characterized. Afterward, nanomicelle-loaded floating mucoadhesive beads (NFM beads) were prepared. Swelling, degradation, mucoadhesion, and the ability to float were examined *in vitro*. The formations of nanomicelles and NFM beads were identified via FTIR spectroscopy.	The *in vivo* gastroretentive behavior from NFM beads was evaluated via X-ray imaging based on $BaSO_4$, which showed that the NFM beads could be retained in a rabbit's stomach for at least 8 h. Overall, the NFM-bead system could effectively improve the therapeutic potential of drugs for gastric cancer.	Chen et al., 2019
HPMC K100M, chitosan	Determine the optimum composition from the combination of HPMC K100M with chitosan that follows the requirements for manufacturing floating-mucoadhesive diltiazem HCl tablets	The tablets were molded with a single punch tablet press (mini tab) using direct compression. The tablets were evaluated for hardness, friability, and weight uniformity.	The optimum formula for HPMC K100M was 175 mg, and chitosan was at 50 mg. This combination of polymers produced a floating lag time of 45.3 s, a floating duration time of >12 h, and a mucoadhesive strength of 81.6 g.	Triastutik et al., 2020

7. CONCLUSION

Mucoadhesive floating systems are used in gastroretentive preparations to prolong the GRT for optimum absorption. The design of floating-mucoadhesive systems involve the careful selection of the polymers, with chitosan being widely evaluated for floating bead gastroretentive delivery systems in numerous studies. Chitosan has considerable potential to be used as a polymer in the floating-mucoadhesive system because of its excellent mucoadhesive ability whether used in combination with other polymers or as a single entity. Single-unit floating dosage forms, which include floating tablets, floating capsules, etc., are designed to prolong the residence of dosage forms in the GIT and thereby enhancing absorption. Floating multi-particulates can be developed in various forms, such as granules, pellets, beads, and microspheres. The utilization of multiple-unit dosage forms, aims to keep most particles above the stomach contents for an extended period. This approach not only reduces the intersubject

variability in absorption but also mitigates the risk of dose dumping and bursting associated with a single-unit system.

ACKNOWLEDGMENT

The authors acknowledge the Institute for Education Development and Quality Assurance (LPPMP) of Sebelas Maret University for developing a project-based learning method that has led to the development of drug pre-formulation studies.

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