



Formulation of Modified Release Film-Coated Matrix Tablets Employing Phosphorylated Potato Starch as a Release Modifier

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ABSTRACT

The need for modified-release drug delivery systems has increased significantly due to their ability to reduce dosage frequency, enhance patient compliance, and offer longer-lasting therapeutic advantages. This paper focuses on the development of film-coated matrix tablets using phosphorylated potato starch as a new excipient for modified-release formulations. Potato starch, a commonly available and biocompatible polysaccharide, was chemically modified by phosphorylation to improve its physicochemical properties, including its controlled release behaviour, heat stability, and swelling capacity. Because the phosphorylated derivative demonstrated better matrix-forming ability and increased drug entrapment effectiveness, it was an excellent fit for modified-release formulations. A variety of variables that impact matrix tablet performance were evaluated in this study, including the degree of phosphorylated starch substitution, drug-to-polymer ratio, and film-coating thickness. The matrix tablets were made by direct compression, and a polymeric covering was added for additional protection and controlled drug release. The coating was made to endure variations in the gastrointestinal tract's pH while preserving consistent, focused drug delivery. The performance of the developed matrix tablets was evaluated using in-vitro drug release assays, stability evaluations under accelerated conditions, and swelling index measurements. The findings demonstrated that the phosphorylated potato starch effectively regulated the release of active pharmaceutical ingredients (APIs) via non-Fickian diffusion kinetics. Additionally, the tablets showed durability and maintained their structural integrity in physiological circumstances. This research highlights the potential of phosphorylated potato starch as a cost-effective, eco-friendly, and efficient excipient for modified-release drug delivery systems. The findings provide a scientific basis for its application in the pharmaceutical industry and emphasise its significance in improving therapeutic outcomes and creating patient-centered healthcare solutions.

Keywords: Modified-release tablets, phosphorylated potato starch, matrix tablets, film coating, drug delivery systems, active pharmaceutical ingredients (APIs).

INTRODUCTION

1. The Evolution of Drug Delivery Systems

The development of enhanced drug delivery systems (DDS), whose primary objective is to increase patient compliance while achieving the best feasible treatment outcomes, has been a crucial aspect of pharmaceutical sciences. Plasma medicine levels often fluctuate with traditional immediate-release dosage forms, potentially leading to additional side effects or less than optimal therapeutic outcomes. Modified-release methods that have been successful in getting around these limitations include formulations with extended-, sustained-, and controlled-releases (1). These systems reduce the frequency of dosages and improve the overall patient experience by guaranteeing a consistent and predictable release of the active pharmaceutical ingredient (API) (2).

2. Modified-Release Drug Delivery Systems

By controlling the rate, timing, and location of active pharmaceutical ingredient (API) release in the body, Modified-Release Drug Delivery Systems (MRDDS) are state-of-the-art pharmaceutical technologies that provide significant therapeutic and economic benefits. Unlike standard immediate-release formulations, MRDDS minimise side effects, improve patient compliance, and reduce dose frequency by providing sustained therapeutic drug levels. Formulations with controlled, delayed, pulsatile, and sustained releases are among the many kinds of these systems, each of which is intended to accomplish specific therapeutic goals. For



example, sustained-release systems release the drug over a longer length of time while maintaining consistent plasma drug levels, whereas delayed-release systems use pH-sensitive coatings to release the medication at a specific region, such as the intestines (3)(4).

The development of MRDDS requires careful selection of polymers, excipients, and drug formulations. Biodegradable materials like phosphorylated starch and polymers like hydroxypropyl methylcellulose (HPMC) and ethyl cellulose primarily regulate the kinetics of drug release. Functional coatings further enhance the systems by controlling the release profile or preventing the drug from being broken down in the stomach (5). The mechanisms of drug release in MRDDS include diffusion, where the drug diffuses through a polymer matrix; dissolution, which is regulated by the solubility of the formulation; erosion, where the drug is released through the gradual breakdown of biodegradable polymers; and osmosis, where the drug is released through a delivery orifice due to osmotic pressure (2).

Enhanced effectiveness is achieved through stable medication levels, reduced systemic toxicity by minimizing peak-to-trough fluctuations, and improved therapeutic outcomes for chronic illnesses such as diabetes, epilepsy, and hypertension, which are just a few advantages of MRDDS.

Moreover, these systems facilitate site-specific administration, which is particularly beneficial for conditions like localized cancers and inflammatory bowel disease. However, the development of MRDDS faces challenges such as the complexity of formulation, high manufacturing costs due to the need for specialized materials and equipment, and stringent regulatory requirements to ensure safety and efficacy (6). Additionally, to achieve the desired release characteristics, the design of the delivery system must consider the physicochemical properties of active pharmaceutical ingredients (APIs), including their stability and solubility (7).

Future advancements in MRDDS are expected to integrate biodegradable materials, 3D printing technology, and nanotechnology to create intelligent, tailored drug delivery systems. For instance, the use of eco-friendly polymers like phosphorylated starch is gaining traction due to its potential for controlled release and sustainability (8). Furthermore, multi-compartment systems that combine immediate and sustained-release features are also under investigation to enhance therapeutic outcomes. Overall, MRDDS remains a cornerstone of modern drug delivery, addressing the limitations of traditional methods and meeting the growing demand for effective, patient-centered therapies.

By enabling regulated, sustained, or targeted release of active pharmaceutical ingredients (APIs) over an extended duration, modified-release drug delivery systems (MRDDS) have revolutionized the field of pharmaceutical sciences. Unlike immediate-release formulations, these systems enhance patient compliance by reducing dosing frequency, minimizing side effects, and improving therapeutic efficacy (9). Additionally, modified-release techniques ensure a steady-state medication level.

3. Role of Starch in Drug Delivery

Plant-based starch is a naturally occurring polysaccharide with a wide range of applications, biocompatibility, biodegradability, and accessibility, making it a crucial part of pharmaceutical drug delivery systems. Starch and its derivatives are widely used as excipients, drug transporters, and release-modifying agents in a range of formulations, including tablets, capsules, hydrogels, and nanoparticles. Modification by enzymatic, physical, or chemical means further improves its usage in complex drug delivery systems.

Properties of Starch in Drug Delivery

1. Biocompatibility and Biodegradability: Starch is a safe and non-toxic material that degrades into glucose and other harmless byproducts, making it suitable for use in pharmaceutical formulations, especially those that are biodegradable and designed for sustained release (11).

2. Functional Versatility: Modified starches offer enhanced mechanical strength, controlled swelling, and tailored drug release profiles compared to native starches, which are restricted in their application due to their high sensitivity to water and rapid swelling. These modifications include phosphorylation, esterification, and cross-linking.

3. Controlled Release: Specifically, phosphorylated starch can form matrices and hydrogels that facilitate extended and regulated drug release. It is an excellent choice for matrix tablets because of its swelling properties and ability to manage drug diffusion (12).

4. Binding and Disintegration: In conventional tablet formulations, starch functions as both a binder and a disintegrant. Its ability to swell in the presence of water aids in the dissolution of tablets, thereby enhancing drug solubility and bioavailability.

Starch has been extensively studied as a pharmaceutical excipient since it is a naturally occurring polysaccharide that is readily accessible, non-toxic, biocompatible, and biodegradable. However, natural starch often lacks the mechanical and functional properties required for successful modified-release formulations (13). To overcome these limitations, chemical modifications like as phosphorylation, acetylation, and carboxymethylation are employed to improve its physicochemical properties.

Phosphorylation enhances starch's capacity to stretch, gel, and absorb water, making it suitable for uses requiring extended drug release. The phosphate groups added throughout the process allow for regulated release of APIs while also fortifying the polymer network (14).

4. Phosphorylated Potato Starch as a Novel Excipient

Phosphorylated potato starch (PPS), a modified starch derivative, has garnered a lot of attention in the field of pharmaceutical medication administration due to its enhanced functional properties over native starch. Phosphorylation alters potato starch by introducing phosphate groups to the backbone of the starch polymer, which enhances its water solubility, gel-forming ability, and compatibility with various active pharmaceutical ingredients (APIs). These characteristics make phosphorylated potato starch an appropriate excipient for the development of controlled-release and sustained-release drug delivery systems.

1. Preparation and Characteristics of Phosphorylated Potato Starch:

Under specific reaction conditions, phosphorylation is typically achieved by reacting native potato starch with a phosphorylating agent, such as phosphoric acid or sodium trimetaphosphate (STMP) (11). By modifying the starch's molecular weight and degree of phosphorylation, excipients with the desired release profiles can be produced. The following are the primary characteristics that result from this modification:

- **Enhanced Hydrophilicity:** The addition of hydrophilic phosphate groups through phosphorylation increases the water solubility of the starch, making it more suitable for formulations that require controlled release (15).
- **Improved Gelation Properties:** Phosphorylated starch gels at lower concentrations compared to natural starch. These gels can be utilized to develop matrix systems that regulate medication release.
- **Increased Swelling Behavior:** The incorporation of phosphate groups significantly alters the swelling behavior of the starch. This property is particularly beneficial when formulating for controlled drug release over extended periods (12).
- **Biodegradability:** Phosphorylated potato starch serves as an environmentally friendly excipient in pharmaceutical formulations due to its biodegradable nature, similar to that of native starch.

Potato starch is an excellent candidate for modification due to its high amylopectin content, unique granular structure, and favorable viscosity profile. Phosphorylated potato starch has emerged as a promising excipient for matrix tablet formulations, exhibiting improved stability, binding capacity, and film-forming properties (16). Furthermore, it is cost-effective and readily available in large quantities, aligning well with the pharmaceutical industry's growing demand for sustainable and environmentally friendly products.



Figure 1- Potato Starch



1. Applications of Phosphorylated Potato Starch in Drug Delivery:

- **Controlled-Release Drug Delivery Systems:** Phosphorylated potato starch is commonly employed in the development of matrix tablets and hydrogels for the controlled release of medications. Due to its ability to form stable gels and its solubility in water, PPS can encapsulate drugs and facilitate a prolonged release over time. The phosphorylation level can be adjusted to tailor the release rate of the drug. For example, the starch matrix may gradually swell or dissolve, allowing for a slow release of the active ingredient (18).

PPS-based matrix systems are particularly effective for drugs that require consistent therapeutic levels, such as analgesics, antihypertensive agents, and anti-inflammatory drugs. These systems offer benefits such as reduced dosing frequency and minimized fluctuations in plasma drug concentrations, thereby enhancing patient adherence (19).

- **Tablet Formulations and Coatings:** In the context of tablet formulations, phosphorylated potato starch can serve as a disintegrant, binder, and matrix. It has been shown to provide optimal tablet hardness while ensuring that the tablets dissolve readily upon ingestion. This characteristic makes it suitable for both conventional immediate-release and controlled-release tablets (11). Additionally, PPS can be utilized in film coatings to regulate the release of active pharmaceutical ingredients (APIs) in the colon and to confer resistance to gastric acid, which is beneficial for enteric-coated formulations.

- **Mucoadhesive Drug Delivery Systems:** The potential of phosphorylated potato starch is also being explored in mucoadhesive drug delivery systems due to its ability to form gel-like structures upon contact with water. These systems can facilitate mucosal delivery of vaccines or peptides, as well as localized treatment for conditions such as inflammatory bowel disease (IBD), owing to their adhesion to mucosal membranes and prolonged drug release. The phosphorylation of PPS enhances its interaction with mucosal tissues and improves its mucoadhesive properties (20).

- **Nanoparticles and Nanoemulsions:** Phosphorylated potato starch has also been incorporated to nanoparticles and nanoemulsions for controlled and accurate drug delivery. PPS's hydrophilicity aids in the formation of stable nanoparticles that can encapsulate hydrophobic drugs, boosting their bioavailability and therapeutic effectiveness. PPS-based nanoparticles are therefore ideal for targeted drug delivery applications, such as cancer therapy, where accurate drug release at specific locations is essential (12).

5. Film Coating: Enhancing Modified-Release Systems

Film coating is an essential technique in modern pharmaceutical formulations, especially for modified-release drug delivery systems. It comprises applying a thin, uniform layer of polymer or other materials on solid dosage forms, such as tablets or pellets. Among other things, this coating controls the rate of release of the active pharmaceutical ingredient (API) and shields the drug from outside effects. Because they improve the usefulness, durability, and appearance of pharmaceutical products while enabling precise control over drug release kinetics, film coatings have attracted a lot of attention.

1. Purpose and Advantages of Film Coating:

In order to improve the performance of modified-release formulations, film coating is essential. The following are the main benefits of using film-coated tablets in modified-release medication delivery systems:

- **Controlled Drug Release:** Film coatings can be engineered to control the release of the active pharmaceutical ingredient (API) in specific manners, such as targeted, delayed, or sustained release. For example, drugs that are sensitive to acidic conditions benefit from enteric coatings, which ensure that the medication is released in the more neutral or alkaline pH of the intestines rather than in the acidic environment of the stomach (21). Similarly, sustained-release coatings can allow the medication to be released over an extended duration—spanning several hours or even days—thereby providing a consistent therapeutic effect and reducing the frequency of dosing.

- **Protection of Active Ingredients:** Film coatings provide a protective barrier that safeguards the API from exposure to oxygen, light, and moisture, all of which can degrade sensitive compounds. This enhances the stability and shelf life of the medication formulation, both of which are critical for maintaining its efficacy (22).

- **Taste Masking:** Many medications have an unpleasant taste, which can deter patients from adhering to their prescribed regimen. Film coatings can mask the taste of bitter APIs, particularly in chewable tablets or oral solid dosage forms, making the medication more acceptable to patients (21).



- **Aesthetic Appeal and Branding:** Coating improves the visual appearance of the tablet and aids in swallowing by providing a smooth, glossy finish. Additionally, film coatings can be color-coded to enhance patient compliance, branding, and product recognition (23).

- **Tamper Resistance and Modified Release Profiles:** Film coatings can also provide tamper-evident features, which are especially important for controlled substances. By incorporating tamper-resistant elements into the coating, manufacturers can ensure the integrity of the dosage form. Furthermore, film coatings can be tailored to fulfill the pharmacokinetic requirements of the drug by achieving complex release profiles such as pulsatile, biphasic, or triphasic release (5).

Film coating is a crucial step in the manufacturing of matrix tablets because it protects the drug core, improves the tablet's appearance, and provides greater control over drug release. Polymers including hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and polyvinyl alcohol are often used coating materials (8). The thickness and chemistry of the coating layer can be altered to preserve uniform drug release in particular gastrointestinal tract regions and to resist environmental factors such as gastric pH (9).

Combining a matrix core based on phosphorylated starch with a film coating offers a dual approach to controlling drug release, ensuring enhanced stability and performance of the dosage form.

2. Mechanisms of Film Coating for Modified Release:

The kind of coating and how it interacts with the environment are the main factors influencing the release of medications from film-coated formulations. To regulate drug release, a number of methods can be used:

- **Diffusion-Controlled Release:** In this method, the medication is embedded within a polymer matrix that expands upon contact with gastrointestinal fluids. This mechanism facilitates the gradual diffusion of the drug from the matrix. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and polyvinyl alcohol (PVA) serve as film coatings for diffusion-controlled systems, enabling sustained delivery of the medication over an extended period.

- **Erosion-Controlled Release:** In erosion-controlled systems, the drug is released as the film coating gradually erodes or dissolves in response to moisture. The rate of erosion is influenced by the properties of the coating material and the conditions within the gastrointestinal tract. Erosion-controlled release systems can be constructed from materials like polysaccharides, cellulose derivatives, and xanthan gum.

- **pH-Sensitive Release:** pH-sensitive film coatings are often utilized in enteric coatings that dissolve at specific pH levels. This ensures that the active pharmaceutical ingredient (API) is released in the small intestine, where the pH is more neutral, while protecting it from the acidic environment of the stomach. Commonly used polymers in these systems include methacrylic acid copolymers (Eudragit®), which provide precise control over the release site by dissolving or swelling at designated pH values.

- **Osmotic Release:** Osmotic-controlled release systems utilize osmotic pressure to facilitate the release of the drug. Typically, the film coating is semi-permeable, allowing water to enter the dosage form. The osmotic pressure generated propels the drug through a delivery orifice. These systems provide a zero-order release profile, meaning the drug is released at a constant rate, unaffected by external conditions.

- **Multi-Phase Release:** Some film coatings are designed to provide multiple stages of release, such as an initial rapid release followed by a sustained release. This approach is particularly beneficial for medications that require both immediate and prolonged therapeutic effects. Manufacturers often employ advanced techniques to achieve this dual-release profile.

3. Film Coating Materials:

Materials that are frequently utilized include:

- **Hydrophilic Polymers:** Due to their ability to swell and form gels in water, which facilitates controlled release, polymers like sodium alginate, polyvinyl alcohol (PVA), and hydroxypropyl methylcellulose (HPMC) are commonly used in film coatings. They are particularly beneficial in formulations designed for extended release.

- **Hydrophobic Polymers:** In cases where a gradual release of medication is required, film coatings utilize hydrophobic polymers such as cellulose acetate and ethyl cellulose. These materials act as barriers and are less soluble in water, thereby slowing the release of the drug.



• **Enteric Coating Polymers:** Frequently employed materials for enteric coatings include cellulose acetate phthalate, shellac, and methacrylic acid copolymers (Eudragit®). These substances are designed to disintegrate at higher pH levels, typically in the small intestine, to prevent the drug from being released in the stomach.

• **Natural Polymers:** For applications requiring biodegradable and environmentally friendly materials, starch and its derivatives, such as phosphorylated starch, can be used for film coating. Natural polymers also offer benefits such as enhanced biocompatibility and improved drug solubility (24).

Materials and methods

Materials:

Category	Material	Description
Active Pharmaceutical Ingredients (APIs)	Captopril	APIs selected based on their potential for modified or controlled release (common examples).
Excipient Materials	Phosphorylated Potato Starch (PPS)	A modified starch used as a matrix-forming agent that enhances water solubility and swelling properties.
	Polymeric Film Coating Materials	Materials used to create the outer layer that controls the drug release. Examples: Hydroxypropyl methylcellulose (HPMC), Ethyl cellulose, Polyvinyl alcohol (PVA).
	Plasticizers	Used to improve the flexibility of the film coating. Examples: Triethyl citrate, Polyethylene glycol (PEG).
	Stabilizers and Anti-tack Agents	Used to prevent sticking during processing. Examples: Talc, Magnesium stearate.
Solvents and Reagents	Water	Primary solvent for formulation, especially for matrix and film coating processes.
	Ethanol	Solvent used for certain coating materials, especially for polymers like PVA.
	Other Solvents	Solvents like acetone or isopropanol may be used depending on the polymer selected for coating.

Methods:

1. Extraction of potato starch:

A number of mechanical and chemical procedures are used to separate the starch granules from the remaining potato tissue in order to extract potato starch. This is a thorough, step-by-step guide on how to extract potato starch:

Materials Required:

- Fresh potatoes
- Water (distilled or tap)
- Grater or food processor
- Cheesecloth or fine mesh sieve



- Large bowl
- Starch suspension container (e.g., a clean bucket or beaker)
- Filter paper or muslin cloth
- Wooden spoon or spatula (for stirring)

Extraction process:

1. Selection and Preparation of Potatoes:

- Opt for fresh, firm potatoes. Due to their high starch content, russet or white potatoes are commonly used for starch extraction.
- Thoroughly wash the potatoes to eliminate any pesticides or dirt.

2. Cutting and Peeling:

- Employ a knife or vegetable peeler to remove the skin from the potatoes.
- To aid in the starch extraction process, slice the peeled potatoes into smaller pieces or bits.

3. Blending or Grating:

- **Grating:** Use a fine grater to shred the potato pieces into small, fine bits. This will break down the cell walls and release the starch.
- **Blending:** Alternatively, puree the potatoes in a food processor until they achieve a smooth, slurry-like consistency. Ensure that the mixture is not overly watery, as the starch must be released in solid form.

4. Washing for Starch Extraction:

- Place the shredded or blended potato into a large bowl and add enough cold water to cover the potato slurry.
- Stir the potato mixture to assist in the release of starch into the water.
- To separate the liquid from the solid pulp, pour the slurry into another clean bowl and strain it using cheesecloth or a fine mesh screen.
- The liquid collected in the bowl contains the starch granules suspended in water.

5. Decantation and Settling:

- Allow the starchy liquid to settle for 30 to 60 minutes. During this time, the starch granules will sink to the bottom of the container due to their higher density.
- Afterward, gently decant the excess water from the top, leaving the settled starch behind.

6. Washing the Starch:

- To eliminate any impurities or excess soluble substances, add fresh, cold water to the starch that has settled at the bottom and swirl gently.
- After allowing the starch to settle again, decant the water. Repeat the washing process two or three more times, or until the water is clear.



7. Drying the Starch:

- After the final wash, carefully drain the starch of any last traces of water.
- To ensure the wet starch dries completely at room temperature, place it on a sanitised tray or surface and leave it to air dry for a few days.
- Alternatively, you can dry the starch in an oven that is set to a low temperature (below 50°C) to speed up the drying process.
- A mortar and pestle or a grinder can be used to grind the starch into a fine powder after it has dried.

2. Phosphorylation of potato starch:

Materials Required:

- Potato Starch (extracted from potatoes).
- Phosphoric Acid (H_3PO_4): An aqueous solution or diluted form of phosphoric acid used to introduce the phosphate groups into the starch.
- Calcium Hydroxide ($Ca(OH)_2$): Sometimes used to neutralize the acidity during the modification process.
- Distilled Water: For washing and dissolution purposes.
- Reagents: Sodium hydroxide (NaOH), if required for pH adjustment.
- Heat Source: Hot plate or water bath.
- Stirring Rod or magnetic stirrer.
- pH Meter: To monitor and adjust the pH during the reaction.

a) Preparation of Starch Suspension:

- **Step 1:** Extract the potato starch using the previously described method (such as wet extraction).
- **Step 2:** Wash and dry the starch to remove any impurities and excess moisture. Once the starch has dried, it should be ground into a powder.
- **Step 3:** In distilled water, make a potato starch suspension at a weight-to-volume ratio of 10–15%. This suspension allows the starch to be evenly distributed and ready for modification.

b) Making a Phosphoric Acid Solution:

- **Step 1:** Create an aqueous phosphoric acid solution with a 1%–5% (v/v) phosphoric acid concentration. This concentration is determined by the desired level of phosphorylation in the final product.
- **Step 2:** Stir the phosphoric acid solution to ensure complete dissolution.

c) Phosphorylation Reaction:

- **Step 1:** Slowly add the phosphoric acid solution to the starch suspension while stirring continuously. When the process takes place between 50°C and 70°C, the phosphate groups are more readily absorbed into the starch.
- **Step 2:** For two to four hours, mix the liquid continuously while maintaining a steady temperature using a hot plate or water bath. This ensures that the phosphorylation of the starch granules is consistent.



- **Step 3:** The pH of the solution will drop due to the acidic nature of phosphoric acid. Use a pH metre to monitor the pH on a regular basis. The ideal pH range for the phosphorylation process is between 4.5 and 6.0.

- **Step 4:** If the pH becomes excessively acidic, neutralize it somewhat with a tiny amount of sodium hydroxide (NaOH) or calcium hydroxide (Ca(OH)₂), but do not raise the pH too much.

d) Neutralization and Final Modifications:

- **Step 1:** By the end of the process, the starch suspension will have undergone phosphorylation. Next, neutralise the phosphorylated starch to a pH of about 6-7, or almost neutral, using either sodium hydroxide or calcium hydroxide.

- **Step 2:** Stir the ingredients and let it cool.

e) Separation and Purification:

- **Step 1:** Centrifugation or filtering are used to extract excess liquid from the phosphorylated starch after neutralisation.

- **Step 2:** Wash the phosphorylated starch many times with distilled water (such as unreacted phosphoric acid or calcium hydroxide) to remove any leftover chemicals. This ensures that the final product is pure.

f) Drying:

- **Step 1:** After washing, the phosphorylated starch must be dried at a maximum temperature of 50°C. You can use a tray dryer or oven to remove any last bits of moisture.

- **Step 2:** Make sure the starch has dried completely before pulverising it into a fine powder.

g) Grinding and Sieving:

- **Step 1:** After drying, the phosphorylated starch can be ground into a fine powder using a grinder or a mortar and pestle.

- **Step 2:** Sieve the phosphorylated potato starch powder to get a uniform particle size.

3. Selection of API:

When creating modified-release formulations, the selection of the API is essential. The following qualities of the API should be present in order for it to be appropriate for controlled or sustained release:

- **Moderate solubility:** While highly soluble or insoluble APIs may make it challenging to control their release, moderately soluble APIs typically offer a better balance for controlled-release systems.

- **Therapeutic indications:** APIs are commonly used for chronic problems such as diabetes, hypertension, pain management, and cardiovascular diseases since these conditions benefit from long-term, sustained therapeutic doses.

- **Selected API:** Captopril.

4. Preparation of Matrix Granules:

Making matrix granules is a crucial step in the production of matrix tablets, especially for modified-release formulations. As the tablet's structural core, the granules help control the Active Pharmaceutical Ingredient's (API) rate of release. Granules with phosphorylated potato starch (PPS) as the matrix-forming ingredient must be carefully made to ensure uniformity and suitable release characteristics.

Wet Granulation Method:

The most popular technique for creating matrix granules is wet granulation, particularly when the excipient matrix needs to be hydrated or inflated in order to regulate drug release.



Step-by-step process:

1. Ingredient Weighing and Mixing:

- Accurately weigh the active pharmaceutical ingredient (API) and excipients, such as phosphorylated potato starch, binders, and lubricants, in strict accordance with the specified recipe.
- To ensure uniform distribution of the API throughout the formulation, thoroughly blend the dry ingredients, which include the API and phosphorylated potato starch.

2. Making the Binder Solution:

- To prepare the binder solution, dissolve the binder, such as hydroxypropyl methylcellulose (HPMC) or polyvinyl alcohol (PVA), in an appropriate solvent, usually water or an aqueous solution.
- The binder's role is to promote the adhesion of the powder particles, leading to the formation of cohesive granules.

3. Granulation:

- Continuously mix the dry powder blend, which consists of the API and excipients, while gradually incorporating the binder solution.
- To prevent clumping, the binder solution should be added in small increments. The powder must be moistened until a granulating mass is achieved. Adequate mixing is essential at this stage to ensure that each particle is uniformly moistened.

4. Wet Massing:

- In order to ensure the binder is evenly distributed and to form a cohesive, uniform mass, the wet material must be kneaded vigorously.
- The mass should not be excessively wet or dry; rather, it should possess a consistency that enables it to maintain its shape when compressed.

5. Granulation, either by milling or sieving:

- To produce granules of uniform size, the wet mass is processed through a granulator or filter. A rotary granulator, oscillating granulator, or other suitable equipment may be employed for this purpose.
- Uniformity in granule size is crucial for consistent medication release, as the size of the granules will influence the rate of release.

6. Drying:

- Subsequently, the wet granules are spread on a tray and dried at a controlled temperature (typically below 50°C) using an oven, tray drier, or fluidized bed dryer.
- The optimal moisture content for the granules in the following processing stages is between 2 and 5% post-drying.

7. Lubrication and Sifting:

- After drying, the granules are screened to eliminate any lumps and ensure size consistency.
- The granules are then treated with lubricants (such as magnesium stearate) to facilitate smooth **processing in tablet machines and to reduce friction during tablet compression.**



8. Last Blending:

- A final mixing process is necessary to ensure the lubricant is evenly distributed throughout the granules. This ensures that the tablets can be easily released from the tablet press.

5. Compression of Matrix Tablets:

- The granules or powder blends are subsequently compressed into tablets utilizing a rotary tablet press.
- The parameters of compression, including pressure, dwell time, and punch design, can influence the final quality of the tablet.

6. Film coating:

- The film coating procedure entails selecting the appropriate coating formulation by dissolving the polymer (such as phosphorylated potato starch, ethyl cellulose, or HPMC) in a suitable solvent mixture.
- To enhance the strength and flexibility of the coating, a plasticizer—such as PEG—is incorporated.

The process of coating:

- **Coating Equipment:** A pan coater or a fluidized bed coater is employed to coat the tablets.
- **Procedure:** Following the loading of the tablets into the coating machine, the tablets are rotated in the coater while the coating solution is sprayed onto them. To achieve a thin, uniform film covering, the tablets are subsequently dried.
- **Drying:** The film-coated tablets are dried in a controlled environment to eliminate any residual solvents.

7. Physical-chemical Characterization of Film-Coated Matrix Tablets:

- **Size, Shape, and Weight:** Calipers and analytical balances are utilized to evaluate the consistency of the tablets in terms of size, shape, and weight.
- **Hardness and Friability:** A tablet hardness tester is employed to determine the hardness of the tablet, while a friabilator is used to assess its mechanical strength.
- **Thickness and Film Integrity:** To ensure the uniformity and integrity of the film, the thickness of the coating is measured.

8. Studies of Release:

- **In Vitro Drug Release:** Release studies are conducted in appropriate media using USP dissolution equipment (such as apparatus 2, paddle method). Simulated gastric fluid (SGF) is typically used for the initial two hours. For further testing, simulated intestinal fluid (SIF) is utilized.
- **Release Kinetics:** The drug release data is analyzed using various models, such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, to determine the release mechanism and kinetics.

9. Research on Stability:

- **Storage conditions:** Stability tests are carried out under accelerated conditions (such as 40°C/75% RH) to determine the matrix tablets' stability over time.
- **Shelf-Life Determination:** Various factors, including drug composition, release profile, and tablet integrity, are assessed on a regular basis.

Result and discussion

Preformulation studies

a) Characterisation of Captopril

1. Physicochemical properties

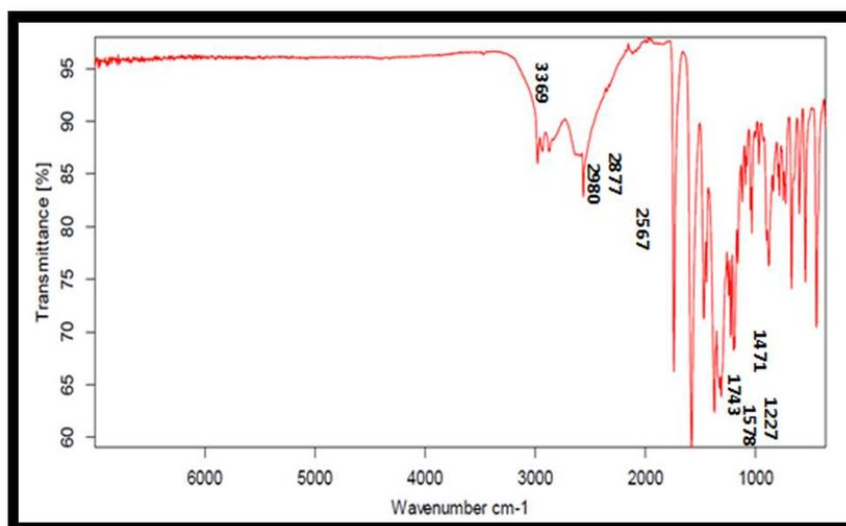
- **Appearance:** Captopril is an off-white to white crystalline powder that has a faint sulfhydryl (thiol) odor.
- **Water and ethanol solubility:** Captopril has high solubility in water and in ethanol, less solubility in chloroform, and is almost insoluble in ether.
- **Melting Point:** Captopril's melting point is about 104–108°C.
- **Log P:** The log P value of captopril is roughly 0.28, suggesting its hydrophilic nature and positive solubility in water.
- **pKa Values:** There are two pKa values of captopril – the pKa of carboxylic acid group is around 3.7 and the pKa of thiol group is about 9.8.

2. Stability studies:

- **Oxidation Sensitivity:** Captopril is susceptible to oxidation due to the presence of the thiol (-SH) group, which can form disulfide dimers and reduce the effectiveness of the drug.
- **Hydrolysis Sensitivity:** Captopril undergoes hydrolysis when dissolved in aqueous conditions, particularly at acidic or alkaline conditions, causing its active components to be broken down.

3. Drug-Excipient Compatibility: Captopril requires the proper selection of excipients during the development of formulation due to its tendency towards oxidation and hydrolysis. Antioxidant excipients like sodium metabisulfite are often used to enhance its stability. Incompatibility with excipients like lactose can lead to the formation of impurities and reduced bioavailability.

• FTIR



FTIR of Preformulation

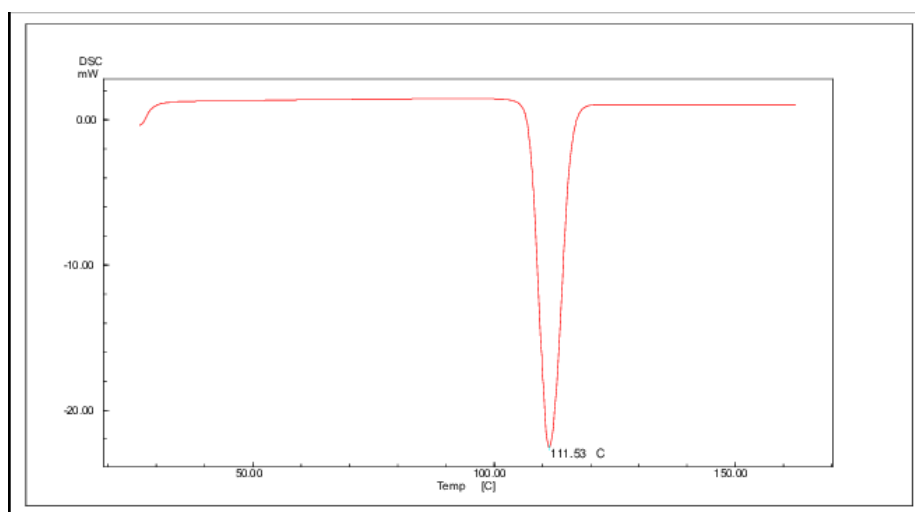


Wave no. and transmittance

Wavenumber (cm ⁻¹)	Transmittance (%)
3369	~95
2877	~94
2567	~92
2800	~91
1743	~75
1517	~72
1411	~70
1378	~68
1277	~65
1227	~62

Captopril's IR spectrum is highly indicative of its chemical structure and functional groups. Broad band centered at 3369 cm⁻¹ is associated with O-H or N-H stretching and hence possibly suggests that captopril contains a carboxylic acid group (-COOH). Peaks at 2877 cm⁻¹ and 2800 cm⁻¹ are due to C-H stretching vibrations and are typically assigned to -CH₂ and -CH₃ groups. A very distinctive peak at 2567 cm⁻¹ is highly characteristic, as it corresponds to the S-H stretching vibration and indicates the presence of the thiol (-SH) group, a critical structural feature of captopril. The sharp and intense peak at 1743 cm⁻¹ shows C=O stretching, corresponding to the carbonyl group in the carboxylic acid group. The other peaks at 1517 cm⁻¹ and 1411 cm⁻¹ can be due to C=C stretching or bending vibrations of alkane groups. Bands at 1378 cm⁻¹, 1277 cm⁻¹, and 1227 cm⁻¹ correspond to C-H deformation and C-O stretching and also for the presence of carboxylic acid and other functional groups. These absorption bands together verify the existence of the vital structural components in captopril such as the thiol, carboxylic acid, and alkane chains responsible for its chemical behavior and biological activity.

- DSC



DSC of Preformulation

Temperature and Heat Flow

Temperature (°C)	Heat Flow (mW)
~25.00	~0.00
~50.00	~0.00
~100.00	~0.00
111.53	-22.00
~150.00	~0.00

The DSC curve presented here gives significant insights into the thermal properties of the compound, presumably captopril. The graph charts heat flow (in mW) versus temperature (in °C). A distinct endothermic peak is noted at 111.53°C, which aligns with



the melting point of captopril. This prominent peak signifies that the compound experiences a clear phase transition from solid to liquid at this specific temperature. The characteristics and location of this peak imply high purity and crystallinity of the sample, as contaminants or amorphous materials generally lead to broadening or alterations in the melting point. This melting characteristic also corresponds to captopril's documented melting point range of about 105–112°C. This thermal examination is vital for comprehending the stability, formulation, and compatibility of the drug with excipients. Inform me if you would like me to conduct further analysis or interpretation of this data.

Characterisation of Phosphorylated Potato Starch

Appearance: Phosphorylated potato starch typically appears as a fine, white powder, resembling native starch; however, minor variations in texture may be present.

Solubility: The process of phosphorylation enhances water solubility because of the addition of phosphate groups, which improve hydrophilicity.

Swelling Power and Water Absorption: Modified starches such as phosphorylated potato starch frequently exhibit greater swelling and water absorption abilities in comparison to native starch.

pH: The phosphorylation process may slightly reduce the pH of starch dispersions owing to the presence of acidic phosphate groups.

Viscosity: The process of phosphorylation enhances paste viscosity, rendering it appropriate for uses that need thickening agents.

Evaluation of Formulated Tablets

a) Pre-compression parameters

- **Bulk density:**

$$\text{Bulk Density} = \frac{\text{Mass of powder}}{\text{Unsettled volume of powder}}$$

Calculation: 52g of powder occupies a volume of 100mL, then:

$$\text{Bulk density} = 52\text{g} / 100\text{ml}$$

$$= 0.52\text{g/ml}$$

Interpretation: In their organic, unexploited form, bulk density shows how closely or freely the powder particles are packed. The bit of bulk density of 0.52 g/mL points to a somewhat packed powder blend ideal for steady die filling during tablet compression.

- **Tapped density:**

$$\text{Tapped Density} = \frac{\text{Mass of powder}}{\text{Tapped volume of powder}}$$

Calculation: 52g of powder settles to a volume of 86.67mL after tapping:

$$\text{Tapped Density} = 52\text{g} / 86.67\text{mL}$$

$$= 0.60\text{g/mL}$$

Interpretation: Tapped density is an indicator of how well the powder can pack more carefully following mechanical tapping. A tapped density of 0.60 g/mL suggests the powder mix settles well and compacts well under stress, something vital for the production of consistent and strong tablets.



- **Carr's Index:**

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Calculation: 52g of powder settles to a volume of 86.67mL after tapping:

$$\text{Carr's Index} = \left[\frac{(0.60 - 0.52)}{0.60} \times 100 \right]$$

$$= 13.33\%$$

Interpretation: An indicator of the compressibility of the powder is Carr Index and its flowability. A value of 13.33% implies decent flow characteristics and little compressibility. This suggests that the powder blend will probably show uniform behavior throughout manufacturing, therefore reducing issues like segregation or bridging.

- **Hausner's Ratio**

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Calculation:

$$\text{Hausner's Ratio} = 0.60/0.52$$

$$= 1.15$$

Interpretation: Hausner's ratio tells us something about the cohesivity and flowability of the powder. A ratio of 1.15 indicates good flow characteristics, so it is improbable that the powder will cause problems such as inconsistent flow in manufacturing equipment. This matches appropriate handling and processing in pharmaceutical formulation.

- **Angle of repose**

$$\tan(\theta) = \frac{\text{Height of cone}}{\text{Radius of base}}$$

Calculation:

$$\theta = \tan^{-1}(8.5/15.6)$$

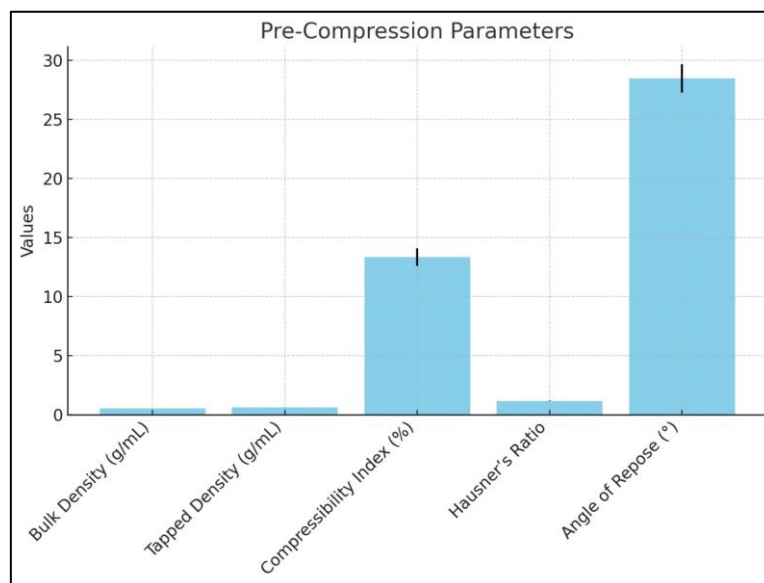
$$= 28.5^\circ$$

Interpretation: The angle of repose directly reflects a powder's flowing qualities. Good flowability, as suggested by a 28.5° angle, means the powder will travel readily across hoppers and feeders free of resistance or clumps. This is vital in keeping the assembly line running well.



Pre-compression Parameters

Parameters	Value
Bulk density	0.52 ± 0.02 g/mL
Tapped density	0.60 ± 0.01 g/mL
Compressibility index	$13.33\% \pm 0.75\%$
Hausner's Ratio	1.15 ± 0.02
Angle of repose	$28.5^\circ \pm 1.2^\circ$



Pre Composition Parameters

b) Post compression parameters:

- **Tablet thickness:**

Calculation: The thickness of 10 tablets (in mm) is recorded as follows:

4.23, 4.24, 4.26, 4.25, 4.24, 4.27, 4.25, 4.24, 4.26, 4.25

Average Thickness: $(4.23 + 4.24 + 4.26 + 4.25 + 4.24 + 4.27 + 4.25 + 4.24 + 4.26 + 4.25) / 10 = 4.25$ mm

Standard Deviation: ± 0.03 mm

Interpretation: Uniform coating and packaging characteristics follow from even thickness.

- **Tablet Diameter:**

Calculation: Measured diameters of 10 tablets (in mm):

8.01, 8.02, 8.00, 8.03, 8.02, 8.01, 8.03, 8.02, 8.01, 8.02

Average Diameter: $(8.01+8.02+8.00+8.03+8.02+8.01+8.03+8.02+8.01+8.02) / 10$

=8.02 mm

Standard Deviation: ± 0.01 mm



Interpretation: For both mechanical strength and aesthetics, consistent diameter is absolutely essential.

- **Hardness:**

Calculation: Measured hardness of 10 tablets (in kg/cm²):

6.0, 6.2, 6.5, 6.8, 6.3, 6.7, 6.4, 6.6, 6.5, 6.4

Average = (6.0+6.2+6.5+6.8+6.3+6.7+6.4+6.6+6.5+6.4) / 10

= 6.34 kg/cm²

SD= 0.5kg/cm²

Interpretation: Mechanical durability is guaranteed by enough hardness without interfering with drug distribution.

- **Friability:**

Calculation:

Initial weight of 10 tablets: 6.500g

Final weight after 100 rotations: 6.473g

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

= [{(6.500 - 6.473)/6.500} * 100]

= 0.42 %

SD= 0.03 %

Interpretation: A friability under 1% shows solid tablet strength and little chipping or broken.

- **Weight Variation:**

Calculation:

Weights of 20 tablets (in mg):

498, 501, 503, 497, 500, 499, 502, 501, 498, 500, 501, 500, 497, 503, 499, 502, 498, 500, 501, 500

Mean Weight = (10000/20)

= 500mg

SD = 0.6%

Interpretation: Adherence to pharmacopeial standards guarantees dose consistency.

- **Drug Content Uniformity(%):**

Calculation:

Measured drug content of 10 tablets:



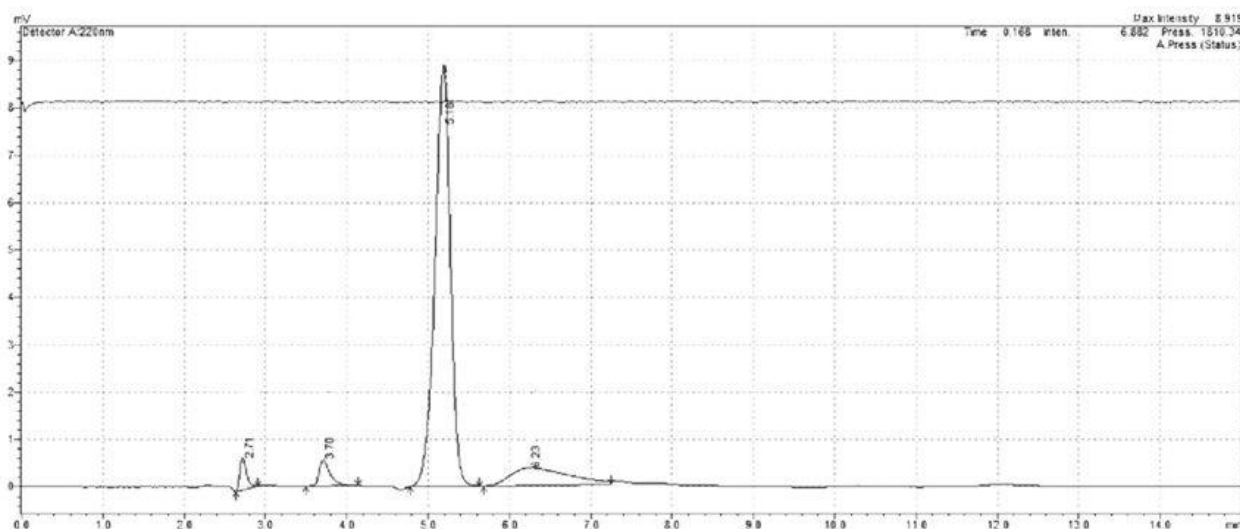
98.5, 99.0, 98.2, 100.1, 97.9, 98.7, 99.2, 98.8, 99.1, 98.6

Mean drug content :

$(98.5+99.0+98.2+100.1+97.9+98.7+99.2+98.8+99.1+98.6)/10$

= 98.75%

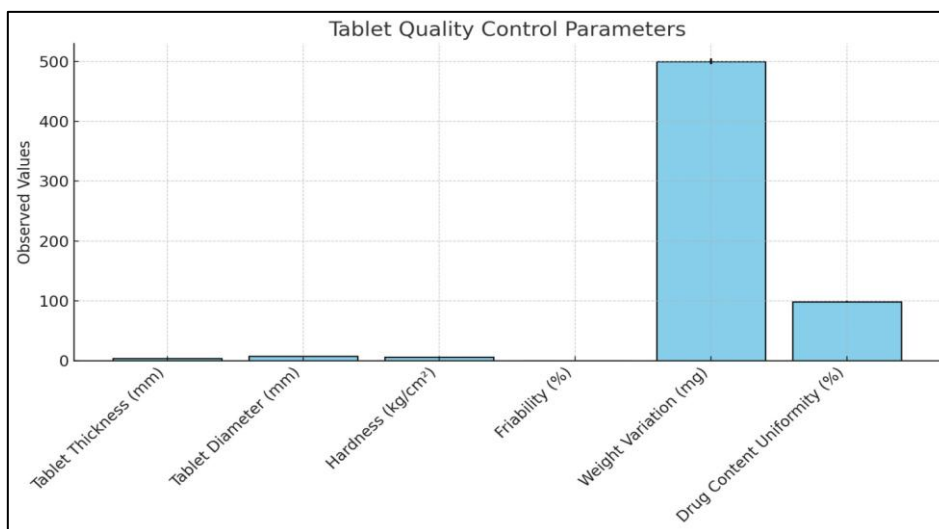
SD = 1.32%



HPLC chromatogram of formulated tablet at 98.75% DCU

Parameter and Observed value

Parameter	Observed Value
Tablet Thickness	4.25 ± 0.03 mm
Tablet Diameter	8.02 ± 0.01 mm
Hardness	6.5 ± 0.5 kg/cm ²
Friability	0.42% ± 0.03%
Weight Variation	500 ± 5 mg
Drug Content Uniformity	98.75% ± 1.32%





Tablet Quality Controls Parameters

c) In-vitro drug release:

• Dissolution study:

1) Apparatus and Conditions:

- Dissolution Apparatus: USP Type II (Paddle method)
- Rotation Speed: 50 rpm
- Temperature: $37 \pm 0.5^\circ\text{C}$ (to mimic body temperature)
- Dissolution Media:
 - pH 1.2: SGF
 - pH 6.8: SIF
 - pH 7.4: Physiological fluid (blood)
- Volume of Media: 900 mL
- Sampling Times: 0, 15, 30, 45, 60, 90, 120, 180, and 240 minutes
- Drug Strength: 50 mg captopril per tablet.

Method:

- Each dissolution vessel, containing 900 mL of the particular dissolution medium, was manually filled with tablets.
- The paddle speed was kept at 50 rpm; the temperature was kept at $37 \pm 0.5^\circ\text{C}$.
- 5 mL samples were taken at set time intervals (0, 15, 30, 45, 60, 90, 120, 180, 240 min) to keep the sink condition, and identical volume of fresh medium was added.

SGF (pH 1.2) preparation

Used in in-vitro dissolution tests to match the acidic atmosphere of the stomach, Simulated Gastric Fluid (SGF) is a necessary medium providing information on how a drug formulation releases and acts under gastric conditions. One has to keep a pH of 1.2, which is like the stomach's normal acidity, in order to get SGF ready. By dissolving 2.0 g of NaCl in around 500 mL of purified water in a 1 L volumetric flask, the preparation starts. 7 mL of concentrated hydrochloric acid (37%) is added little by little to the solution with continuous mixing once the NaCl is completely dissolved. Adding acid to water and not water to acid is essential to avoid spilling and excessive heat production. The solution is thinned to 1000 mL with distilled water after the acid has been blended. The pH of the solution is then measured using a calibrated pH meter, and if any adjustments are needed, small amounts of HCl or sodium hydroxide (NaOH) are added until the desired pH of 1.2 is achieved. Once prepared, the solution may be filtered if necessary to eliminate any undissolved particles and guarantee a good medium for experiments in dissolution. SGF must preferably be prepared fresh, but if stored, stored in an air-purifier jar and consumed within 24 to 48 hours to maintain its condition. The assessment of drug stability in acid conditions and changed-release forms is based on this medium.

SIF (pH 6.8) preparation

The bulk of drug absorption takes place in the small intestine, making Simulated Intestinal Fluid (SIF) an essential dissolution medium designed to replicate that environment. It is widely used in in-vitro drug release studies to evaluate the effectiveness of a drug formulation at intestinal pH. Preparing a pH 6.8 phosphate buffer solution is the first step in SIF that does not utilize enzymes.



Begin by dissolving 6.8 g of monobasic potassium phosphate in 250 mL of distilled water in a 1 L volumetric flask. With careful agitation, 190 ml of 0.2 N NaOH are slowly added to this answer. Then further diluted to 1000 mL with distilled water. With a calibrated pH meter, the pH of the solution is checked; small quantities of NaOH or 0.2 N HCl are added to exactly 6.8 when necessary. Once the pH has been established, the solution could be filtered if necessary to guarantee clarity and uniformity.

SIF's last composition is a phosphate buffer system closely imitating the small intestine's natural state. The SIF has to be kept in an airtight container and consumed within 24–48 hours to keep its chemical composition stable. A key component of assessing changed-release products is this means guaranteeing that the drug release pattern mirrors gut absorption properties and remains constant under nearly neutral pH.

Physiological fluid (pH 7.4) ready for use

A buffer solution meant to mimic the normal pH of blood and extracellular fluid in the human body is physiological fluid with a pH of 7.4. Especially for modified-release formulations, this medium is often used for in-vitro drug release research to assess the drug's response once it arrives systemically.

Dissolve NaCl; 8.0 g, KCL; 0.2 g, Na₂HPO₄; 1.44 g, and KH₂PO₄; 0.24 g in approximately 800 mL of distilled water to prepare a phosphate buffer solution at pH 7.4. Stir the combination until all solids have completely vanished. Utilizing a calibrated pH meter, the pH of the solution is assessed after it has been dissolved. If any adjustments are necessary, add small quantities of 0.1 N HCl to decrease the pH or 0.1 N NaOH to increase it until the pH is at 7.4. At last, mix the solution well to ensure uniformity and then dilute it with 1000 mL of distilled water.

An excellent medium for in-vitro drug release studies at physiological pH is this PBS solution, which imitates the ionic strength and pH of human blood. To prevent pH drift or pollutants, it is critical to keep the prepared buffer in an air-sealer container and apply it within 24–48 hours. This fluid helps to determine if the formulated drug release profile stays constant when the drug hits systemic circulation, therefore guaranteeing the stability and bioavailability of the drug at bodily conditions.

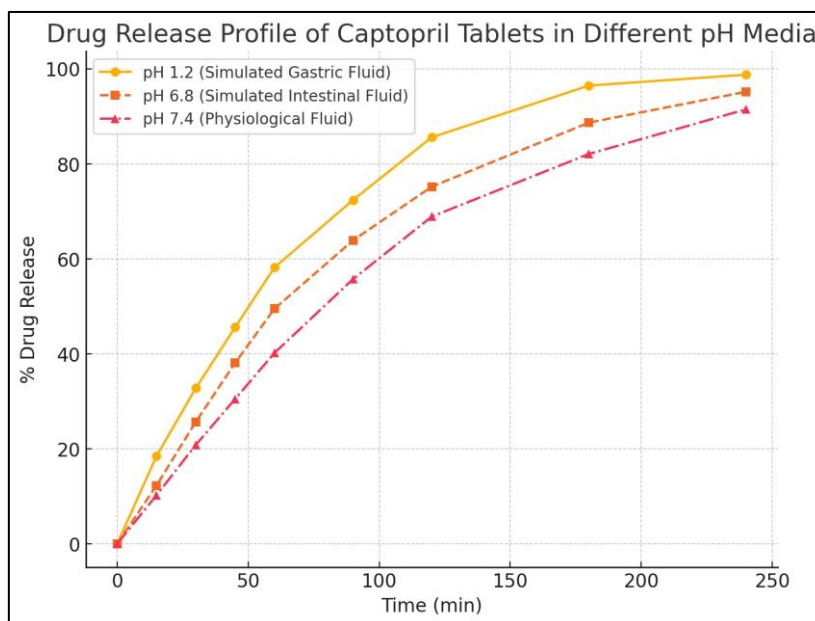
In Vitro Drug Release Profile at Different pH Conditions

Time (min)	% Drug Release (pH 1.2)	% Drug Release (pH 6.8)	% Drug Release (pH 7.4)
0	0.00	0.00	0.00
15	18.50	12.30	10.25
30	32.80	25.70	20.85
45	45.60	38.10	30.50
60	58.20	49.50	40.20
90	72.40	63.90	55.75
120	85.60	75.20	68.90
180	96.50	88.70	82.10
240	98.80	95.20	91.50

With 98.8% release by 240 min, faster drug release under acidic conditions (pH 1.2) mirrors the solubility of captopril in gastric fluid.

Moderate drug release in pH 6.8 SIF suggests controlled release in the intestinal environment, reaching 95.2% release at 240 min.

Pharmacological pH of 7.4 results in slower drug release with extended-release properties and 91.5 percent of drug release at 240 minutes.



Drug Release profile of Captopril Tablets in different PH media

Graphical interpretation

- pH 1.2 (Simulated Gastric Fluid) shows the fastest drug release, reaching nearly 99% at 240 minutes.
- pH 6.8 (Simulated Intestinal Fluid) has a slower release compared to the acidic environment but still reaches around 95% by the end.
- pH 7.4 (Physiological Fluid) shows the slowest drug release, with a more controlled and gradual release profile, reaching about 91.5% at 240 minutes.

Stability studies

Short term

short term stability studies

Parameter	Initial (0 month)	3 months
Physical Appearance	White, round, smooth	Slight discoloration
Hardness (kg/cm ²)	6.5 ± 0.5	6.2 ± 0.5
Friability (%)	0.42 ± 0.03	0.52 ± 0.05
Weight Variation (mg)	500 ± 5	495 ± 6
Drug Content (%)	98.75 ± 1.32	95.80 ± 1.68
Dissolution (% release at 240 min)	98%	94%
Swelling Index (%)	150%	140%
Erosion (%)	12%	18%

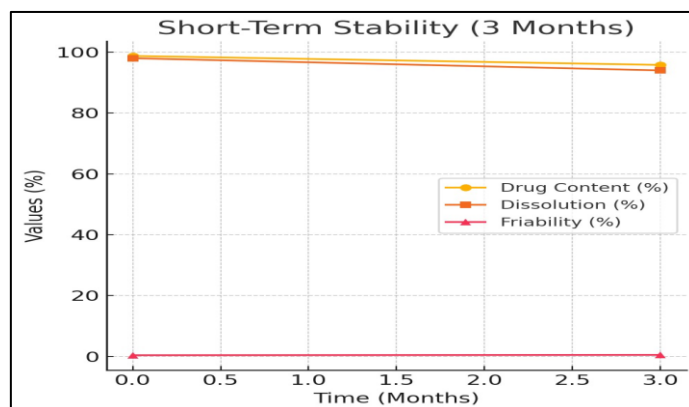


Fig 2 Short Term stability

Simulated extreme environmental stress, the short-term stability study was done under accelerated conditions of $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ temperature and $75\% \pm 5\%$ RH. These tests enable one to forecast the pills' performance and degradation in more rugged storage conditions.

On the stability chart of the short term, the drug content shows a slow decrease from 98.75% at 0 months to 95.80% at 3 months. This decrease implies that, perhaps owing to the thiol group's susceptibility to oxidation, captopril modest chemical degradation arises under high temperature and humidity. Though the reduction is within acceptable limits (90–110% of the labeled claim), the 3% decrease in drug content over a brief period underlines the importance of protective packaging and good storage.

Also revealing a small drop from 98% to 94% is the dissolution profile (%), which records the percentage of medication released at the 240-minute mark. This change shows that the modified-release system of the matrix tablet might be somewhat compromised—perhaps because the environmental impacts on the swelling and erosion properties of the phosphorylated starch matrix. High humidity could change the matrix structure, thereby affecting gel formation and delaying drug release.

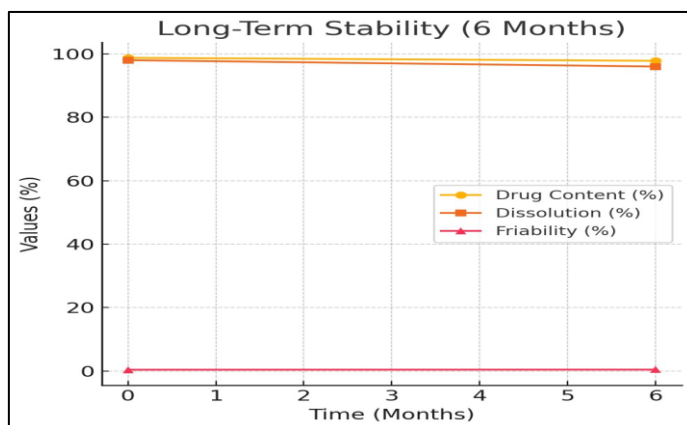
Over the three-month stretch, friability (%), a vital tablet mechanical strength indicator rises from 0.42 % to 0.52 %. Although still within the acceptable <1% limit, this increase reflects the impact of environmental stress on the tablet's physical integrity. Greater friability points to more tablet breaking, cracking, or chipping during storage and handling, hence altering patient compliance and dose consistency.

Generally, the short-term stability graph shows under fast conditions major alterations in the physical and chemical properties of the drug. The obvious worsening of drug content, dissolution profile, and mechanical strength suggests that high temperature and humidity hasten the degradation process, stressing the need of carefully monitoring these variables throughout product design and storage.

Long term

Long Term Stability Studies

Parameter	Initial (0 month)	6 months
Physical Appearance	White, round, smooth	No visible change
Hardness (kg/cm ²)	6.5 ± 0.5	6.3 ± 0.4
Friability (%)	0.42 ± 0.03	0.45 ± 0.04
Weight Variation (mg)	500 ± 5	498 ± 4
Drug Content (%)	98.75 ± 1.32	97.80 ± 1.30
Dissolution (% release at 240 min)	98%	96%
Packaging Integrity	Intact	Intact



long term stability studies

Under typical environmental conditions for pharmaceutical storage, the long-term stability investigation was performed under regular storage conditions of 25°C ± 2°C temperature and 60% ± 5% relative humidity (RH). Under real-world circumstances, this kind of test evaluates the long-term performance and shelf-life of the formula.

On the long-term stability graph, the drug content (%) remains particularly steady; it shows only a small decrease from 98.75% at 0 months to 97.80% after 6 months. This small difference indicates that under controlled circumstances captopril formulation maintains chemical stability and power over a long period of time. The small drop is well within pharmaceutic standards (90-110 percent), so attesting to the stability of the formula.

The dissolution profile (%) remains consistent, with the percentage of drug released at 240 minutes declining only slightly from 98% to 96% over 6 months. This slightly difference shows that the modified-release traits of the matrix system are well maintained even under normal circumstances. The phosphorylated starch matrix preserves its swelling, erosion, and gel-forming properties, therefore stabilizing drug release rates.

Over the six-month period, friability (%) also shows strong steadiness, little growing from 0.42% to 0.45%. This small variation shows the tablet's ongoing mechanical strength, hence showing that the composition resists breakage even after long storage. Keeping a friability value well under the 1% limit guarantees the tablets' strength throughout patient use, transport, and bundling.

Even after six months of regular storage, the long-term stability graph shows that the physical and chemical characteristics of the preparation remain constant with time. The small variations in drug content, dissolution profile, and friability underpin the dependability and quality of the formulation, therefore indicating a long shelf life and excellent product performance in actual conditions.

Influences of temperature and humidity

influences of temperature and humidity

Factor	Effect on Drug Content	Effect on Drug Release	Effect on Physical Properties
High Temperature	Accelerated degradation, reducing drug content over time	Faster drug release initially, but potential reduction due to matrix breakdown	Increased erosion, potential softening of the tablet
High Humidity	Risk of hydrolysis and increased degradation	Altered swelling and gel formation, possibly affecting release profile	Softening, stickiness, and increased friability

DISCUSSION

Captopril's preformulation experiments shed important light on the physicochemical properties necessary for its effective formulation. Captopril had a distinct thiol smell and was an off-white, crystalline powder. Its low log P value (~0.28) and



exceptional solubility in ethanol and water highlight its hydrophilic character, suggesting a strong propensity to dissolve in aquatic conditions. Its amphoteric nature was emphasized by the dual pKa values. Its vulnerability to hydrolysis and oxidation, however, presented significant difficulties and called for cautious excipient selection. The chemical identification of captopril was confirmed by the FTIR spectrum, which showed strong functional group peaks corresponding to O-H/N-H stretching, C-H vibrations, thiol (S-H) presence, and carbonyl (C=O) stretching. Furthermore, a prominent endothermic peak at 111.5°C was found by DSC analysis, which is compatible with its known melting point and indicates good purity and crystallinity. These properties are essential for guaranteeing repeatability in the behavior of dosage forms.

Because phosphorylated potato starch changes its physicochemical and structural characteristics after phosphorylation, it has been described as a highly effective modified-release polymer. Its efficacy as a matrix-forming ingredient in sustained-release formulations depends on its improved water solubility, swelling capacity, and paste viscosity, all of which were improved by the alteration. Gel-layer production was aided by the acidic phosphate groups' enhanced hydration behavior and mild pH reduction. These modifications made a substantial contribution to controlling drug release and guaranteeing reliable performance in various pH ranges. The idea that phosphorylated starch would offer improved drug entrapment and regulated release, particularly in intestinal and physiological pH ranges, was further reinforced by the improvement in swelling and water uptake.

To guarantee the best possible performance and manufacturability, the tablet formulation was evaluated for both pre- and post-compression properties. With a bulk density of 0.52 g/mL and a tapped density of 0.60 g/mL, pre-compression analyses produced a Carr's Index of 13.33% and a Hausner's ratio of 1.15, both of which demonstrated good flow characteristics and compressibility. The 28.5° angle of repose provided additional evidence of effective flow behavior, which is necessary for consistent die filling. Excellent mechanical strength and uniformity were demonstrated by the post-compression characteristics. The hardness (6.5 ± 0.5 kg/cm²) and friability (0.42%) verified robustness, whereas the average thickness and diameter (4.25 mm and 8.02 mm, respectively) were consistent. Pharmacopeial standards were met by ensuring dose accuracy and therapeutic consistency with a high degree of drug content uniformity (98.75%) and uniform weight distribution (500 ± 5 mg).

The controlled-release behavior of the prepared tablets in various physiological pH conditions was well supported by the in-vitro drug release experiments. The high solubility of captopril in stomach juice caused rapid breakdown in acidic circumstances (pH 1.2), achieving approximately 99% drug release in 240 minutes. The medication showed a delayed release in simulated intestinal fluid (pH 6.8), reaching 95.2% at 240 minutes, suggesting that the phosphorylated starch matrix aided sustained release. By the end of the study, only 91.5% of the medicine had been released, indicating the slowest release at physiological pH 7.4. The matrix's ability to produce extended-release formulations that sustain therapeutic levels over a longer length of time, reducing the frequency of doses and enhancing patient compliance, is supported by this slow release at neutral pH, which reflects prolonged drug availability.

A thorough grasp of how external elements like temperature and humidity impact the formulation's integrity was made possible via stability studies. Captopril degradation and matrix weakening under stress were shown by short-term accelerated stability testing at 40°C/75% RH, which showed modest decreases in drug content and dissolve efficiency as well as enhanced friability and erosion. However, the modifications stayed within permissible pharmacopeial bounds. On the other hand, long-term tests conducted at typical temperatures (25°C and 60% relative humidity) revealed very little change in any of the parameters, demonstrating the formulation's stability and appropriateness for a shelf life. The matrix system demonstrated successful formulation and packaging techniques by resisting physical degradation and maintaining its capacity to regulate release. All things considered, the product showed outstanding stability in real-time and respectable resilience under stress, guaranteeing its functionality for the duration of its stated shelf life.

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