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Article review: Gastroretentive drug delivery system (GRDDS) in captopril

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ABSTRACT

Captopril is an antihypertensive drug that belongs to the Angiotensin Converting Enzyme Inhibitor (ACE-Inhibitor) class and is widely applied for first-line therapy. This drug has a pharmacokinetic profile with a short half-life of about 2-3 hours, is easily soluble in water, and is stable under acidic conditions (pH 1.2). However, its stability decreases as the pH increases, making it susceptible to degradation. Absorption of captopril in the stomach does not take place completely due to the low gastro retention time (GTR), causing its bioavailability to be low (around 65%). To increase drug effectiveness, reduce degradation, and improve patient compliance, various drug delivery systems have been developed. One promising approach is the Gastroretentive Drug Delivery System (GRDDS), which is a sustained release drug delivery system deliberately designed to maintain the drug longer in the stomach. This review article aims to examine GRDDS methods that can be applied to captopril, including modification of the matrix and polymer used, in order to obtain a better drug release profile and improve drug characteristics. The literature review was searched using databases namely PubMed, Google Scholar, and Science Direct, with publication year coverage from 2014 to 2024. The keywords used included: "Gastroretentive Drug Delivery System (GRDDS)".

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INTRODUCTION

Captopril is one of the antihypertensive drugs from the ACE-I group or the abbreviation of Angiotensin Converting Enzyme Inhibitor often implemented for first-line drugs. This drug is also often used as a drug for heart failure and kidney failure due to comorbid hypertension and diabetes (Obied & Ahmed, 2021).

Captopril works by inhibiting the enzyme that plays a role in the formation of the hormone angiotensin II, a hormone that causes narrowing of blood vessels and also causes blood pressure to increase, forcing the heart to pump harder (Fajarsari, 2021)(Firnanda, 2021)(Yanita, 2022)(Firmanda, 2024). The decrease in angiotensin II levels due to the work of ACE inhibitors,

blood pressure becomes lower and the workload of the heart is reduced (Purwaningtyas & Barliana, 2021).

According to the World Health Organization or WHO, hypertension is also known as high blood pressure disease which is characterized by a condition when the pressure in the blood vessels increases (140/90 mmHg or higher). According to Riskesdas data, the prevalence of hypertension disease nationally, namely through the results of blood pressure measurements on the population in Indonesia aged≥18 years old has actually increased from 25.8% in 2013, increasing to 34.1% in 2018. Hypertension is known as the silent killer because it often does not show any clear symptoms, so many patients or people who experience hypertension do not feel that they have this condition (Hintari & Fibriana, 2023).

Pharmacokinetically, captopril has a relatively short biological half-life of around 2–3 hours, and relatively low bioavailability (Nadjamuddin et al., 2022)(Kurnianta et al., 2023)(Rosyadi et al., 2024). This drug shows the best stability at pH 1.2, but becomes unstable and easily degraded as the pH increases. The antihypertensive effect of captopril after oral administration lasts for 6–8 hours. Therefore, clinically, captopril needs to be given three times a day with a daily dose ranging from 37.5 to 75 mg (Amalia, 2022).

A drug delivery system (DDS) is a formulation designed to deliver therapeutic substances or drugs into the body, while increasing their effectiveness and safety by regulating the rate, time and location of drug release in the body (Barkah et al., 2023). Drug delivery is a system used as a vehicle or "carrier" to deliver therapeutic agents/drugs to the patient's body (Blair, 2022).

Types of drug delivery systems include: drug delivery through the mouth (oral), nose (nasal), eyes (ocular), buccal and sublingual drug delivery, pulmonary drug delivery, transdermal drug delivery, and vaginal/anal drug delivery (Blair, 2022).

In addition to the conventional drug delivery systems above, the development of pharmaceutical technology has now given birth to various new, more sophisticated drug delivery systems that can overcome the limitations of conventional drug delivery systems (Nainggolan et al., 2023)(Nusaly et al., 2024)(Khasanah et al., 2025). New drug delivery systems cure certain diseases by precisely targeting the affected areas in the patient's body and delivering drugs to those areas. Various drug delivery and drug targeting systems are currently being developed to minimize drug degradation and loss, prevent harmful side effects, increase drug bioavailability, and target drugs to the site of the disease and improve patient compliance (Devi et al., 2010).

Various innovations in drug delivery systems have been developed, such as controlled release drug systems (controlled release DDS), targeted drug delivery directly to a specific location (targeted DDS), particle-based systems such as nanoparticles, microparticles, and liposomes, as well as protein and prodrug-based delivery systems. In addition, there are also delivery systems designed to retain drugs in the digestive tract (gastroretentive DDS), delivery via non-oral routes such as nasal, pulmonary, ocular, and transdermal, as well as systems that allow drug delivery to the brain (Devi et al., 2010).

Gastroretentive drug delivery system, also known as Gastroretentive Drug Delivery System (GRDDS), is a drug delivery technology designed to release drugs gradually (sustained release). This system allows drugs to remain in the stomach for a long period of time, thereby increasing the effectiveness of therapy by maintaining stable drug levels in the body and minimizing fluctuations in drug concentrations (Annisa, 2021). The advantages of GRDDS include increased bioavailability, poor solubility of drugs at high pH, control of therapeutic levels to reduce fluctuations, and a prolonged half-life that allows for reduced frequency of drug administration (Jassal et al., 2015). However, this system is not suitable when applied to drugs that irritate the stomach, are unstable at gastric pH, or are affected by the first-pass effect (Annisa, 2021).

Drugs that have the potential to be developed with a gastroretentive delivery system include: (Jassal et al., 2015): Drugs that are mainly absorbed in the stomach, for example:

Amoxicillin. Drugs that are difficult to dissolve in alkaline pH, for example: Furosemide, Diazepam. Drugs that have a narrow absorption window, for example: Levodopa, Methotrexate. Drugs that are degraded in the large intestine include: Ranitidine, Metformin HCl. Drugs that interfere with the normal microbes in the colon e.g.: antibiotics against Helicobacter pylori. Drugs that are rapidly absorbed from the digestive tract, for example: Tetracycline. Drugs that work locally in the stomach

As explained, captopril absorption in the stomach is not optimal because it is affected by the residence time in the stomach (Gastro Residence Time/GRT) and rapid gastric emptying, so that the drug cannot last long. To overcome this, an increase in GRT is needed. The longer the drug is in the stomach, the more drug can be absorbed, which ultimately increases its bioavailability. Therefore, a drug delivery system is needed that can extend the contact time with the stomach, such as the Gastroretentive Drug Delivery System (GRDDS).

RESEARCH METHOD

The method applied in writing this article is by using the Literature Review Article (LRA) approach, namely by collecting various relevant library sources. The library sources used consist of articles published in English and Indonesian. These articles were obtained through trusted databases such as PubMed, Google Scholar, and Science Direct, with a publication year range between 2014 and 2024. The keywords used are "Gastroretentive Drug Delivery System (GRDDS)" AND "Captopril" or "Controlled release DDS" AND "Captopril". The identification process, full text screening and eligibility, and journal analysis were carried out according to the formulation of the problem and objectives.

RESULTS AND DISCUSSIONS

Gastroretentive Drug Delivery System (GRDDS) Method

Floating System

Floating system, or low-density system, is one of the most widely used approaches in the development of Gastroretentive Drug Delivery System (GRDDS) preparations. In this system, the density of the drug must be lower than the density of gastric fluid, which is less than 1.004 g/ml, allowing the drug to float and remain in the gastric fluid longer. In this way, the drug suspended in the gastric fluid can be released in a controlled manner at a specific rate, which in turn affects the drug residence time in the stomach (Gastro Residence Time/GRT) and helps reduce fluctuations in drug levels in the blood plasma. After the drug release process is complete, the remaining unused drug will be excreted from the stomach. One of the main advantages of this floating system is that it does not cause adverse side effects on the gastrointestinal tract. This system can be divided into two main types of mechanisms, namely effervescent systems, which produce gas to help float the drug, and non-effervescent systems, which rely on low-density materials to keep the drug afloat (Annisa, 2021).

a. Effervescent, the gas generating system consists of two layers: an inner layer containing gas agents such as sodium bicarbonate and citric acid, and an outer layer consisting of a hydrophilic polymer membrane. CO2 gas is formed from the effervescent reaction with gastric fluid, allowing the preparation to float. These systems are divided into four categories: single layer, bilayer, multilayer, and ion exchange resin. The bilayer consists of an immediate release layer containing the drug and a controlled release layer with the drug, polymer, and CO2 gas generating agent. The CO2 gas formed prolongs the residence time of the drug in the stomach and slows down the release of the drug (More et al., 2018). Multiple layers have a controlled release pill surrounded by two layers: an inner layer containing an effervescent agent and an outer layer of polymer. This system expands in the body and floats. Ion exchange resin systems use a resin containing bicarbonate ions and the drug, where the ion exchange produces CO2 gas

that is trapped in the polymer, allowing the system to float (More et al., 2018). Volatile Liquid Containing Systems consist of two chambers: one for the drug and one for the volatile liquid. Volatile liquids, such as ether, evaporate at body temperature, causing the chamber to expand in the stomach. These systems include three types: intragastric floating, intragastric osmotic and inflatable. Intragastric floating uses a microporous compartment, inflatable contains the drug and polymer in a gelatin capsule that expands after ingestion, and intragastric osmotic uses the process of osmosis to release the drug (More et al., 2018).

b. Non-Effervescent systems include various mechanisms that can be used to extend the residence time of drugs in the stomach, including single-layer systems, microporous compartments, alginate beads, and hollow microspheres. Single-layer systems work by swelling through hydration, which forms a gel layer and allows the system to float in gastric fluid. Microporous compartments incorporate gas within the microporous structure, allowing the system to float in the stomach. Meanwhile, alginate beads, made of calcium alginate, and hollow microspheres can extend the gastric residence time (GRT) of drugs to more than 5.5 hours. Both systems work by increasing viscosity and reducing gastric emptying rate, so that the drug remains in the stomach longer and is absorbed more, which ultimately increases drug bioavailability (Jassal et al., 2015).

Bioadhesive/Mucoadhesive System

Bioadhesive or mucoadhesive systems function by attaching themselves to the surface of gastric epithelial cells or the mucus layer lining the stomach wall. By forming a strong bond between the drug and the biological surface, this system can prolong the residence time of the drug in the stomach. This will increase the duration of contact between the drug and the biological membrane, which in turn can help improve drug absorption and the effectiveness of therapy (Annisa, 2021). Bioadhesive polymers are divided into two types: cytoadhesives that bind to epithelial cells, and mucoadhesives that bind to the mucus layer. Common polymers used include chitosan, tragacanth, sodium alginate, carbopol, HPMC, glycols, and dextran (More et al., 2018).

High Density System

High density system is a type of drug formulation that has a density greater than gastric fluid, which is above 1.004 g/ml. Because the density of the drug is higher, the drug will sink and remain at the bottom of the stomach, allowing the drug to remain in the stomach longer. The longer presence of the drug in the stomach can help extend the contact time of the drug with the stomach wall, which in turn increases drug absorption and bioavailability. This high density system formulation involves several approaches, one of which is coating the drug on a hard core. In this case, the hard core of the drug is coated with a heavy inert material, such as iron powder, titanium dioxide, or zinc oxide, which provides additional density to the drug preparation. The addition of this inert material aims to increase the weight of the drug preparation so that the drug remains in the stomach longer and slows down the gastric emptying process (Jassal et al., 2015).

Super Axis System

The superporous system consists of hydrophilic polymers that have the ability to absorb water quickly, thus forming a large interconnected pore structure. The swelling process that occurs due to water absorption can slow down the gastric emptying process, which in turn prolongs the gastric residence time (GRT), allowing the drug to be absorbed longer and more effectively (More et al., 2018).

Expandable System

Expandable systems are designed to increase the size of the drug, allowing it to remain in the stomach for a longer period of time. These drugs are formulated in large, folded gelatin capsules for easy ingestion. Once they reach the stomach, the capsule shell disintegrates, allowing the drug to expand. There are two types of expandable systems: unfoldable and swellable.

Unfoldable systems use biodegradable polymers that break down over time, while swellable systems expand by absorbing water through osmosis, increasing the size of the drug to prolong the residence time in the stomach (Annisa, 2021).

Raft-Forming System

Raft-forming systems swell upon contact with gastric fluid, forming a cohesive gel that produces a raft-like layer (Rahmi et al., 2025). This layer can remain in the stomach for several hours due to its lower density, which is produced by the formation of CO2 gas, making the raft buoyant. The main ingredients in these systems usually include a bicarbonate or carbonate base, a gelling agent, and a neutralizing acid. These systems also have the ability to prevent reflux of gastric contents into the esophagus (Jassal et al., 2015).

Magnetic System

The magnetic system works by utilizing the interaction between two magnetic poles that attract each other, where the drug contains an internal magnet and is equipped with an external magnetic device that is placed near the stomach. The position and strength of the external magnetic field can affect the location of the drug in the stomach, so proper placement is required. However, this can be a challenge and has the potential to affect the level of patient compliance with the use of this system (More et al., 2018).

Table 1. Development of a gastroretentive drug delivery system (GRDDS) on captopril

No	GRDDS System	Matrix/Polymer	Research result	Library
1	Floating	Hydroxypropyl methylcellulose (HPMC) K100M and Xanthan gum	Formula with HPMC K100M : Xanthan gum (40:80) shows a good release profile	(Ahsan et al., 2015)
2	Mucoadhesive	HPMC, NaCMC, HPC, Carbophol 934, and Na alginate	The formula with a combination of Carbophol 934 and cellulose polymers (HPMC, NaCMC, HPC) gave good results with a release profile for 8 hours following the Korsmeyer-Peppas kinetic model.	(Abbasi et al., 2016)
3	Floating	Cross-linked alginate with Ca chloride	The release profile of sustained release captopril tablets is able to maintain the release of captopril for up to 8 hours (51.226%) by following zero-order kinetics.	(Triyanto et al., 2018)
4	Mucoadhesive	Carbopol 934P and NaCMC	The quality of mucoadhesive tablets with a ratio of Carbopol 934P: NaCMC (35%: 15%) and (15%: 35%) has a good controlled release profile following the Korsmeyer-Peppas and Higuchi kinetic models.	(Ismail et al., 2020)
5	Floating	Poly ethylene oxide water soluble resin (PEO WSR) 303 (5-30%)	Dissolution test showed controlled drug release up to 12 hours (97.97%)	(Vydana et al., 2021)

CONCLUSION

Based on the phytochemical screening results, the liquid smoke derived from coconut shell contains several bioactive compounds, including flavonoids, tannins, saponins, steroids/triterpenoids, and glycosides. Meanwhile, the phytochemical screening of liquid smoke from coconut husk shows the presence of alkaloids, flavonoids, tannins, saponins, steroids/triterpenoids, and glycosides. The total flavonoid content in the liquid smoke from coconut shell for grades I, II, and III is 0.0720±0.828, 0.08975±0, and 0.3002±0.001 mg QE/mL sample, respectively. In contrast, the total flavonoid content in the liquid smoke from coconut husk for grades I, II, and III is 0.04393±0, 0.05336±0, and 0.52776±0 mg QE/mL sample. Additionally, the

average total phenolic content in the liquid smoke from coconut shell for grades I, II, and III is 13.425±0.0447, 14.3583±5.1691, and 19.4416±0.1084 mg GAE/mL sample, respectively. For coconut husk, the total phenolic content for grades I, II, and III is 17.016±0.0423, 18.40±0, and 18.9083±0.0423 mg GAE/mL sample.

Based on the results of the reviewed studies, the combination of hydroxypropyl methylcellulose (HPMC K100M) and xanthan gum in a ratio of 40:80 in floating systems, as well as the combination of Carbopol 934 with cellulose polymers such as HPMC, NaCMC, and HPC in mucoadhesive systems, are promising formulations with controlled release up to 8-12 hours. Polymers such as polyethylene oxide (PEO WSR 303) also show high potential in long-term drug release. Therefore, selection and optimization of appropriate polymers is an important focus in the development of effective and economical captopril GRDDS. By increasing the retention time of the drug in the stomach and improving the release profile, GRDDS enables a lower frequency of drug administration (e.g. from three times to once daily), which has a positive impact on patient compliance and lowers the overall cost of therapy. In addition, the increased bioavailability of captopril in GRDDS may reduce the need for higher doses or the addition of other drugs, ultimately reducing the risk of side effects and long-term treatment costs.

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