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The Role of Polymers and Excipients for Better Gastric Retention of Captopril

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ABSTRACT: Captopril is an angiotensin-converting enzyme (ACE) inhibitor that prevents angiotensin I (ATI) from being converted to angiotensin II (ATII). However, it offers certain limitations like instability, dose dumping and burst release due to its usage in the native state. In the last two decades, different polymers and excipients have been used to make captopril more accessible and well-accepted. The present work discusses the efforts made by various scientists so far to make the oral administration of captopril more acceptable by overcoming its limitations. The different factors affecting gastric retention, approaches to achieve better gastric retention. The oral managed release dosage forms have enormous curative benefits such as improved therapeutics and better patient compliance. The polymer based gastro-retentive drug delivery systems (GRDDS) include microspheres, soild inclusion complex, floating tablets, alginate based beads, etc utilizes better retention in the stomach for longer duration of action and improved bioavailability. Overall, the work aims to summarize the attempts made as novel drug delivery approaches over the last two decades in reverse chronological order to make captopril more gastro retentive and orally acceptable by the patients.

KEY WORDS: gastrointestinal, fluctuation, hyperkalemia, superporous, captopril

I. INTRODUCTION

Polymers can be found everywhere around us. We began to use science and technology not just for food and nutrition, but also for clothing, cups, fiber, glass, bearings, bags, paints, glues, heart valves, and cookware, to name a few applications. Apart from all of this, medicine is the key field that is causing the most concern these days due to the pandemic. Polymers have transformed medicine by allowing drug/medication release to be sustained and controlled while also being targeted to a specific spot in the body (Table 1). Polymers are molecules with high molar weights and a large number of repeating units compacted into a single molecule. Polymers can both generate solid dosage form particles and alter the flow properties of liquid dosage forms. Pharmaceutical medication delivery systems are built on polymers. Polymers have been used to modulate the rate at which drugs are released from a formulation.[1] The bio-acceptability of the polymer will determine the optimal polymer, particle size, and production procedure.[2]

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TABLE 1: List of polymers used to develop captopril gastro retentive medication formulation

Name of polymer	Comments	Refs.
Hydroxypropyl methyl cellulose (HPMC) and its variants (K4,K15 M, and K100M)	Acts as a regulator of drug release and inhibit excessive erosion of tablets. HPMC derivatives were useful in increasing bioavailability of the drug. These chemicals can also absorb water from the stomach juices, resulting in an increase in the system's volume	21,26,29,32,33,35,36,38
Na-CMC	Used to increase the viscosity of preparation	
Xanthan gum	It has the advantage of being able to release drugs with zero order kinetics. It aids in the lowering of Captopril release rate by forming a highly viscous gel structure on the surface of floating tablets	22,27,29
Chitosan	Useful for stomach-specific drug delivery system. It helps systems with the capacity to remain and release drugs in the stomach	
Sodium alginate	Acts as a as a drug release modifier	23,28
Karaya gum	It's a type of swellable hydrophilic chemical that's utilized to regulate drug release	24
Badam gum	It increases bioavailability by increasing gastric residence time, either alone or in conjunction with karaya gum	
Senna tora gum, guar gum and locust bean gum	These natural polymer influence the pore size and network complexity of the formulated bead	25
Carbopol 934	It helps the drug to adhere to the gastric mucosa	28,32
Carbopol 940	This shows significant effect of on the floating lag times along with swelling ability of the tablets	30,31
Ethyl cellulose (EC)	It shows slowest buoyancy lag time due to its hydrophobic property	31,40
Low methoxy pectin and gellan gum	Natural hydrocolloids or gel-forming compounds that swell when in contact with stomach fluid, maintain relative shape integrity, and have a bulk density less than the gastric contents	37
Eudragit	It stops the medicine from breaking down until it reaches a pH-balanced location in the gastrointestinal (GI) tract	41

Polymers can be found in both natural and synthetic forms. Proteins, starches, latex, and cellulose are examples of naturally occurring polymers. Synthetic polymers are mass-produced and have a wide range of characteristics and applications.[3] Polymers are inert carriers that can be conjugated with a specific medication. The different strategies like increasing plasma half life, decreased immunogenicity, and stability improvement are the ways via they can improve the pharmacodynamic and pharmacokinetic properties of biopharmaceuticals.[4] Polymers such as polyvinyl pyrrolidone (PVP) and hydroxypropylmethylecellulose (HPMC) have been proven to be effective binders for improving the flow and compaction properties of tablet formulations prior to tableting.[5] Polymers play a critical role in the delivery of colon-targeted drugs. It keeps the medication from being degraded or released in the stomach and small intestine. It also ensures that the medicine is released in a regulated or sudden manner in the proximal colon.[6] Site specific mucoadhesive polymers will likely be used for the buccal distribution of a wide variety of medicinal drugs due to advantages such as increased polymer residence duration, penetration augmentation, site specific adhesion, and enzyme inhibition.[7] Other natural polymers also have been studied for their potential in stomach-specific medication delivery. Polymers such as pectin, xanthan gum, guar gum, gellan gum, karkaya gum, psyllium, starch are commonly used in floating drug delivery systems to focus medication distribution to a specific area of GIT.[8] Apart from that, a wide range of natural origin polymers, with a particular focus on proteins and polysaccharides, could be beneficial as carriers for active biomolecules or as cell carriers in tissue engineering applications targeting a variety of biological tissues.[9] New ideas for managing drug pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy were explored further. These innovative techniques, known as drug delivery systems (DDS), combine pharmaceutics, polymer science, analytical chemistry, and molecular biology.[10]

The simplest and most frequently acknowledged technique of delivering a drug/medicine into the systemic circulation is by oral administration. To improve therapeutic benefits, the pharmaceutical industry is interested in oral controlled release medication delivery. Drugs having short half-lives and simple absorption are quickly eliminated in the GI tract from systemic circulation (GIT). For effective therapeutic effectiveness, frequent doses are required.[11] To avoid the need for repeated dosage, oral formulations with a long-term release have been created employing a blend of polymers and excipients. The main benefit is that the medicine will be kept in the stomach and released in a regulated manner after oral administration, allowing the drug to be supplied to its GIT absorption sites continually. The low gastric retention time (GRT) and the unusually long gastric emptying time (GET) are also disadvantages of this drug delivery strategy. As a result of the dosage type, there will be insufficient medication release in the absorption region.[12] A gastro retentive drug delivery system (GRDDS) is used to delay GRT by allowing for targeted medication release in the upper GIT for local or systemic effects. Drug GRT may be delayed if similar formulations sit in the esophagus for a long time.[11] Polyvinylpryolidone and polyethylene glycol acrylate based hydrogels are two promising synthetic polymers that have been created for biomedical purposes. Both

are biodegradable and can combine with natural macromolecules to generate copolymers.[13] Natural polymers, on the other hand, have a high biocompatibility and are less immunogenic. Gelatin and collagen, which are natural polymers, have received special attention.[14]

A. Factors That Affect the Stomach's Ability to Retain Dosage Forms

The anatomy and physiology of the stomach must be considered while developing GR dosage forms. The pH range of 1 to 2 is sufficient for passage into the small intestine via the pyloric valve.[15] The GRT of oral dose forms is regulated by density, size, and food intake, calorie content and intake frequency, gender, age, sleep, BMI, physical activity, and individual illness status. Figure 1 summarizes these factors, which are further discussed below.

1. Dosage Form Density

Dosage form density determines the system's position in the stomach and regulates the rate of gastric emptying. To float on the surface, the dose type must have a lower density than the gastric contents. Because of the increased bulk structure, the stomach's heart may be affected. The dosage mechanism can be removed from the pylorus in either situation. One of the floating properties is a density of 1.0 gm/cm^3.[11,12]

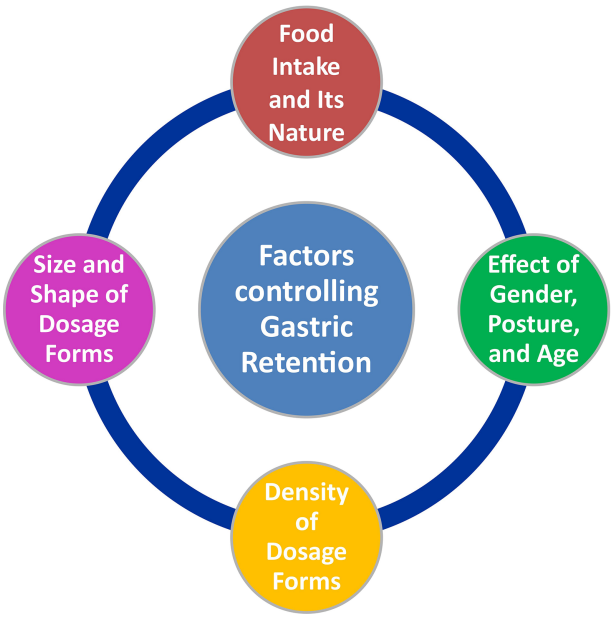

FIG. 1: Factors controlling gastric retention

2. Dosage Form Shape and Size

The ideal size and shape of the drug candidate are one of the most significant components in developing an indigestible single-unit dose form. Due to the non-floating dosage kinds, GRT is exceedingly varied and mostly reliant on its size. It could be tiny, medium, or large. The GRT is typically proportionate to the dose type's scale. Because a larger dosage form takes longer to pass through the pyloric antrum and into the gut, this is the case.[11,15]

3. Food Intake

The key elements that determine GRT are meal intake, food viscosity and volume, calorie value, and frequency. Food in the GI system affects dosage type GRT, and some researchers suggest that it can improve dosage form GRT. As a result, increasing the amount of time a drug spends at the absorption site boosts drug absorption.[14–17]

4. Effect of Gender, Posture, and Age

Females, on average, have a far slower rate of stomach emptying than men. For people in the upright, ambulatory, and supine states, the influence of posture on the mean GRT is not significant. In the elderly, the pace of stomach emptying slows down.[14,15,18,19]

B. Approaches to Achieving Gastric Retention

The researchers used a variety of ways to improve drug retention time in the gastrointestinal tract (GIT), taking into account all aspects that influence drug retention in the GIT.

C. Non-Floating Drug Delivery System or High Density (Sinking) System

It includes generating dose forms that are denser (1.004 g/cm^3) than usual stomach contents. A heavy core is blended with iron powder or barium sulfate, both of which are inert ingredients, to make this formulation. A density of 2.5 g/cm^3 should be sufficient for considerable GRT extension. Humans, on the other hand, do not affect this system.[11]

1. Floating Drug Delivery Systems

GRT and adequate drug bioavailability are two of the most critical methods for administering drugs. The optimum areas for medications to be absorbed are the stomach and upper small intestine. GRDDS is less dense than stomach fluids in terms of bulk density. As a result, it lingers in the stomach for longer without decreasing gastric emptying. The drug is subsequently removed from the body gradually and effectively. After that, the stomach's residual system is evacuated. GRT improves as a result of this mechanism, as does the regulation of variations in plasma drug concentration.

The intrinsic low density will be provided by the suffocating of air or the introduction of low-density materials. For single and multiple-unit systems, this method can be utilized to create floating dosage forms. This system's good floating behavior can be paired with drug release patterns. The main downside of single-unit dosage kinds is that they may clump together in the GI tract or become unpleasant. Multiple-unit floating systems, on the other hand, have been demonstrated to anticipate medication availability between and among subjects while lowering the danger of dose dumping.[12,15–17,20]

2. Non-Effervescent Systems

This type of system can be made with gel-formed or extremely swellable cellulose hydrocolloids, polysaccharides, or matrix-forming polymers like polyacrylate and polymethacrylate. Following oral administration, the medicine is mixed with a gel-forming hydrocolloid into gastric fluid contact, maintaining relative shape integrity and a bulk density of less than one in the stomach. These dose forms float because to the air included in the expanded polymer.[18]

3. Hydrodynamically Balanced Systems

This system typically consists of drug-containing hydrocolloids, which are a type of gel needed to keep the contents of the stomach afloat. This single-unit dosage form contains a gel-forming hydrophilic polymer or many gel-forming hydrophilic polymers. HEC, HPMC, HPC, Na-CMC, and other excipients are commonly employed. The medicine is combined with the polymer and administered as a balanced hydrodynamic system capsule. The pill dissolves in the water, causing the mixture to swell. As a result, a gelatinous barrier forms in the stomach fluid, giving long-term buoyancy for the dose type. The combination of drug loading and the effect of the polymer on the drug's release profile determines the influence of the polymer on the drug's release profile. A variety of solutions have been claimed to have been utilized to improve the efficiency of floating hydrodynamically balanced systems in many publications.[12–18]

4. Micro-Balloons/Hollow Microspheres

To lengthen the GRT of a dosage form, solvent evaporation, also known as the solvent diffusion/evaporation method, is employed in conjunction with a variety of polymers such as Polycarbonate, cellulose acetate, and low methoxylated pectin. GRDDS buoyancy and drug release are affected by polymer concentrations, plasticizer proportions, and the solvent used to create them. In the presence of surfactant, the micro balloons floated in an acidic dissolving liquid for more than 12 hours. Because of the advantages of a multiple-unit system and substantial flotation, this solution is regarded as one of the strongest systems that float.[21]

5. Alginate Beads

Ca^{2+} low methoxylated pectin and sodium alginate were used to make multi-unit floatation cross-linked scheme beads. Calcium alginate was made using sodium alginate and an aqueous solution of calcium chloride in this experiment. The beads were subsequently separated and dried using air convection and freeze-drying techniques, resulting in a porous device with a floating force of over 12 hours and a GRT of over 5.5 hours, respectively.[19]

6. Microporous Compartment System

The microporous compartment system works by enclosing a drug reservoir in a microporous compartment with porous top and bottom walls. The device's peripheral walls were completely sealed to prevent undissolved material from coming into direct touch with the stomach surface. Because the flotation chamber includes trapped air, the delivery mechanism floats in the stomach fluid. The medicine is dissolved in gastric fluid, which enters through the aperture and continues to flow through the intestine, allowing the drug to be absorbed.[17,22]

7. Effervescent (Gas-Generating) Systems

Gas bubbles made from swellable polymers like polysaccharides and effervescent chemicals can attain floating properties. The best citric acid and sodium bicarbonate stoichiometric ratio for gas production, according to sources, is 0.76:1, resulting in the release of carbon dioxide and the floating of the formulation in the stomach. Both floating micro capsules and floating systems including a core of sodium bicarbonate, lactose, and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC) and can be constructed as a bilayer or multilayer device contain gas (carbon dioxide) when eaten (carbon dioxide). The gas-generating agent can be blended separately from the medications and excipients in each layer.[16,17,22]

8. Bioadhesive or Mucoadhesive Drug Delivery Systems

This method employs bioadhesive polymers that adhere to the stomach's epithelial surface, causing gastric retention. The capacity of a dosage form to bind with the mucosal surface is influenced by the wetting, diffusion, absorption, and electron principles. Bioadhesion products such as chitosan, dextrin, HPMC, PEG, sodium alginate, tragacanth, polylactic acids, and others are available, although mucus preservation in the GIT is problematic due to rapid turnover.[18,23,24]

9. Expandable and Swellable Systems

A dose type that is greater than the stomach's pyloric sphincter can survive gastric transit. When taken alone or in combination, the dosage type must be modest enough to be

swallowed and not block the stomach. Improved gastroretentivity can be achieved by using a very stiff, bigger dosage form that can survive peristalsis and stomach mechanical contractility. To construct an efficient gastro retentive medication delivery system, unfoldable and swelling systems are being developed. Biodegradable polymers come in a variety of shapes (for example, geometric shapes, cubic shapes, or a planner membrane) and are compressed within a capsule to form the substance. The GIT frequently contains mostly swellable systems that swell owing to osmotic water absorption, and the dosage form is tiny enough to dissolve in stomach fluid and ingested.[12,25,26]

10. Super-Porous Hydrogel Systems

These swellable structures are distinct enough from other forms to merit their classification. GRT super porous hydrogels with typical pore diameters > 100 micro metres expand to equilibrium size in less than a minute due to rapid water absorption by capillary wetting via many interconnected open pores. They swell to a large size (swelling ratio of 100 or more) to withstand the stress of gastric contraction. The co-formulation of hydrophilic particle material implies this.[20,27,28]

11. Magnetic Systems

The purpose of this technique is to improve GRT by placing a small internal magnet on the abdomen near the stomach. Aside from that, an external magnet can be precisely placed, jeopardizing patient enforcement even further.[21,29,30]

For many years, the oral drug delivery system has been the most extensively used root of administration among all the roots that have been used for systemic drug delivery via diverse pharmaceutical goods for varied dose forms. A wide range of synthetic and natural materials have been investigated for use in medication delivery systems.

D. Potential Drug Candidates for GRDDS

Having a local effect on the stomach (for example, Misoprostol), having a short absorption window in the GIT (for example, L-DOPA), and being unsuited for the intestinal or colonic environment are all key factors to consider. Diazepam, chlordiazepoxide, and verapamil HCl are examples of drugs that disrupt typical colonic bacteria and having poor solubility at elevated pH.[19–27]

II. ADVANTAGES OF GRDDS

This GRDDS technique can dramatically boost therapeutic agent bioavailability as compared to non-gastro retentive drug delivery, especially for those metabolized in the upper GIT.[24]

- Drugs having a short half-life and prolonged release can flip pharmacokinetics, allowing for less frequent dosage and better patient compliance.[26]

- They also have a competitive edge over traditional systems since they can be utilized to solve issues like stomach retention or gastric emptying time.[31]
- Drugs from dose formulations that involve the stomach and small intestine can be released for longer and more consistently using GRDDS.[28]

A. Captopril

It is a medicine with the chemical formula C9H15NO3S and a molecular weight of roughly 217.29 g/mol that belongs to group III of probable options.

Captopril, the drug we've chosen, works as a competitive inhibitor of ACE, the enzyme that converts ATI to ATII (ATII). The renin-angiotensin-aldosterone (RAAS) system, which controls blood pressure, contains ATII. The medicine can be used alone or in combination to treat hypertension. It's also used to treat people with left ventricular dysfunction who have congestive heart failure or a myocardial infarction.[31,32] Apart from that, medicine has been associated with aldosteronism, anatomy, renal artery stenosis, and neuropathy.[33] The RAAS, which is known to govern several processes in the human body such as hemodynamics and mineral balance, is counteracted by captopril. When renal blood pressure or blood flow is reduced, renin is released from the granular cells of the juxtaglomerular apparatus within the kidneys. It also converts circulating angiotensinogen to ATI, which is then converted to AT-II in the bloodstream, causing blood pressure to rise through a variety of mechanisms. In the first place, the adrenal cortex induced aldosterone secretion. The acquired aldosterone travels to the nephron's distal convoluted tubule (DCT) and accumulating tubule, increasing the sodium channels and sodium-potassium ATPases number and therefore enhancing Na and H_2O reabsorption. Second, AT-II increases the production of vasopressin by the posterior pituitary gland. More water is reabsorbed from the kidneys when aquaporin-2 channels are inserted on the apical surface of DCT and tubule cells are removed with ADH. Third, ATII produces direct arterial vasoconstriction, which raises blood pressure. A series of events begins when the Type 1 ATII receptor are activated, resulting in myocyte contraction and vasoconstriction.[34]

The activity of captopril is mediated through ACE inhibition. The testicular isoform has a reduced molecular weight and is assumed to be involved in sperm maturation and oviduct epithelial interaction, whereas the somatic isoform is a glycoprotein with a single 1277-amino-acid polypeptide chain and is likewise involved in sperm maturation and oviduct epithelial binding. Somatic ACE has two functionally active domains, N and C, due to simultaneous gene replication. Despite their considerable sequence similarity, these two domains have separate physiological activities. The C-domain is in charge of blood pressure management, whereas the N-domain is in charge of stem cell differentiation and proliferation. Both domains are inhibited by ACE inhibitors, although the C-domain has a stronger affinity and inhibitory action. Captopril is one of the few ACE inhibitors that isn't a medication. By decreasing the pressor effects of AT-II, reduces AT I to AT-II enzymatic proteolysis and lowers AT-II levels.[35] Captopril absorption is increased by 60–75% when you

fast. In addition, food reduces absorption by 25–40%. It produces captopril-cysteine disulfide and captopril disulfide dimers as main metabolites. It is claimed to have a half-life of two hours. An overdose of captopril might result in emesis and low blood pressure. A dose-dependent rash (typically maculopapular), taste changes, gastrointestinal discomfort, cough, and angioedema are all possible side effects. When it comes to drug interactions, acebutolol enhances the severity of hyperkalemia. Aceclofenac and acemetacin both worsen renal failure and hypertension, while acetazolamide and acetylsalicylic acid reduce captopril excretion and therapeutic efficacy, respectively.[36]

B.Captopril-Related Problem

Formulations for captopril oral controlled release doses have been developed throughout the previous three decades. Furthermore, the time it takes for the stomach to empty in humans is only about 2–3 hours. Certain dose forms linger in the stomach after oral delivery and releases in prolonged manner. Captopril is a vasoconstrictor that also works as a negative feedback mediator for renin function, lowering blood pressure and angiotensin II levels. To treat congestive heart failure, it is administered orally in doses ranging from 50 to 150 mg per day. The maximum hemodynamic response is seen after 45–90 minutes after oral absorption of a single dose. In its natural condition, the medication is water-soluble, with a half-life of 2–3 hours after an oral intake. The drug is stable at pH 1.2, but it becomes unstable and degrades as the pH rises. The antihypertensive action of the medication, on the other hand, only lasts 6–8 hours after a single oral dose. Because of its *in vivo* and *in vitro* instability, captopril oral controlled-release formulations are difficult to develop. When made as a controlled or sustained release formulation, the medication experiences dose dumping and burst events due to its high water solubility.[37,38] Several attempts have been made to address these concerns. The current study aims to highlight how different polymer and excipient combinations have been used to create novel captopril gastroretentive formulations during the last two decades.

C. Work Done in the Development of Captopril GRDDS

Sayyad et al. have synthesized and investigated the antihypertensive potential of captopril quercetin (cap-que) in a niosomal formulation. The formulation's particle size and drug entrapment efficiency (EE%) were 418.8 nm and 87.74%, respectively. Over the course of 24 hours, the active ingredient from the niosomal formulation was released at a higher rate than the parent medication. The formulation's biosafety was established by a cell viability assay. When compared to separate, naked medicines, the hybrid molecular and niosomal formulation exhibited greater antihypertensive effectiveness in a rat model, lowering systolic and diastolic pressure. According to their findings, captopril's antihypertensive potential can be increased by combining it with quercetin and then delivering it by niosomal nano drug delivery.[39]

Michalowski et al. prepared a liquid formulation of a multi-wall lipid-core nanocapsule (MLNC) functionalized with captopril and nanoencapsulating furosemide within the core in the year 2020. The nanocapsules had a mean particle size of less than 200 nm, and their size distributions were unimodal and narrow, with modest dispersion. On the first day, the formulations had an antihypertensive impact and lasted longer than the respective medication solutions in terms of systolic pressure. The antihypertensive impact was prolonged when both medications were used together. Except for the nanocapsule formulation including both medicines, all treatments showed a temporal effect reduction on the fifth day. The study found that these formulations preserved the antihypertensive impact of the medications after oral delivery and even prolonged it when compared to solutions, indicating potential prospects.[40]

In the same year, the European Medicines Agency's Pediatric Committee noted the need for age-appropriate captopril formulations in the paediatric population for the treatment of cardiovascular illnesses and diabetic nephropathy. Thus, using cellulose acetate phthalate (CAP) and chitosan (CH) via nanoprecipitation method-dropping technique without surfactants, polymeric nanoparticles for transdermal delivery of captopril were developed for obtaining a prolonged release as well as an easy dosage control with high compliance of paediatric patients. The findings demonstrate that CAP nanoparticles have no drug loading potential, whereas CH permits captopril to be encapsulated; the maximum drug loading was achieved when a 1:3 CAP:CH w/w ratio was utilized (64.67%). The interaction of captopril with the polymer matrix is improved by particle pretreatment at 60°C. The size of loaded CAP nanoparticles is 515.65 nm, whereas CAP-CH nanoparticles are 279.82 nm (1:1 w/w ratio) and 408.19 nm (1:1 w/w ratio), respectively, with PDI values around 0.2, resulting in a homogenous system. All formulations have shown good physical stability over time. The drug captopril appears to be stable in the dispersions at the moment. Finally, CAP-CH nanoparticles produced with a 1:3 w/w ratio demonstrate promising capabilities for creating CAT transdermal administration formulations.[41]

Captopril is quickly absorbed its activity lasts 6–8 hours after a single oral dose. A controlled released captopril formulation would assist patients by reducing the frequency of delivery, increasing patient compliance and treatment effectiveness, reducing plasma concentration fluctuations, and reducing adverse effects, thanks to its relatively short half-life. For regulated delivery, Tayyab et al. produced compressed tablets containing captopril-loaded microsphere.[42] Captopril-loaded microspheres were made using a double emulsification process combined with solvent evaporation. Particle size analysis, entrapment efficiency, DSC, TGA, XRD, EDS, SEM, swelling index, and release investigations were all performed on the developed polymeric carriers. Microspheres have a spherical shape and a size in the micrometre range. They demonstrated remarkable encapsulation efficiency (95%) when the polymer to drug ratio was low (1:5:5). All of the elements were in good working order. Zero-order medication release was seen in the optimized formulation ST1.[42]

Musuc et al. used the paste method of complexation to make solid inclusion complexes of captopril with cyclodextrin in a 1:2 molar ratio. Nonprocessed captopril,

nonprocessed -CD, processed -CD, a physical mixing of captopril and -CD with no processing, and the inclusion complex all underwent the identical physical-chemical tests. The inclusion complex contains strong bonding, as evidenced by considerable increase in the intensity of the bound O–H band in FTIR spectra. When comparing the separate components and their physical mixing to the morphology of the analysed specimens, SEM indicated a significant change in shape, crystallite sizes, and structure of the new pharmaceutical formulation. The β-CD fingerprint is still visible in the physical mixture, whereas captopril's is significantly weakened, according to powder X-ray diffraction patterns. The XRD pattern of the novel compound obtained from the paste complexation procedure, on the other hand, demonstrated the production of a new compound with some β-CD features. The current study's findings show that the CAP- β CD inclusion complex can be embedded as an active ingredient in sublingual tablets, which can then be employed in clinical practice.[43]

To make captopril floating tablets, Nur and Zhang employed two viscosity grades of hydroxypropylmethylcellulose (HPMC 4000 and 15000 cps) and Carbopol 934P. The USP apparatus 2 basket method was used to perform *in vitro* dissolution in simulated stomach fluid (enzyme free) at 37°C ± 0.1°C. The release of captopril from these floating tablets appeared to be longer than that of conventional tablets, resulting in a 24-hour controlled-release dosage form for captopril. The Higuchi model and the Korsmeyer and Peppas equation showed best fit drug release, followed by first-order kinetics.[44]

Raza et al. developed zein-based porous floating tablets with almost nil lag time and extended floating time using l-menthol as porogen. The direct compression was used to prepare tablets. The method used sublimation process during which l-menthol sublimed, created pores and decreased the density of the tablets which made them float. These tablets were observed to withstand the gastric enviornemntal conditions, were lighter hence floated and capable to prolong the release of captopril. The sustained release was revealed in the *in vivo* studies with higher T_{max} and MRT values.[37]

Bhegade et al. used a blend of polymers such as chitosan and xanthan gum in ratios of 0:200, 25:175, 50:150, 75:125, 100:100, 125:75, 150:50, 175:25, and 200:0 to create a gastroretentive floating captopril tablet. The concentration of this dose type is 0%–60%. *In vitro* drug release profile was determined using a USP type II dissolution apparatus, and the sample was examined using a UV-Vis spectrophotometer calibrated to 211 nm. The floating time was discovered to be 8 hours for all produced pills. It was discovered that the swelling index ranged from 145T to 195%. The drug content homogeneity was found to be 95T–105%. After 8 hours, *in vitro* drug release was determined to be 95%, showing that the medication was floating in the stomach. As a result, designing a gastro retentive tablet formulation is an attempt to solve the short half-life and pH sensitivity restrictions.[45]

Shetty et al. produced mucoadhesive captopril microspheres to improve absorption and bioavailability by prolonged retention in the upper gastrointestinal tract. The microspheres were created by emulsifying sodium alginate with captopril in various ratios before cross-linking with calcium chloride. Captopril and other excipients were found to be compatible in an FTIR investigation. The impact of polymer concentration

on medicine release was looked at. The pharmaceutical release profile was systemically optimized using the response surface technique. As independent variables, the polymer to drug ratio and stirring speed were used. After 6 hours, the dependent variables are drug entrapment efficacy, percentage mucoadhesive, and drug release (*in vitro*). After 6 hours, the improved formulation (MM10) had an 80.34% drug entrapment effectiveness, a mucoadhesive percentage of 95.75%, and a drug release rate of 26.08%. The particles were found to be spherical with a smooth surface using scanning electron microscopy. With an average particle size of 51.43 m, the particles were free-flowing. Bioavailability was reported to be higher in captopril mucoadhesive microspheres with increased performance, probably due to the drug's extended-release in the stomach.[46]

Habeeb et al. developed gastroretentive floating matrix Captopril tablets with natural polymers using an effervescent technique. The effervescent component was made with sodium bicarbonate and crushed utilizing direct compression and wet granulation processes. The tablets were evaluated in 0.1 N HCl for 12 hours for physicochemical qualities, floating characteristics (floating lag time, floating time), swelling index, and drug content and found to be adequate. Low polymer concentration formulations were unable to attain the optimal outcomes. Drug release was delayed by up to 12 hours in formulations prepared using a blend of polymers (karya gum + badam gum) (F11 = 96.68). The formulation utilizes Higuchi's release mechanism, according to the release kinetics data.[38]

The alginate based beads have also been explored to sustained the delivery of captopril by Pawar et al. The probable mechanism proposed for the sustained drug release of captopril was swelling of natural polymer used for formulation, followed by drug diffusion through the swelled polymer; and slow erosion of the captopril loaded sodium alginate bead. These beads loaded with captopril were prepared using the very simple and feasible method of inotropic gelation. Galactomannans' natural gums such as Senna tora seed gum, guar gum and locust bean gum were also used along with sodium alginate and calcium chloride. The optimization of various independent variables (the concentration of calcium chloride, sodium alginate,natural polymer; rpm; curing time and provided condition of drying etc.) was performed and its effect of the dependent variables were observed and quantitatively measured. One of the formulation with the sodium alginate: guar gums :: 2:1 showed satisfactory sustained release of captopril for 12 h.[47]

Captopril tablets were developed by Rajput et al. as a gastroretentive medication administration dosage form. According to optimization under the factorial design of formula and classed formulation batches, the polymer HPMC concentration of different grades (HPMC K15M, HPMC K100M, and HPMC K4M) differs with the sodium bicarbonate ratio and microcrystalline cellulose in the formulation of GRDDS types. As a result, the study's main goal is to develop and test a gastroretentive captopril dosage form (tablets) for effective long-term release after oral administration in patients with congestive heart failure and diabetic kidney disease.[48] Chauhan et al. used different grades of HPMC to prolong the release of captopril in orally consumed floating tablets. To improve the formulation, different viscosity grades of HPMC were used. To create the best-optimized formulation for increasing stomach residence time, lactose and citric

acid, as well as the natural polymers chitosan and carbopol, were used in varied dosages as a channeling and chelating agent (GRT).[49]

Effectiveness of oral and sublingual captopril in patients hospitalized to the emergency department with high blood pressure, as well as BP decrease was performed by Kaya et al. It was reported that sublingual captopril successfully lowers blood pressure in the first 30 minutes of the trial, but the difference is equivalent to 60 min.[50] Abbasi et al. used traditional mucoadhesive polymers to make fast-dissolving and sustained-release captopril formulations (sodium alginate) using HPC, HPMC, sodium CMC, Carbopol 934 (CP934), and sodium alginate. Based on the average dissolving time, the formulations with the best-sustained release were chosen (MDT). Formulations containing a mix of CP934 and cellulose-based polymers were found to have the best swellability, durability, and adhesive strength. These formulations matched the Korsmeyer-Peppas model perfectly by extending drug release for up to 8 hours. Furthermore, at an oral pH of 6.5, the chosen fast-disintegrating tablet may release up to 100% of the drug in 3 min. Finally, a new dual long-acting mucoadhesive bilayer tablet was developed, which released 30% of the medication in 15 min and the remainder for up to 8 hours, making it excellent for treating hypertension crises.[51] To create and optimize a zero-order sustained release floating formulation, Ahsan et al. used a variety of natural polymers and calcium carbonate as a gas generator. After preliminary experiments validated the values, nine tablet formulations (F1–F9) were created using the wet granulation process and polymer combinations recommended by Design Expert Software®. Three more checkpoints were constructed to assess the validity of the developed mathematical equations. The hydrophilic matrix-forming agents were found to be suitable for the formulation of captopril-controlled release floating tablets in the answer surface plots. In both physical mixes and formulations, FTIR and DSC spectra revealed no significant incompatibility between the drug and the polymers.[52]

A very different approach lead to the bidirectional release of captopril from a doughnut shaped directly compressed tablets. A water insoluble polymer and a mucoadhesive coating were used to coat the top and bottom of the tablet.[30] The batches were formulated using hydroxypropyl methyl cellulose (HPMC) E15, HPMC E50 and sodium CMC; and the formulated batches were optimized. The optimized batch showed 80% w/w release of captopril in 4–5 h. These batches were further tested for water penetration, tensile strength and stability, etc.[53]

Captopril and hydrochlorothiazide were combined in a compression-coated formulation (HCTZ) by Pathuri et al. to improve antihypertensive therapy efficacy while taking both medications' half-lives into account. When administered together, captopril with a long half-life and HCTZ with a short half-life has been shown to have a synergistic effect.

Captopril sustained release floating tablets were made using a 2^3 factorial design with two layers of three polymers viz ethyl cellulose (EC), carbopol, and xanthan gum, respectively. Using ANOVA, the formulations (CF1–CF8) were optimized for the two response variables, buoyancy, and T50%. The coefficients and *P* values for the three

polymers for the response variables, buoyancy and T50 percent utilizing EC, were determined to be 3.824, 0.028, and 0.0196, 0.046, respectively.

Formulation CF2, which contains solely EC polymer at a high stage, was fine-tuned based on these findings. The CF2 formulation was then given a gastric dispersible HCTZ layer (HF9). The drug release kinetics of the compression coated tablet were also examined. The HCTZ layer's Q value was measured 20 min after the first order release, while captopril's Q value was measured 6.5 hours after the Higuchi model, indicating that both rapid and slow-release HCTZ is possible. The drug release mechanism was investigated using the Peppas equation, and $n > 0.90$ was discovered, indicating that the case II drug release transportation method is plausible.[54] Captopril mucoadhesive films were created by Anupam et al. as a gastroretentive mucoadhesive drug delivery method. They used polymers like EC, HPMC, and Carbopol 934, as well as a plasticizer like glycerine, in a solvent casting method. Captopril mucoadhesive films were found to follow Korsmeyer Peppas kinetics in gastroretentive mucoadhesive films. Code F8 was determined as a suitable formulation for delivering captopril as a mucoadhesive gastroretentive film with the optimal mucoadhesive strength and 99.06% drug release at 24 hours after a thorough study of several performance metrics and drug release kinetics.[55] Gaikwad et al. created a bilayer-floating tablet (BFT) with citric and tartaric acid, as well as the polymers HPMC-K15M, PVP-K30, and Carbopol 934p, using direct compression technology. The floating device and *in vitro* dissolution data were studied in simulated stomach juice missing enzyme and pH 1. In all experiments, the final formulation released roughly 95% of the medication in 12 hours *in vitro*, with a floating lag period of 10 min and a floatable table. It also followed Higuchi's release timetable. There are no noticeable changes in physical appearance, drug consistency, floating behaviour, or *in vitro* dissolution pattern after three months of storage at 45°C/75% RH. As a result, it appears that increasing stomach retention time improves drug absorption and bioavailability. We attempted to build a captopril floating device in this work.[56] When the pH rises above 1.2, captopril becomes unstable and undergoes a degradation reaction. Kiran et al. developed a floating alginate microspheres formulation that increases gastric retention time. These floating beads release captopril more slowly than regular capsules, resulting in an 8-hour controlled-release dose form for captopril. The Higuchi, Korsmeyer, and Peppas models, as well as zero-order kinetics, best fit drug release. The drug's release at 8 hours ranges from 39.49% to 67.34%, according to the Korsmeyer and Peppas equation, with the diffusion coefficient (n) ranging from 0.24 to 0.62. To discover the optimal formulations, the diffusion coefficient and drug release limitations at 6 hours (percent) were used (n). The responses of the optimized formulations were evaluated, and According to the findings, it was discovered that drug release is mediated by diffusion and follows the fickian transport model.[57]

To increase captopril's stomach retention time, Baswaraj et al. used gas-driven tablets (floating tablets). Direct compression was used to create the gas-powered tablets. Captopril, a gas-generating agent (6%–18% sodium bicarbonate), and water-soluble polymers (40%–60% HPMC K4M) were utilized in this work to accomplish the desired regulated release throughout a 10-hour cycle. FTIR and DSC testing were utilized to ensure medication compatibility with excipients. The formulation K3 with captopril,

HPMC K4M, sodium carbonate, mannitol, magnesium stearate, and talc was found to be promising, with a 97.47% *in vitro* drug release and a moderate floating lag time (25 sec).[58]

Captopril floating microspheres were created and characterized by Devesh et al. in order to establish long-term retention in the upper GI tract, perhaps improving absorption and bioavailability. Using a solvent evaporation approach, the microspheres could be generated using a variable ratio of hydroxyl propyl methylcellulose (HPMC K4M) in a melange of dichloromethane and ethanol (1:1) with tween 80 as a surfactant. Both the medicine and the excipients are compatible, according to the DSC data. A 3^2-factorial design was created on a systemic level to optimize the pharmaceutical release profile. As independent variables, the polymer to drug ratio (X1) and stirring speed (X2) were chosen. The optimized formulation, on the other hand, was determined to be stable after a three-month accelerated stability test. The floating microspheres worked better and might have been used to postpone captopril absorption in the stomach, boosting captopril bioavailability.[59]

Anand et al. produced and tested hollow and porous varieties of floating captopril beads based on the floating pulsatile principle. Preliminary study was carried out to discover the optimal polymer combination (low methoxy pectin and gellan gum). Based on preliminary research, the best polymer concentration for formulation design was established, allowing the sodium bicarbonate content to be changed. Physical characterisation, *in vitro* release, *in vivo* gamma-scintigraphy analysis, and stability testing were all required of the resulting floating beads. The floating beads in Formulation F1E had a porosity of 38.41% and a bulk density of 1. Formulation F1E had an entrapment efficacy of 83.10%, and the particle size of the beads was 1.124 mm. The floating beads were released at 96.77% for about 8d immunity hours *in vitro* after an initial lag time in an acidic medium followed by a fast pulse release in phosphate buffer media.[60]

Using the direct compression technique, Vijayasankar et al. created captopril tablets with a lower GRT. According to experiments utilising differential scanning calorimetry, there were no polymorphic alterations during tablet development (DSC). The physical assessment of all formulations demonstrated that they all meet the requirements of the official pharmacopoeia. The formulation (F5) containing captopril, HPMC K15M, sodium bicarbonate, lactose, and magnesium stearate was the most promising *in vitro* release profile results, with the highest degree of drug release compared to the other formulations. The F5 formulation has a high swelling index as well as Higuchi modal release profiles. The formulation F5 had the highest medication release rate, at roughly 96.22% at the desired time of 8 hours, according to the findings. This batch likewise showed immediate floating after a floatation time of more than 8 hours.[61]

To investigate the drug's release pattern, Sameer et al. employed a variety of kinetic treatments and discovered that it was released by diffusion and followed square root or Higuchi's kinetics. *In vitro* drug release profiles in all of the plots are extremely linear, with r^2 values ranging from 0.9813 to 0.9954. The thickness, friability, stiffness, material uniformity, weight uniformity, and *in vitro* dissolution of the optimized formulations were all examined again. The floating Captopril formulation was shown to be the best

for achieving a greater therapeutic effect when hydroxypropylmethylcellulose was used at a concentration of 35%. It increases the drug's bioavailability to some level, allowing the dosage type to remain on the target site for longer periods of time.[62]

In 2011, captopril microspheres were produced that float in the stomach and lengthen the drug's GRT. Floating microspheres were created using biocompatible polymers such as Eudragit S100 and Ethylcellulose in varying concentrations, as well as a solvent evaporation process. The microspheres' practical yield was found to be 76.40%, with free-flowing and good packing properties. Scanning electron microscopy confirmed the particles' spherical shape, with diameters ranging from 57.66 to 93.21 nm. Microspheres coated with ethylcellulose were more buoyant than Eudragit S-100 microspheres. In terms of percent buoyancy, both formulations performed well *in vitro*. *In vitro*, drug release percentages ranged from 75.95 to 88.27%. Non-Fickian drug diffusion was observed *in vitro* when drugs were released from the microsphere.[63]

To optimize the product, Gohel and Nagori employed a 32 full factorial design with Compritol® ATO 888 ratio (X1) and extragranular percentage of ethyl cellulose (X2) as independent variables in a 32 full factorial design. The proportion of drug released in one hour (Y1) and the time required to release 80% of the drug (Y2) were chosen as dependent variables. A eutectic mixture of camphor and menthol was used as a solvent to improve drug dispersion in matrix. An ideal batch containing 50 mg captopril, 160 mg Compritol® ATO 888, and 220 mg ethyl cellulose was generated by overlaying the contour plots of Y1 and Y2. The Y1 and Y2 answers of the improved batch were 25% and 520 min, respectively. Drug release kinetics were best explained by the Korsmeyer-Peppas model. In terms of prediction power, the artificial neural network findings exceeded the factorial design for both responses (Y1 and Y2).[64]

The gas production approach was used by Kesavan et al. to increase captopril's stomach residence duration and bioavailability. The captopril-containing core modules were compressed right away before being coated in three layers: an inner seal coat, an effervescent layer, and a gas-tight polymeric membrane. Even a system made up of Eudragit RL30D and other materials should be able to float in the presence of gas. The time until float decreased as the volume of the effervescent agent increased and the coating level of both the gas-entrapped polymeric membrane and the gas-entrapped polymeric membrane dropped. The drug release was lowered as the coating amount of the gas-entrapped polymeric membrane was increased. There was no significant difference in the parameter dissolution outcomes after 3 months of storage at 40°C and 75% RH, implying that the two dissolution profiles may have been considered identical (F2 value is more than 50).[65]

Nouhsin et al. created and improved a captopril sublingual tablet formulation. Captopril-containing tablets were created and optimized using the direct compression method. In a D-optimal experimental plan for a post-compression study, the generated tablets were evaluated as responses dependent variables. For disintegration time and friability outcomes, a certain cubic model and polynomial mathematical equations were discovered to be statistically significant ($P \leq 0.05$). Furthermore, the hardness data is best suited by a linear model. After that, the data was used to construct an optimized

overlay. The numerical optimization data and regression analysis forecasts were compared and found to be quite close.[66]

Martinez et al. looked at the *in vitro* sustained release of captopril from Metolose SH 4000 SR/sodium bicarbonate floating tablets with various Metolose and bicarbonate concentrations. Other aspects explored include hydration volume kinetics, matrices floating time, and matrix density. Matrixes compacted at 55 MPa float in the dissolving media for more than 8 hours, whereas those compacted at 165 MPa float only when sodium bicarbonate is added to the formulation, according to the findings. As the amount of matrix polymer grows, so does the maximum hydration volume and the time it takes to attain it. The hydration volume of the matrix increases when sodium bicarbonate is added to the formulation. The drug release constant (k) decreases as polymer concentration increases, but the exponent representing the release mechanism (n) increases. The amount of drug released over time is lowered when sodium bicarbonate is included in the formulation. Carbon dioxide bubbles impede the diffusion pathway, reducing matrix coherence.[67]

Patel et al. produced and tested a sustained release gastroretentive dosage version of captopril in several studies. The introduction of the hydrophobic polymer EC in the granulation fluid resulted in a consistent medicine release pattern, according to their findings. *In vitro* drug release, buoyancy, and swelling behavior were unaffected by changes in pH and osmolarity. The formulation stayed stable at 40°C/75% RH for 3 months.[68]

Using direct compression technique, Rahman and Khar produced a bilayer-floating tablet (BFT) for captopril. The floating layer was made up of HPMC, K-grade, and an effervescent mixture of citric acid and sodium bicarbonate. Captopril and other polymers, such as HPMC-K15M, PVP-K30, and Carbopol 934p, were present in the release layer, either alone or in combination with the medication. In simulated gastric fluid, the floating behaviour and *in vitro* dissolution tests were conducted out in a USP 23 apparatus 2. *In vitro*, the final formulation released roughly 95% of the medication in 24 hours, with a floating lag time of 10 min and a tablet that was floatable throughout all experiments. After three months of storage at 45 degrees C/75% RH, the final formulation followed the Higuchi release model and showed no significant changes in physical appearance, drug content, floatability, or *in vitro* dissolution pattern. BFT considerably enhanced the stomach residence time when a placebo formulation with barium sulphate in the release layer was given to human volunteers for *in vivo* X-ray experiments.[69]

Groning et al. tested innovative collagen gastro retentive dosage forms (GRDFs) in the same year, reporting that GRDFs should be retained in the stomach for a long period due to their size. Collagen sponges were used to make the dose forms (manufactured by freeze-drying a riboflavin collagen solution). A computer-controlled material supply designed to provide pre-compressed collagen to a tablet machine. A second form of tablet is made by mixing crushed collagen sponges with hydroxypropyl methylcellulose hydrophilic matrix layers. Captopril or acyclovir-containing matrix layers were produced. Both sorts of dose formulations were used in *in vitro* investigations. After a few minutes of contact with artificial gastric juice, the collagen tablets expand to create an 8 mm × 18

mm × 60 mm drug delivery system. Riboflavin is released over the course of 16 hours. The composition of the sustained release layer can influence the release of acyclovir or captopril in two-layer tablets.[70]

III. CONCLUSION

Captopril treat hypertension by preventing the conversion of angiotensin I (ATI) to angiotensin II, which is mediated by the angiotensin-converting enzyme (ATII). However, the short half-life, instability *in vitro* and *in vivo*, especially at higher pH values, dose dumping and burst release, as well as the major side effects at the effective dose, make captopril difficult to use. The poor bioavailability of oral dosage forms, on the other hand, is a major challenge in their design. Aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms all affect its oral bioavailability. To address these limitations, gastro retentive drug delivery systems appear to be a viable option for extending a drug's ability to maintain itself in the stomach, thereby increasing its gastric residence time and improving drug bioavailability. The goal of our current study is to summarize the evolution of different gastroretentive captopril dosage forms over the last two decades in reverse chronological order.

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