REVIEW ARTICLE

The Use of Natural and Synthetic Polymers in the Formulation of Gastro retentive Drug Delivery System

Ahmad Ainurofiq*, Amalia Daryati, Faradisania A. Murtadla, Fatimatus Salimah, Nila M. Akbar, Rizka A. Faizun

Department of Pharmacy, Sebelas Maret University, Ir. Sutami 36A, Surakarta, Indonesia

Received: 15th January, 2023; Revised: 10th Fabruary, 2023; Accepted: 08th March, 2023; Available Online: 25th March, 2023

ABSTRACT

The gastric emptying process drastically reduces the bioavailability of drugs that target the stomach for their action. A gastro retentive drug delivery system (GRDDS) becomes a solution to retain drugs in the stomach and release drugs from the formulation system within a certain period. The polymer used in the GRDDS formulation is the essential excipient that can retain the drugs in the stomach. Several ways for GRDDS to maintain its existence in the stomach are using some systems, such as mucoadhesive, low-density, high-density, swellable, effervescent, and expandable systems. A polymer is a macromolecular substance with a long repeating chain consisting of natural and synthetic polymers, each with different potentials. It is considered for its ability to regulate drug release, good flow properties, can improve drug dissolution to improve bioavailability and stability during processing in the body. Combining natural and synthetic polymers is often carried out to obtain advantages and cover the existing polymer's disadvantages. Polymers can release drugs using three different mechanisms, i.e., diffusion, degradation, and expansion. These techniques are often chosen for the formulation of GRDDS because of their more flexible system and fit for almost all types of GRDDS. The polymer used in the GRDDS system is chosen from its physicochemical properties and the number of floating times, drug release rate, viscosity, floating lag times, bioavailability, and solubility.

Keywords: Evaluation of polymers, Gastro retentive drug delivery system, Natural polymers, Physicochemical properties, Synthetic polymers, Utilization,

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.1.69

How to cite this article: Ainurofiq A, Daryati A, Murtadla FA, Salimah F, Akbar NM, Faizun Ra, The Use of Natural and Synthetic Polymers in the Formulation of Gastro retentive Drug Delivery System. International Journal of Drug Delivery Technology. 2023;13(1):434-441.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The oral drug delivery system is used in most formulations of pharmaceutical drugs due to its ease of administration, non-evasive, patient compliance, and flexible formulation. The absorption of oral drugs mostly occurs in the stomach and intestines. Stomach absorption can reduce the drug's bioavailability due to the gastric residence time (GRT). Gastric emptying will reduce the bioavailability of oral drugs because they do not have much time to retain in the stomach.[1] Oral administration drugs can reduce consumption compliance in several patients who consumed drugs with too many dose regimens. Therefore, reducing dosage frequency, ease of administration, and minimizing infection related to administration are ways to be considered in improving medication compliance. One of the most relevant systems to fulfill this requirement is the gastroretentive drug delivery system (GRDDS). GRDDS tends to maintain a preparation shape on the upper part of the gastrointestinal through various approaches. It can float on the surface of gastric fluid without affecting the gastric emptying rate because of its low density.[2]

The GRDDS is a sustained drug delivery system that can keep the drug for a longer time. The advantages of GRDDS include increasing bioavailability, increasing solubility in high pH, control of therapy level to reduce fluctuation, and prolonging half-time to reduce the frequency of drug administration. However, GRDDS is not suitable for drugs that irritate the stomach, are unstable in stomach pH, or have a significant first-pass effect metabolism. GRDDS delivery formulation has several systems, including superporous, floating, high-density, bioadhesive, raft forming, expandable, and magnetic.[1]

An understanding of the materials used in the formulation of GRDDS, such as excipients and polymers, is important. Polymer characteristics highly affect the success of GRDDS formulation, such as molecular weight, viscosity, and physicochemical properties.[1] The polymer in GRDDS

*Author for Correspondence: rofiq@mipa.uns.ac.id

formulation can increase the ability to float and adhere. The requirements of polymer used in GRDDS include the lightweight, slow release of drug active substance, and can expand easily.[3] In the mucoadhesive theory, synthetic or natural polymers are bioadhesive agents that aid in the attachment of drugs to the intestinal mucosa and produce interactions.[4]

There are three types of polymers based on the source, synthetic polymer, a natural polymer, and semi-synthetic polymer. Natural polymers are derived from plants or animals, usually in the form of proteins and polysaccharides.[5] Various natural polymers, include polysaccharides, proteins, peptides, and polyester. Based on their biocompatibility and processing ability, polysaccharides and protein polymers are widely used for GRDDS because of their extracellular matrix resemblances. Therefore, drugs with this polymer base are minimally invasive.[6] Meanwhile, synthetic polymers are obtained from monomer polymerization. A mixture of natural and synthetic polymers is called semi-synthetic polymers.

System in the GRDDS

Low Density (Floating System)

Low-density is one of the most practical types of GRDDS and is widely developed in studies. In this system, the preparation must have a lower density from gastric fluid, which is under 1.004 g/cm^3. This is fundamental for the preparation to float temporarily during gastric emptying as illustrated in Figure 1. This system has two floating mechanisms, effervescent and non-effervescent. Some examples of effervescent systems are gas-generating and volatile liquid-containing systems. The non-effervescent system can involve single and bilayer floating tablets, alginate beads, and hollow microspheres.[7] These systems are sometimes combined with a bioadhesive system to improve the bioavailability of the preparation. An example of application is with meloxicam active substance.[8]

High Density (Non-Floating System)

The high-density system is depicted in Figure 2. The development formula makes the system have a high density (2,5 to 3,0 g/mL) to resist peristaltic movement and keep drugs in the stomach by the GRT movement. Based on gastric emptying time, this system can maintain drugs for 5,8 to 25 hours.[9] The ingredients commonly used in this system include zinc oxide, barium sulfate, titanium oxide, and iron powder. These

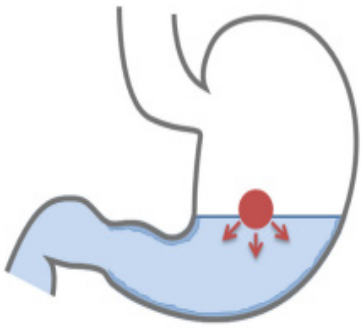

Figure 1: The floating system.

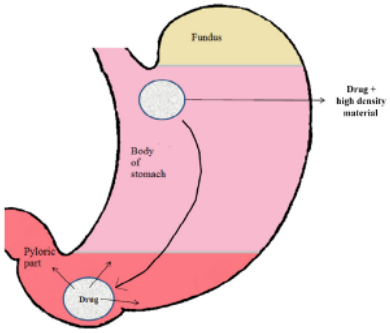

Figure 2: Non-floating system.

ingredients can increase the density of the tablet system. In another experiment, a magnetic field is used to keep the drug on the stomach floor. This formula contains an active magnetic substance with an external magnet placed on the desired location on the stomach.[10]

Mucoadhesive System

The mucoadhesive system is a system that utilizes the bioadhesive properties of polymers as adhesives on hydration in forming bonds with the mucous membrane to increase drug residence time, which is illustrated in Figure 3. The polymers will adhere to the mucin layer of the mucosa.[11] This drug delivery system is an efficient strategy for increasing bioavailability and controlling delivery with solubility that depends on the instability of the intestinal pH. The advantages of this system include close contact with the mucosal surface, high surface area to longer residence time and volume ratio of drug, and efficient absorption which can enhance the bioavailability and can be adjusted to adhere to mucosal tissues in the gastrointestinal tract.[12]

Polymers are important in designing a mucoadhesive system by increasing the GRT of drugs in desired locations. The polymer's structure and function group are used to impact the mucoadhesive ability and interaction strength directly. The mucoadhesive polymer must be non-toxic, non-irritating, inert, and rapidly adhere to the majority of mucous membrane tissues. Furthermore, mucoadhesive polymers must have a strong non-covalent bond between mucin epithelial cell surface and polymers.[12] The mucoadhesive polymer adheres the drug to the surface of gastric mucosa and extends gastric retention in the gastrointestinal tract. Therefore, these polymers are very useful as an excipient for GRDDS. Natural polymers used in this mucoadhesive system are gelatin, chitosan, guar gum, and sodium alginate. Semi-synthetic polymers include hydroxypropyl methylcellulose (HPMC), Carbopol, and sodium carboxymethyl cellulose.[13]

Mucoadhesive polymer mucous membrane adhesion can be mediated by bonding, hydration, or receptors. Hydrophilic polymers become mucoadhesive and sticky during hydration in hydration-mediated adhesion. The bonds that mediate adhesion are either mechanical or chemical. A chemical bond comprises an ionic or covalent bond or Van der Waals forces between mucous membranes and polymer molecules. Adhesion mediated by receptors occurs in certain polymers and specific

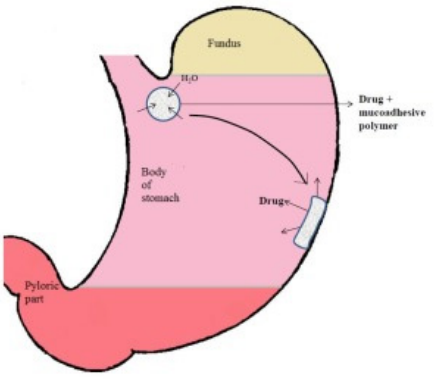

Figure 3: Mucoadhesive system.

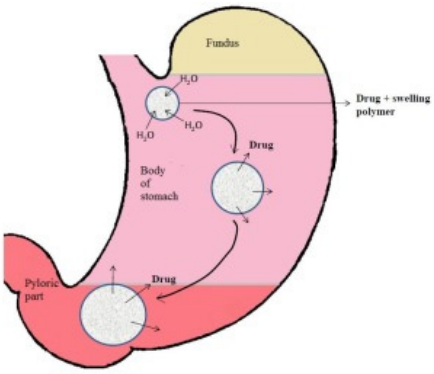

Figure 4: Swellable and expandable system.

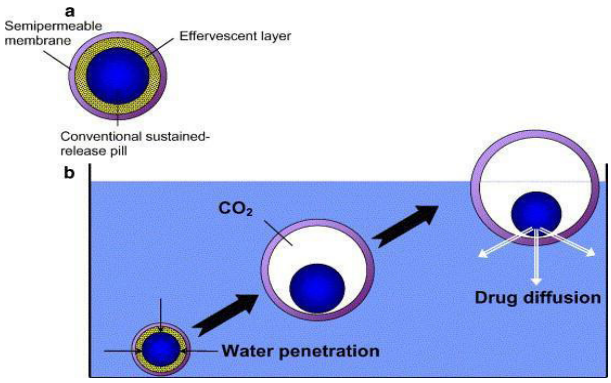

Figure 5: Gas-generating system.

receptors expressed on gastric cells. The polymers can be anionic, cationic, or neutral.[13]

Swellable and Expandable System

This system is one of the GRDDS with longer residence time through increased volume or as represented in Figure 4. At first, this system was designed for animal medication. However, over time, this system can be applied to humans. If the gastric transit is greater than the pyloric sphincter, this preparation system can remain in the stomach for a long time. However, the size of the preparation must be small enough to be swallowed and must not have a risk of causing bowel obstruction. After the hydration process, preparations using the swellable delivery system will expand when in contact with gastric fluid.[14] Drug release from this system depends on the surface area of the drug as the expansion area, swelling without hindrance, and drug solubility in water.[15]

Effervescent (Gas Generating) System

This method is included in the low-density system because it enables preparations to float in gastric fluid due to CO_2. This system uses a gas-generating agent such as tartaric acid, sodium bicarbonate, and citric acid to achieve a floating ability with foam. As shown in Figure 5, a floating formulation floats in the stomach for a prolonged time due to the production of carbon dioxide from the reaction of an effervescent agent with water molecules in gastric fluid. The resulting CO_2 helps reduce the system's density to release drugs at the desired rate slowly.[14,16]

Natural and SPDDS

Polymers are long repeating chains of macromolecules that are widely used to increase solubility or target drug delivery properties. Polymers act as a precipitation inhibitor by maintaining the supersaturated phase through polymer-drug interactions so that precipitation does not occur within a certain time. Therefore, drugs that dissolve in a supersaturated state can be easily absorbed.[1]

There are two types of polymers, natural and synthetic. Natural polymers are more favorable because of non-toxic, more affordable, biodegradable, and widely available. On the other hand, synthetic polymers are chosen because they can regulate drug release and stability, determine the drug carrier's properties, have good flow properties, and improve drug dissolution to increase bioavailability.[14] However, in the application, a combined polymer (synthetic and natural) is used to achieve the therapeutic goal.[17] The advantages and disadvantages of synthetic and natural polymers are described in Table 1.

Natural Polymer

Natural polymers are often used as hydrocolloids, effectively controlling drug release from a swellable system. Natural polymers have advantages in the field of pharmaceutical and biocompatibility, biomedical, and safety.[25]

Guar Gum

One of the Leguminosae families, *Cyamopsis tetragonolobus*, produces seeds in the form of guar gum. Other names for guar gum are cluster bean, guaran, Calcutta lucerne, Cyamopsis, and Guarana. This gum takes the form of a whitish-yellow powder with no smell or taste. Guar gum is soluble in water but difficult to dissolve in organic solvents.[16]

Furthermore, guar gum can increase viscosity because it can swell rapidly due to water with translucent suspension from guar gum's double content, such as Guarana, or water-soluble fraction (ca. 85%), and insoluble part. Guarana is a hydrocolloid polysaccharide with a high molecular weight that comprises two units of D-galactose per unit of D-mannose.[26]

Xanthan Gum

Xanthan gum is a polysaccharide with a main chain of D-glucose and high molecular weight. Naturally, the bacterium

Table 1: Advantages and disadvantages of natural and synthetic polymers

Polymer	*Type*	*Advantage*	*Disadvantage*
Guar gum	Natural	Increased viscosity due to rapid swelling[18]	Unsuitable to be used for sustained release[18]
Xanthan gum	Natural	Dissolve in warm and cold water, non-toxic, non-irritating[19]	Incompatible with cationic substance and oxidation substance, sodium carboxyl methylcellulose, dry aluminum hydroxide gel, and several drugs (amitriptyline and tamoxifen)[19]
Chitosan	Natural	Biodegradable and non-toxic[20]	Low stability[20]
Carrageenan	Natural	Good compatibility and high stability[18]	Very limited single use of carrageenan as GRDDS polymer[21]
HPMC	Synthetic	Inert and has high solubility, which is often used in sustained release preparations[22]	Only certain types can float in ethyl alcohol and have limited flow properties[22]
Eudragit	Synthetic	Has many variations according to pH[23]	Non-biodegradable[23]
Polyvinylpyrrolidone (PVP)	Synthetic	Easily dissolved in water[24]	Difficult to float[24]

Xanthomonas campestris produces this gum synthesis. This gum is fine powder or cream and odorless. Xanthan gum is insoluble in ether and ethanol, soluble in cold or warm water, and anionic. An aqueous solution of xanthan gum is stable within pH 3–12 at 10–60°C with the existence of an enzyme, acid, base, and salt. This gum is non-toxic and non-irritating. Therefore, it is often used as a thickening agent, emulsifier, suspension, stabilizer, gel shaper, and viscosity changer.[27]

Xanthan gum is anionic, thus incompatible with cationic substances. Xanthan gum is not compatible with oxidizers, sodium carboxymethylcellulose, and dry aluminum hydroxide gel with several medications such as amitriptyline and tamoxifen.[19,28]

Chitosan

Chitosan is a cationic polysaccharide that comprises glucosamine and N-acetyl glucosamine. Chitosan is made from chitin deacetylation from crabs. Chitosan takes the shape of an odorless white powder that is mostly dissolved in 95% ethanol and water. This polymer is non-toxic, biocompatible, and biodegradable. Chitosan is usually used along with other excipients such as a mucoadhesive, viscosity enhancer, film former, tablet binder, coating agents, and disintegrating agents.[16]

Carrageenan

Carrageenan is a high molecular weight anionic polysaccharide obtained from red algae in the Rhodophyceae class. Carrageenan comprises three families, depending on the number of its sulfate group, i.e., iota (ι-carrageenan, mono sulfate); kappa (κ-carrageenan, di sulfate); and lambda (λ-carrageenan, tri sulfate) that produce a thick solution, but not gel. Kappa and iota carrageenan can form gels but are non-dissoluble in water. Carrageenan is a gel former because it contains an anionic sulfate group, which tends to interact with non-ionic hydrocolloids and produce increased gel viscosity.[25]

Synthetic Polymer

Synthetic polymers are naturally occurring polymers that are processed and purposely shaped for use as polymers. Below are examples of synthetic polymers that are frequently encountered.

HPMC

HPMC contains methoxy and hydroxy propoxy with 10000–1500000 Dalton molecular weight. HPMC can dissolve in water and form colloids. HPMC is a bioadhesive polymer that can increase the coating activity of preparations, control media release, act as an emulsion agent, and as a thickening agent. HPMC is commonly used in topical, ophthalmic, nasal, and oral formulations. HPMC polymers are bonding material for tablets, coating solutions, and controlled and delayed release.[29]

Eudragit

Eudragit is an amorphous polymer component. It is obtained from the polymerization of methacrylic acid and acrylic acid, widely used for a coating material and flavor cover in the form of oral preparations with spray atomization technique. The atomization technique requires a temperature of 90 to 150°C. Eudragit is not naturally degradable, non-absorbent, or non-toxic. Eudragit has two levels of polymers, L and S. L is dissolved in pH 6, and S is dissolved in pH 7, which is used to target the gastrointestinal system.[23]

Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) with a molecular formula of C6H9NO. PVP is also known as polyvidone, povidone, PVP, povipharm, colidone, and plasdone. Meanwhile, the chemical nomenclature is a 1-ethenyl-2-pyrrolidone homopolymer. Chemically, PVP is an inert, non-toxic, and non-antigenic additive. PVP is widely used in drug delivery as a hydrophilic polymer, drug carrier at a concentration of 10 to 25%, dispersion material, and suspending agent.[24]

Utilization of Polymers as a Drug Delivery System

Drug delivery systems are formulations designed to penetrate therapeutic substances into the body. Thus increasing the efficacy and safety of drugs by controlling the location, timing, and rate of drug release in the body without harming the body. Biodegradable and bioabsorbable polymers can be

utilized in new drug delivery systems. Biologically absorbed polymers can come from hydrogels, such as polylactic acid and polyglycolic acid, and their copolymers have been used to make the components of a delivery system.[30]

There are three main mechanisms of drug release from polymers or active substance release from a delivery system, i.e.,[31]

Diffusion

The process when the drug or active substance penetrates the polymer layer and forms a polymer matrix is called diffusion. In this system, the combination of polymer matrix and chosen bioactive agent must enable drugs to diffuse through pores or macromolecular structures of polymers when the delivery system contacts the biological environment without making any changes to the polymer.

Degradation

Biodegradable polymers are degraded in the body by natural biological processes designed to eliminate drug delivery systems once the active substances are completely released. Polymer chains hydrolyze the most degraded biodegradable polymers into smaller substances that can be biologically accepted. In several degradable polymers, especially polyanhydride and polyorthoesters, degradation only occurs on the surface of the polymers, producing a release rate equivalent to the surface area of the drug delivery system.

Expansion

The preparation starts dry, and then it will absorb water or body fluid when it enters the body and swells or expands. This expansion will increase the water content in the system and the size of the polymer, enabling drugs to diffuse through swelled tissue to the external environment.

Ideal polymer characteristics are generally as follows[31]:

- Versatile and has various mechanical, physical, and chemical characteristics.
- It must be non-poisonous, have great mechanical strength, and be easy to administer.
- It must be affordable and easy to make.
- It must be inert to the gastric tissue and compatible with the environment.

The criteria for choosing a polymer to use as a drug delivery system are as follows[31]:

- Must be biodegradable.
- Should dissolve and easy to synthesize.
- Must be compatible with the biological environment.
- Should have a limited molecular weight.
- Should have a good drug-polymer relation.

Physicochemical properties of polymers as a GRDDS

Polymers in GRDDS have a significant role. They need to have specific properties. Several physicochemical characteristics of polymer interaction with drugs that need to be considered are presented in the following review.

The Effect of Hydrogen Bond

Some polymers, such as PVP and HPMC, always have a hydrogen bond. The interaction between polymer and drug through hydrogen bonds is an example is in hydrocortisone acetate, which has three carbonyl function groups and two hydroxyl groups. Hydrogen bonds can inhibit the formation of the core receptor to avoid precipitation and floating. The nucleation process depends on the hydrogen bond of drugs or the polymer function group.[32]

Effect of Hydrophobic Interaction

Hydrophobic interaction between drugs and polymer function groups can determine polymers' adsorption on the drug core's primary surface. This process is an important step to determine the effectivity in inhibiting precipitation. The hydrophobic property used depends on the substitution of the methyl group in polymers. HPMC type E has 29% substitution of the methyl group, while type K has 22% of substitution. Higher methyl substitution leads to high hydrophobic interaction between polymers and drugs.[33]

Molecular Weight

The higher the molecular weight of a polymer, the stronger the interaction between polymers and drugs. This effect is correlated with increased viscosity or the number of functional groups and polymer chains. Xie *et al.* investigated PVP K10 and K40 and showed that the higher molecular weight of the pyrrolidone group could interact better with the drug surface.[32]

Effect of Steric Hindrance

Feng *et al.* used TPGS 1000 succinate (TPGS) as a precipitation inhibitor. The results showed that TPGS could provide a steric hindrance that causes delayed crystal development by absorbing the small particle surface.[34] The steric hindrance effect in polymer molecules aids in inhibiting precipitation by stabilizing drugs in the micro-hydrophilic environment of the polymer. Cellulose polymers containing propyl and methyl groups contribute significantly to crystallization inhibition.[18]

Viscosity

Viscosity affects the inhibition of drug release by preventing the diffusion of fluids into the preparation. Polymers with a rigid structure can be adsorbed more effectively to the surface and thus can inhibit drug release better. A rigid planar structure can greatly affect the efficacy of drug-release inhibitors.[1]

Temperature

Drug-polymer binding decreased at higher temperatures as a result of low intermolecular interactions. Temperature is the primary factor for the structure of drugs and polymer structure, as it affects the affinity of the drug-polymer interaction. Elevated temperature leads to increased drug solubility because of the weakened intermolecular bond.[35]

Dielectric Constant

Reduced dielectric constant will reduce the interaction between drug and polymer molecules and usually increase drug solubility because of the affinity of the solvent. Furthermore, there are larger hydrogen bonds between the drug and polymer, causing more hydrogen bond sites in the polymer.[36]

Hydrophilicity or Hydrophobicity

Raina *et al.* performed a study on polymers with various hydrophobic and hydrophilic properties. Polymers that are effective as precipitation inhibitors must interact in two phases,

which are the lipid phase and the fluid phase. Polymers that have properties between hydrophobic or hydrophilic properties, such as PVP VA (Vinyl acetate), HPMC, and HPMC AS, can be good precipitation inhibitors. Polymers have an affinity with the lipid and fluid phases, which can be interpreted from polymer solubility. On the other hand, polymers with more hydrophobic or hydrophilic such as cellulose acetate butyrate, polyacrylic acid, poly 2-vinyl-pyridine, PVP, and carboxymethyl, do not have a good ability to inhibit crystallization. This is due to a higher affinity only for one phase, but a lower affinity for the other phase.[37]

Evaluation of polymers in GRDDS

Several utilization of polymers for GRDDS coating has been widely investigated. For example, Eisenacher *et al.* showed that metformin tablets could expand perfectly within 10 minutes if coated with polyvinyl acetate polymer and expands for 7 minutes when coated with ammonia methacrylate copolymer.[38] Other than floating time, polymer strength can be measured from the ability to release the drug. Polymers that can release the drug slowly are needed to prevent burst release, which has a pharmacokinetic effect on the body.[10] Some evaluations needed for GRDDS are described in the following description.

Floating Lag Time

Floating lag time (FLT) is the time needed requiring for gastric fluid to float on the surface of the gastric.[39] A shorter FLT is more desirable than a longer FLT. Longer FLT may cause preparation to stick to the lower part of the stomach and make it incapable of floating, thus increasing the probability of gastric emptying.[40]

Preparation density is related to floating behavior. Tablets with a density exceeding 1.004 g/cm^3 cannot float over the gastric fluid.[41] Based on Thapa and Jeong, metformin HCl effervescent floating tablet, which uses PEO (polyethylene oxide) synthetic polymer, has a significant increase in FLT as well as increased compression force. Increased compression force also increases the density of the tablet due to reduced porosity. Tablets must have a density lower than gastric fluid to float on the surface of gastric fluid. However, increased PEO can increase the tablet density due to reduced porosity, which will increase FLT. In Addition, a higher level of PEO forms an outer layer of gel rapidly after contact with the gastric fluid and inhibits interaction with sodium bicarbonate, which delays FLT.[40]

Ca alginate beads are natural polymers that can be formulated with a simple and light procedure? However, it has several limitations, such as a long FLT, low trapping of the drug, low floating time, and a burst release of the drug by leaching through the pores of the beads.[42] Meka *et al.* have created a non-effervescent floating drug delivery system through the solvent evaporation technique from carvedilol phosphate, which is difficult to dissolve with release-inhibiting polymers or polymers that can float like xanthan gum and polyethylene oxide. Formulation with a drug delay of up to 12 hours and a FLT of fewer than 10 seconds is the best formulation for xanthan gum.[43]

Floating Time

Floating time is the total time when a drug is floating on the surface of the gastric.[39] While floating in the stomach, the drug will be released slowly at a certain rate. The preparation can be formulated using expanded polymers, such as HPMC, for this phenomenon to occur. The HPMC is one of the hydrophilic polymers that can form a thick-textured gel layer that surrounds the preparation after contact with gastric fluid. This layer of gel formed can serve as a physical barrier for drug release from the matrix.[44]

Andini *et al.* determined the total floating time of a tablet by inserting a floating tablet formulated in a beaker glass containing 100 mL of 0.1 N HCl. c.[44] High-viscosity polymers such as K100M are used for long floating time.[45] The required floating time is at least 12 hours.[46]

Based on Wahyuni *et al.,* the formulation of ranitidine HCl with a combination polymer of pectin and HPMC produced a floating tablet.[47] The formula of polymer combination that can float longer in ranitidine HCl is a formula with more HPMC, i.e., 30 mg of HPMC and 20 mg of pectin. The study used a polymer combination for ranitidine HCl tablet floated for 24 hours.

Drug Release Rate

Drug release is one of the critical quality attributes of gastro retentive preparation. When the preparation enters the body, it will be hydrated by body fluid and slowly released. A system that can control drug release well according to the therapy goal is crucial.[25] A study showed that synthetic polymers have longer release and showed higher concentration after 10 hours of testing compared to natural polymers. Formulations using synthetic polymers are better than natural polymers because they show minimum interval and maximum floating time with maximum drug release percentage.[41]

Viscosity

Polymer viscosity in the development of gastro retentive preparation is influential during the process of tablet molding. As the outermost layer of the gastro retentive system, the viscosity of the polymer will determine the thickness of the bilayer formed. Nguyen *et al.* stated that a mixture containing a small amount of HPMC with a low viscosity resulted in a relatively thin gel layer. In Addition, due to the ability to rapidly reach the threshold of polymer disintegration, making the outer layer thin is eroded by water, causing the polymer to expand. Therefore, high-viscosity polymer required a strong gel matrix for a better diffusion-controlled release design, especially for drugs with high solubility in water.[48]

Bioavailability

Drug bioavailability is expected to increase when delivered in a gastro retentive floating system. The combination of HPMC, ethyl cellulose and PVA in delivering furosemide is proven to provide a larger AUC than a conventional tablet close to an injection (Figure 6).

The initial plasma concentration in injection delivery is high but rapidly decreases. Meanwhile, a gastro retentive formula with a polymer combination provides a more stable concentration of

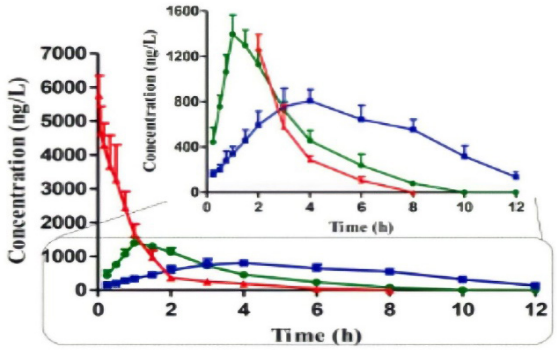

Figure 6: Comparison pattern of furosemide concentrations between conventional tablet (green), GRDDS tablet (blue), and injection (red) in plasma.

the drug in the plasma with a shallow decrease. This showed that the system could describe a better-sustained release.[49]

Solubility

The physicochemical property of a polymer is an important consideration in the design of the GRDDS formula. One of the required physicochemical properties of polymers is the evaluation of solubility. Solubility is the ability of a chemical substance to disperse molecularly in its solvent.[50] In the formation of encapsulation control preparation in GRDDS, drug particles or granules must be coated with polymers that can dissolve slowly. The dissolution of this system depends on the thickness and solubility of polymers in water.[51] Faster or slower solubility will cause the drug to be released into the system uncontrollably and can reduce the effect of the drug.

Polymer fractionation affects polymer solubility. The principle of polymer fractionation is reduced polymer solubility with increased molecular weight. Therefore, the higher molecular weight will lead to lower solubility, and vice-versa. Some examples of polymers with high molecular weight are natural rubber, dammar, natural polyester, graphite, phosphate, carbohydrate, cellulose, protein, polyethylene, polystyrene, and polyvinyl chloride.[52] Most natural polymers have high molecular weight; thus, they have lower solubility than synthetic polymers.

CONCLUSION

The GRDDS system is highly affected by the type of polymers used. In most cases, combining natural and synthetic polymers provides a more optimum result than a single use. A good polymer to deliver GRDDS has a low density with increased porosity to reduce FLT, has high viscosity to increase floating time, and stronger physics to reduce burst release, mixed with synthetic polymers to increase sustained release effect, and does not have too much weight to dissolve easily.

REFERENCES

1. Annisa V, Choiri S, Sulaiman TNS, Nugroho AE. Polymer as precipitation inhibitor of weak base drug: An update and brief review. *Thai J Pharm Sci*. 2021;45(5):326-332.
2. Gupta P, Kumar M, Sachan N. An Overview on Polymethacrylate Polymers in Gastroretentive Dosage Forms. *Open Pharm Sci J*. 2015;9(1):31-42.
3. Febryanto HD, Sari LORK, Irawan ED. Optimization and Formulation of Floating Tablets-Mucoadhesive Glimepiride with Combination of Carbopol Polymer and HPMC K4M. *Pustaka Kesehat*. 2014;2(3):409-415.
4. Kumar M, Kaushik D. An Overview on Various Approaches and Recent Patents on Gastroretentive Drug Delivery Systems. *Recent Pat Drug Deliv Formul*. 2018;12(2):84-92.
5. Tabata Y. Biomaterial technology for tissue engineering applications. *J R Soc Interface*. 2009;6(2009):311-324.
6. Tong X, Pan W, Su T, Zhang M, Dong W, Qi X. Recent advances in natural polymer-based drug delivery systems. *React Funct Polym*. 2020;148(2020):104501.
7. Suradkar P, Mishra R, Nandgude T. Overview on Trends in Development of Gastroretentive Drug Delivery System. *Res J Pharm Technol*. 2019;12(11):5633.
8. Raza M, Jayswal MG, Ahmed DA, Majaz DQ, Khan DGJ. Review on gastro retentive drug delivery system. *World J Pharm Pharm Sci*. 2022;11(9):624-640.
9. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their in vivo success: A recent update. *Asian J Pharm Sci*. 2016;11(5):575-584.
10. Huang X, Brazel CS. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. *J Controlled Release*. 2001;73(2-3):121-136.
11. Mahajan P, Kaur A, Aggarwal G, Harikumar SL. Mucoadhesive Drug Delivery System: A Review. *Int J Drug Dev Res*. 2013;5(1):11-20.
12. Patil H, Tiwari RV, Repka MA. Recent advancements in mucoadhesive floating drug delivery systems: A mini-review. *J Drug Deliv Sci Technol*. 2016;31:65-71.
13. Jassal M, Nautiyal U, Kundlas J, Singh D. A review: Gastroretentive drug delivery system (grdds). *Indian J Pharm Biol Res*. 2015;3(1):82-92.
14. Kumar M, Kaushik D. An Overview on Various Approaches and Recent Patents on Gastroretentive Drug Delivery Systems. *Recent Pat Drug Deliv Formul*. 2018;12(2):84-92.
15. Putheti RR, Patil MC. Pharmaceutical Formulation and development of Floating and Swellable sustained drug delivery systems: a review. *E-J Sci Technol*. 2009;4(1):1-12.
16. Gayakwad BP, Bavaskar SR, Fulzele S, Yadav R, Gauttam V, Sawale J. Natural Polymers In The Development Of Gastroretentive Systems: A Review. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO. 2021 Nov 7:2895-906.
17. Rustiani E, Sari BL, Izmah DSN. Mucoadhesive Microgranules of Bay Leaf Extract (Syzygium polyanthum (Wight.)) with HPMC and Chitosan Polymer Differences. *J Ilm Manuntung*. 2022;8(1):39-46.
18. Singh D, Singh M, Tharmatt A, Tiwary AK, Bedi N. Polymeric precipitation inhibitor as an effective trigger to convert supersaturated into supersaturable state *in vivo*. *Ther Deliv*. 2019;10(9):599-608.
19. Prakash U, Singh L, Sharma V. le of Xanthan Gum (Xanthomonas compestris) In Gastroretentive Drug Delivery System: An Overview. *Int Res J Pharm*. 2016;4(4):35-38.
20. Imtihani HN, Wahyuono RA, Permatasari S ana N. *Chitosan Biopolymer and Its Use in Drug Formulations*. Graniti; 2020.

21. Prihastuti D, Abdassah M. Carrageenan and Its Application in the Pharmaceutical Field. *Farmasetika*. 2019;4(5):146-154.
22. Rahi FA. Review Article on Advanced Polymers Used in Gastroretentive Drug Delivery Systems (GDDS). *Maaen J Med Sci*. 2022;1(1):1-4.
23. Pund AU, Shendge RS, Pote AK. Current Approaches on Gastroretentive Drug Delivery systems. *J Drug Deliv Ther*. 2020;10(1):139-146.
24. Zakaria N, Bangun H, Vonna A, Oesman F, Khaira Z, Fajrina F. The Effect of Using HPMC Polymer and Polyvinyl Pyrrolidone on the Physical Characteristics of Diclofenac Sodium Patch Transdermal. *J Sains Kesehat Darussalam*. 2017;1(2):58-66.
25. Iglesias N, Galbis E, Romero-Azogil L, et al. In-Depth Study into Polymeric Materials in Low-Density Gastroretentive Formulations. *Pharmaceutics*. 2020;12(7):636.
26. Panda S, Sailada NS, Devi B, Pattnaik S, Maharana L. Design of Floating Drug Delivery Systems: An Update on Polymeric Advancements with Special Reference from Natural Origin. *Int J Pharm Sci Rev Res*. 2016;39(1):125-132.
27. Ananthakumar R, Chitra K, Satheshkumar S. A review on applications of natural polymers in gastroretentive drug delivery system. *Drug Invent Today*. 2018;10(3).
28. Bueno VB, Bentini R, Catalani LH, Petri DFS. Synthesis and swelling behavior of xanthan-based hydrogels. *Carbohydr Polym*. 2013;92(2):1091-1099.
29. Sungthongjeen S, Sriamornsak P, Puttipipatkhachorn S. Design of Floating HPMC Matrix Tablets: Effect of Formulation Variables on Floating Properties and Drug Release. *Adv Mater Res*. 2011;311-313(2011):1140-1143.
30. Sung YK, Kim SW. Recent advances in polymeric drug delivery systems. *Biomater Res*. 2020;24(1):12.
31. Gandhi KJ, Deshmane SV, Biyani KR. Polymers in Pharmaceutical Drug Delivery System: A Review. *Int J Pharm Sci Rev Res*. 2012;14(2):57-66.
32. Xie S, Poornachary SK, Chow PS, Tan RBH. Direct Precipitation of Micron-Size Salbutamol Sulfate: New Insights into the Action of Surfactants and Polymeric Additives. *Cryst Growth Des*. 2010;10(8):3363-3371.
33. Gao P, Akrami A, Alvarez F, et al. Characterization and Optimization of AMG 517 Supersaturatable Self-Emulsifying Drug Delivery System (S-SEDDS) for Improved Oral Absorption. *J Pharm Sci*. 2009;98(2):516-528.
34. Feng D, Peng T, Huang Z, et al. Polymer–Surfactant System Based Amorphous Solid Dispersion: Precipitation Inhibition and Bioavailability Enhancement of Itraconazole. *Pharmaceutics*. 2018;10(2):1-15.
35. Warren DB, Benameur H, Porter CJH, Pouton CW. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility. *J Drug Target*. 2010;18(10):704-731.
36. Mejri W, Korchef A, Tlili M, Ben Amor M. Effects of temperature on precipitation kinetics and microstructure of calcium carbonate in the presence of magnesium and sulphate ions. *Desalination Water Treat*. 2014;52(25-27):4863-4870.
37. Raina SA, Van Eerdenbrugh B, Alonzo DE, et al. Trends in the Precipitation and Crystallization Behavior of Supersaturated Aqueous Solutions of Poorly Water-Soluble Drugs Assessed Using Synchrotron Radiation. *J Pharm Sci*. 2015;104(6):1981-1992.
38. Eisenächer F, Garbacz G, Mäder K. Physiological relevant in vitro evaluation of polymer coats for gastroretentive floating tablets. *Eur J Pharm Biopharm*. 2014;88(3):778-786.
39. Gharti KP, Budhathoki U, Thapa P, Bhargava A. Formulation in vitro evaluation of floating tablets of hydroxypropyl methylcellulose and polyethylene oxide using ranitidine hydrochloride as a model drug. *J Young Pharm*. 2012;4(4):201-208.
40. Thapa P, Jeong S. Effects of Formulation and Process Variables on Gastroretentive Floating Tablets with A High-Dose Soluble Drug and Experimental Design Approach. *Pharmaceutics*. 2018;10(3):161.
41. Chauhan MS, Kumar A, Pathak K. Osmotically Regulated Floating Asymmetric Membrane Capsule for Controlled Site-Specific Delivery of Ranitidine Hydrochloride: Optimization by Central Composite Design. *AAPS PharmSciTech*. 2012;13(4):1492-1501.
42. Bera H, Kandukuri SG, Nayak AK, Boddupalli S. Alginate–sterculia gum gel-coated oil-entrapped alginate beads for gastroretentive risperidone delivery. *Carbohydr Polym*. 2015;120(2015):74-84.
43. Meka L, Kesavan B, Chinnala KM, Vobalaboina V, Yamsani MR. Preparation of a Matrix Type Multiple-Unit Gastro Retentive Floating Drug Delivery System for Captopril Based on Gas Formation Technique: In Vitro Evaluation. *AAPS PharmSciTech*. 2008;9(2):612.
44. Andini S, Sa'diah S, Puspa S. Preparation and Characteristics of Floating Tablets of Guava Leaf Extract (Psidium guajava L.) With Variations of Xanthan Gum and HPMC Combinations. *J Sains Dan Kesehat*. 2022;4(4):370-378.
45. Borkar S, Suresh R, Sawant V, Shende V, Mokale V, Dama G. An Approch to Formulate Bilayered Gastro Retentive Floating Drug Delivery System of Cefpodoxime Proxetil. *Int J ChemTech Res*. 2010;2(2):1229-1242.
46. Sagita E, Anwar E, Surini S. Preparation of Famotidine Floating Tablets Using Chitosan-Pectin Polyelectrolyte Complex as a Matrix Material. *Pharm Sci Res*. 2011;8(1):1-56.
47. Wahyuni YS, Lely N, Oktariani S. Formulation of Ranitidine HCl Floating Tablets Using a Combination Polymer of HPMC and Pectin. *J Ilm Bakti Farm*. 2018;3(2):35-44.
48. Nguyen DD, Lai JY. Advancing the stimuli response of polymer-based drug delivery systems for ocular disease treatment. *Polym Chem*. 2020;11(44):6988-7008.
49. Meng S, Wang S, Piao MG. Prescription optimization of gastroretentive furosemide hollow-bioadhesive microspheres via Box-Behnken design: In vitro characterization and in vivo evaluation. *J Drug Deliv Sci Technol*. 2022;70(2022):103235.
50. Ainurofiq A, Putro DS, Ramadhani DA, Putra GM, Santo LDCDE. A review on solubility enhancement methods for poorly water-soluble drugs. *J Rep Pharm Sci*. 2021;10(1):137.
51. Gupta P, Kumar M, Sachan N. An Overview on Polymethacrylate Polymers in Gastroretentive Dosage Forms. *Open Pharm Sci J*. 2015;9(1):31-42.
52. Siburian RAF, Simbolon TR, Sebayang K, Simanjuntak C, Marpaung H, Wirjosentono B, Supeno M. Polymers: Materials Science. Medan: USU Press; 2008.