Pulsatile release drug delivery system based on compression-coated tablets

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To my beloved wife (Nishu), lovely son (Nuayman), and whole family.

Acknowledgements

The Declaration of Independence

Herewith I certify that I have prepared and written my thesis independently and that I have not used any sources and aids other than those indicated by me.

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1 Introduction

1.1 Modified release dosage forms

Modified release (MR) dosage forms are pharmaceutical formulations designed to control the release of active ingredients over an extended period of time. The objective of MR dosage forms is to provide a controlled release of a drug and can offer several advantages over immediate-release dosage forms, which release the drug rapidly after administration [1]. Some of the objectives and advantages of modified-release dosage forms include:

Prolonged therapeutic effect: MR formulations can maintain drug concentrations within the therapeutic range for a longer duration, ensuring a sustained therapeutic effect. This is particularly beneficial for drugs with a short half-life or those requiring continuous therapy.

Improved patient compliance: By reducing the frequency of dosing, MR dosage forms can simplify the medication regimen and enhance patient compliance. Patients may find it easier to follow a treatment plan that involves taking medication less frequently, which can lead to better outcomes.

Reduced fluctuations in drug concentration: Immediate-release dosage forms can cause rapid fluctuations in drug levels, leading to peaks and troughs in plasma concentration. MR formulations help smooth out these fluctuations, providing more consistent drug levels and minimizing potential side effects associated with rapid changes in drug concentration.

Minimized side effects: Controlled release of the drug can help minimize side effects by reducing peak plasma concentrations and maintaining drug levels within a narrower therapeutic window. This can improve tolerability and reduce the occurrence of adverse reactions.

Enhanced bioavailability and absorption: MR dosage forms can be designed to optimize drug absorption by controlling the release rate. This can improve bioavailability, reduce variability in drug absorption between individuals, and potentially increase overall efficacy.

Reduced dosing frequency and improved convenience: With MR dosage forms, the dosing frequency can often be reduced, requiring fewer administrations per day. This can enhance patient convenience and quality of life, especially for chronic conditions requiring long-term medication.

MR dosage forms include extended release and delayed release, with the latter being either time-dependent or site specific (Fig. 1). An extended release dosage form intends to make the drug available over a prolonged period after ingestion, which leads to a reduction in dosing frequency compared to a drug presented in a conventional dosage form [1]. A delayed release dosage forms are characterized by releasing the active substances at a time other than immediately. This type of drug delivery system not only includes enteric release but also colonic release, where the drug release is delayed until it has passed through the stomach and the drug is delivered in the colonic region on the GI tract [1, 2].
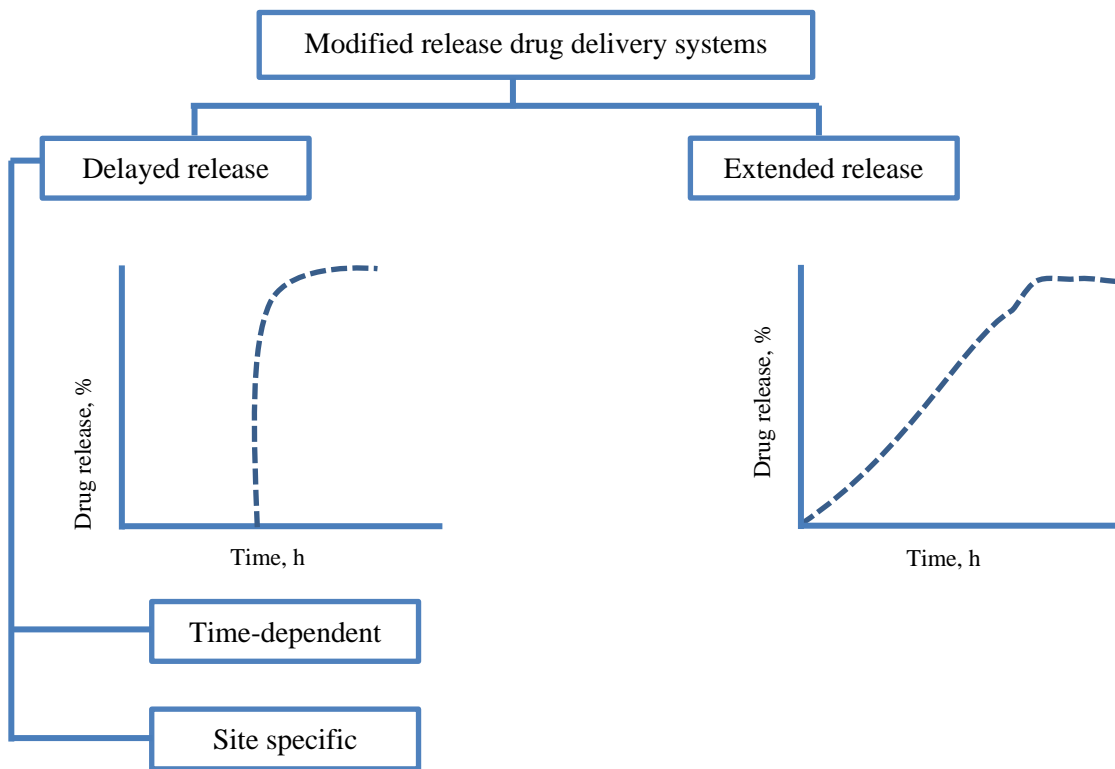
Fig. 1 Modified release drug delivery systems.

1.1.1 Time-dependent drug delivery system

Time-dependent dosage forms are specifically designed to release the drug after a predetermined lag time, providing controlled drug delivery. These dosage forms aim to achieve drug release that is independent of various environmental factors, such as pH, enzymatic activity, and intestinal motility, ensuring consistent performance across different physiological conditions [3]. In this strategy, oral dosage forms are designed to remain intact during their residence in the stomach, as gastric residence time can vary widely and is often unpredictable. Upon entering the duodenum, the dosage form enters a lag phase, during which the drug is not released significantly. It is during this lag phase that the dosage form progresses through the gastrointestinal tract until it reaches the lower intestine, where drug delivery is intended to take place. To establish the desired lag time, an outer coating is applied to the delivery system. This outer coating can consist of plugs or layers designed to seal the drug-containing capsule bodies or coat the inner drug reservoir. This approach ensures a consistent lag phase for time-based colon drug delivery. A study by Gazzaniga et al. in 2006 proposed the use of such plugs or coatings to achieve the desired lag time and ensure reliable drug release in the colon.

Time-dependent drug delivery holds great promise for the treatment of colonic diseases, offering several advantages over conventional drug delivery approaches. One of the key benefits is its ability to provide targeted treatment directly at the site of the disease, resulting in lower dosing requirements and reduced systemic side effects [4]. In addition to localized treatment, time-dependent drug delivery systems offer the potential to improve the bioavailability of poorly water-soluble drugs. The prolonged retention time and high surface area of the colon provide favorable conditions for enhanced absorption of these drugs [5]. The colon is characterized by lower pancreatic activity and a significant amount of lymphoid tissue, which facilitates direct absorption of drugs into the bloodstream. The reduced proteolytic activity and decreased fluid motility in the colon further contribute to improved drug absorption [6]. Moreover, time-dependent drug delivery systems hold promise for the delivery of therapeutic peptides and proteins. The presence of absorption enhancers in these systems can help achieve sufficient concentrations of these biomolecules at the epithelial absorptive layer, thereby enhancing their absorption and targeting [6]. This opens new possibilities for the systemic delivery of peptides and proteins, which are traditionally challenging to administer through conventional oral routes.

The gastrointestinal tract (GIT) is a complex system consisting of various organs with distinct properties that need to be taken into account when designing drug delivery systems targeting the lower intestine (Fig. 1) [7]. The proximal or ascending colon is generally considered the optimal site for drug delivery in the colon [10]. The human large intestine, measuring approximately 1.5 meters in length, is divided into different regions, including the ascending, transverse, and descending colon, as well as the rectum [7]. Each region of the colon exhibits unique physiological characteristics, and the properties of the colonic contents can vary across these regions. This variability in the composition and movement of food and dosage forms within the colon poses challenges in the development of effective colon drug delivery systems [8]. Factors such as pH, transit time, motility, and enzymatic activity can vary along the length of the colon, influencing the behavior and release of drugs within this region [8]. To overcome these challenges, extensive research has been conducted to understand the intricate dynamics of the gastrointestinal tract and to develop drug delivery systems that can navigate these complexities. Various approaches, such as time-dependent release systems, pH-dependent systems, and microbial-triggered systems, have been explored to achieve targeted drug delivery to the colon [7]. These systems aim to overcome the physiological barriers of the gastrointestinal tract and ensure the site-specific release of drugs in the colon.

The gastrointestinal tract (GIT) comprises the oral cavity, esophagus, stomach, small intestine, and colon. Each of these organs presents heterogeneous properties that must be considered in the design of delivery systems intended to deliver drugs in the colon (Fig. 2) [7]. The optimal site for delivery in the colon is considered to be the proximal or ascending colon [9]. The human large intestine is approximately 1.5 m long and is divided into colon (ascending, transverse and descending) and in a small distal part called rectum. The physiological properties of the colonic contents can differ in each region of colon. Moreover, there is variability in movement of food and dosage forms across the colon, which can be a challenge in the development of colon drug delivery system [8].
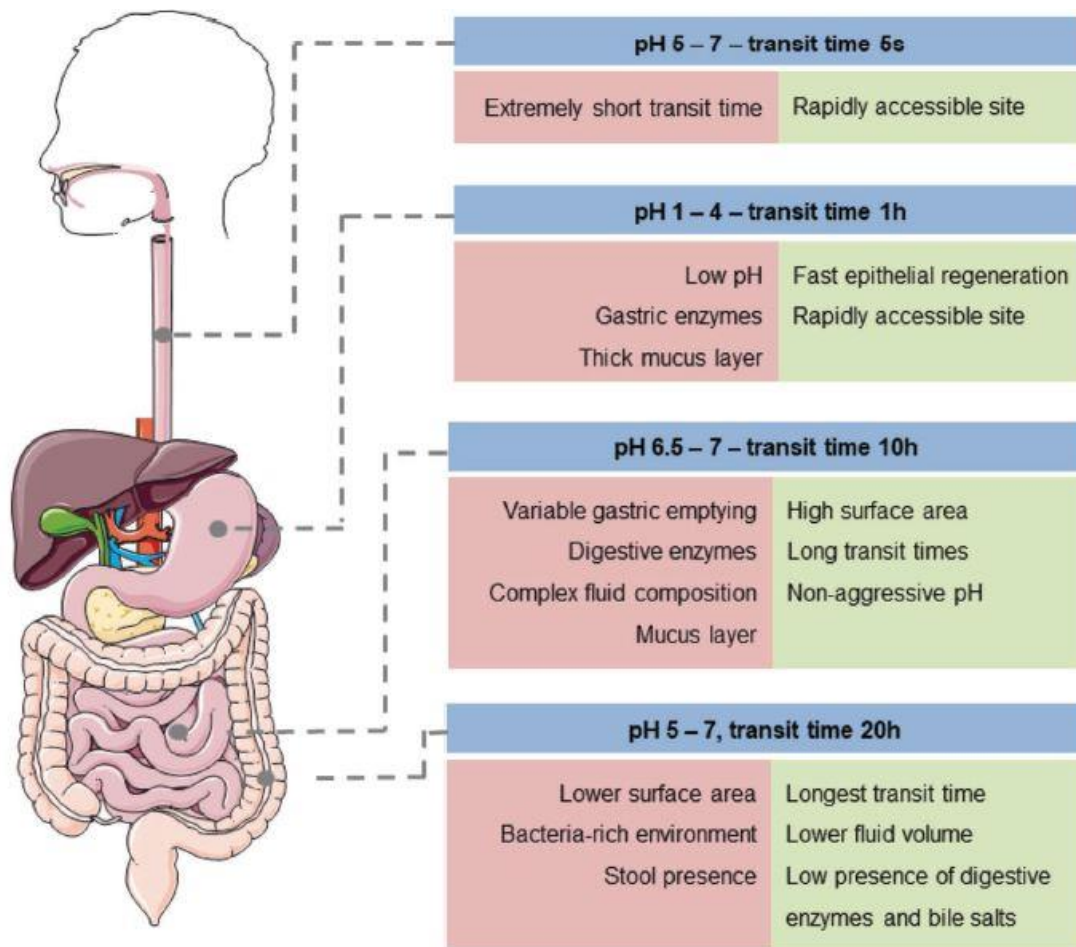
Fig. 2 Schematic representation of GIT sections and their pH, transit time and relevant parameters for drug delivery [7].

Gastric emptying and transit time are crucial factors that significantly impact the performance of colon drug delivery systems. Under normal physiological conditions, gastric emptying occurs within approximately 2 h, while the arrival of dosage forms in the colon takes place around 5 h [10]. However, it is important to note that these timings can vary depending on individual factors and pathological conditions. Certain pathological conditions, such as diarrhea, constipation, ulcerative colitis (UC), and Crohn's disease (CD), can greatly influence gastric emptying and transit time. For instance, patients with diarrhea often experience a shortened transit time, meaning that the passage of food and dosage forms through the gastrointestinal tract is accelerated. Conversely, patients with constipation tend to have prolonged transit time, leading to delayed

arrival of dosage forms in the colon. These variations in transit time can significantly affect the release and performance of colon drug delivery systems in individuals with these conditions. It is worth mentioning that gastrointestinal transit time is also influenced by other factors, including dietary habits, physical mobility, and stress levels. Diet composition, such as high-fiber or low-residue diets, can impact the motility of the gastrointestinal tract and alter the transit time of dosage forms. Physical mobility, exercise, and stress levels can also affect the movement of food and dosage forms through the gastrointestinal tract, potentially altering the timing of drug release and targeting within the colon [11].

In addition to its physiological properties and transit time, the colon is also home to a diverse population of aerobic and anaerobic microorganisms. These microorganisms play a vital role in maintaining the overall gastrointestinal (GI) physiology and contribute to the development of the intestinal immune system. They are involved in the breakdown of indigestible food components, providing benefits to the host [10]. However, certain factors, such as drug intake (especially antibiotics and laxatives) and dietary choices, can significantly impact the composition of the microbiota and enzyme secretion in the colon. Alterations in the microbiome composition caused by drug intake and dietary changes can have implications for colon drug delivery systems. Some therapeutics rely on enzymatic degradation by colonic bacteria to release the active substances. Therefore, changes in the microbiota can potentially affect the release and efficacy of these therapeutics [12]. Colon drug delivery systems are designed as delayed release dosage forms, specifically targeting the large intestine. They offer the ability to modulate the apparent absorption of the drug substance by altering its release profile. Moreover, these systems provide the flexibility to vary the site of drug release within the colon, allowing for specific clinical objectives that cannot be achieved with conventional or immediate release dosage forms [1].

Time-dependent drug delivery systems can be categorized into single-unit and multiple-unit systems, each utilizing different coating techniques (Fig. 3) [13]. In the single-unit category, there are two subtypes: capsular-based and tablet-based systems. The single-unit systems involve coating the dosage form with either an erodible or soluble polymer, or a polymer coating that can rupture. On the other hand, multiple-unit systems offer precise control over drug release timing but require more complex and costly manufacturing methods. These systems are created by coating multi-particulates with pH-dependent barrier membranes. In addition, pulsatile release can be achieved by modifying the membrane permeability or by coating the unit with a soluble, erodible, or

rupturable membrane [14]. Different pulsatile drug delivery systems have appeared on the markets that replaced modified-release dosage forms. Various examples of currently marketed chronotherapeutic dosage forms, the manufacturing techniques, drug release mechanism compiled in Table 1 [14] .

Table 1 List of the chronopharmaceutical dosage forms marketed and the pulsatile drug delivery technologies used [14].

Registered trademark®	Drug	Chronopharmaceutical technology®	Drug release mechanism
Aciphex	Rabeprazole sodium	Enteric coating technology	Delayed release
Cardizem LA	Dilitiazem HCl	CEFORM microsphere technology	Diffusion/erosion
Cardura XL	Doxazosin mesylate	OROS technology	Osmotic regulation
Coreg CR	Carvedilol phosphate	Micropump platform	Immediate-release/ controlled-release
Coruno	Molsidomine	Geomatrix technology	Swelling, gelling, erosion
Covera-HS	Verapamil HCl	OROS technology	Osmotic regulation
Cystrin CR	Oxybutynin HCl	TIMERx technology	Swelling, gelling, erosion
DEXILANT	Dexlansoprazole	DDR technology	Dual drug release
Diamicron MR	Gliclazide	Hydrophilic matrix technology	Swelling, diffusion, erosion
Ditropan XL	Oxybutynin HCl	OROS technology	Osmotic regulation
Glucotrol XL	Glipizide	OROS technology	Osmotic regulation
Glumetza	Metformin HCl	AcuForm technology	Gastric retention delivery system-swelling/erosion
Innopran XL	Propranolol HCl	DIFFUCAPS technology	Controlled release/delayed release
Invega	Paliperidone	OROS technology	Osmotic regulation
Lodotra	Prednisone	GeoClock (Geomatrix) technology	Delayed-release/ immediate-release
Madopar DR	Levodopa/ Benserazide HCl	Geomatrix technology	Dual release
Moxatag	Amoxicillin	PULSYS technology	One immediate-release/ two delayed-release
Oleptro ER	Trazodone HCl	CONTRAMID technology	Diffusion/ rupture
Opana ER	Oxymorphone HCl	TIMERx technology	Swelling, gelling, erosion
Paxil CR	Paroxetine HCl	Geomatrix technology	Swelling, gelling, erosion
Procardia XL	Nifedipine	OROS technology	Osmotic regulation
Proquin XR	Ciprofloxacin HCl	AcuForm technology	Gastric retention delivery system-swelling/erosion
Ritalin LA	Methylphenidate HCl	SODAS technology	Bimodal release

Sanctura XR	Trospium chloride	Pellet coating technology	Controlled release
Seroquel XR	Quetiapine fumarate	Hydrophilic matrix technology	Diffusion, erosion
Sular ER	Nisoldipine	Geomatrix technology	Swelling, gelling, erosion
Uniphyl	Theophylline	CONTIN delivery system	Slow release

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                    ┌─────────────────────────────────────┐
                    │ Coating for time-controlled release  │
                    │              system                  │
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 │ Rupturable coating│ │Swellable/erodible    │ │ Permeable coating│
 │                   │ │    coating           │ │                  │
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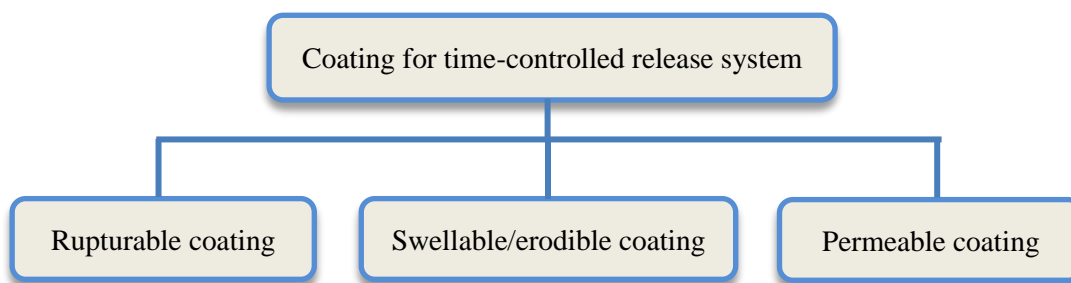
Fig. 3 Schematic presentation of time-controlled release technologies according to relevant formulation strategies.

1.1.1.1 Delivery system with rupturable coating

Pulsatile drug delivery systems, both in single-unit and multi-unit forms, have been developed to achieve specific release profiles. In these systems, drug-containing cores are coated with an outer layer that controls the release of the drug. Upon contact with water, the outer coat allows water penetration, leading to the swelling and expansion of the inner core. This expansion generates outward pressure, eventually causing the rupture of the coating (either partially or completely) (Fig. 4). Once the coating is ruptured, the drug is rapidly released from the inner core [15, 16]. The swelling and expansion of the inner core play a crucial role in breaking the outer coat, and this can be achieved by incorporating superdisintegrants or osmotic agents in the core formulation. The release kinetics are primarily influenced by the composition of both the coat and the core [15]. Various systems utilizing hard or soft gelatin capsules [17] and tablets [18, 19] have been described in recent literature. Researchers have also conducted extensive investigations into the mechanical properties of the coat and the swelling behavior of the core to better understand the pulsatile release mechanism [20].

Rupturable coatings play a crucial role in pulsatile drug delivery systems by providing a controlled and time-dependent release of drugs. These specialized coatings are designed to maintain the integrity of the dosage form until a specific lag time is reached, after which they undergo rupture or breakage, resulting in the immediate release of the drug [14, 21].

Moreover, a combination of swelling and osmotic effect was applied in the system developed by Amidon and Leesman, 1993 [22]. The system consisted of a core containing drug (propranolol HCl), osmotic (NaCl and lactose) and swelling (AcDiSol and NaCMC). The cores were coated with an insoluble, semipermeable polymer, such as cellulose acetate. The model was assuming that cores (tablets or pellets) are spherical with a displaceable volume (Vd). Water diffuses into the core due to an osmotic pressure gradient displaces volume (Vd) and then exerts a pressure on the coating. When the critical pressure is reached, the coating film break and release the drug. The model described that, for a very brittle coat with a very low critical strain (<1%), the coat will break when:

$Tp = Vd/A. \ \alpha. \ Lp. \ \Delta\pi$

Where *Tp* represent the time until film rupture (lag time), *Vd* is the displaceable volume inside the core, *A* is the surface area of the film, *α* constant, *Lp* is the water permeability of the film, and *Δπ* is the osmotic pressure difference across the film.

The author highlighted that core osmotic pressure is the primary mechanism in rupturing the coat. However, this mechanism may not directly apply to compression-coated tablets due to different rupturing mechanisms involved. In the case of compression-coated tablets, water penetration into the core leads to localized swelling at weak points instead of uniform distribution throughout the core. This localized swelling exerts pressure specifically towards the coat, resulting in its rupture and facilitating pulsatile drug release.

It is important to note that the model described has a limitation in terms of not considering drug solubility and loading. These factors can significantly influence the drug release behavior and should be considered in the development of a comprehensive model. Nevertheless, the described model can serve as a useful guide for further refinement and development of more advanced models that incorporate drug solubility and dosage considerations.
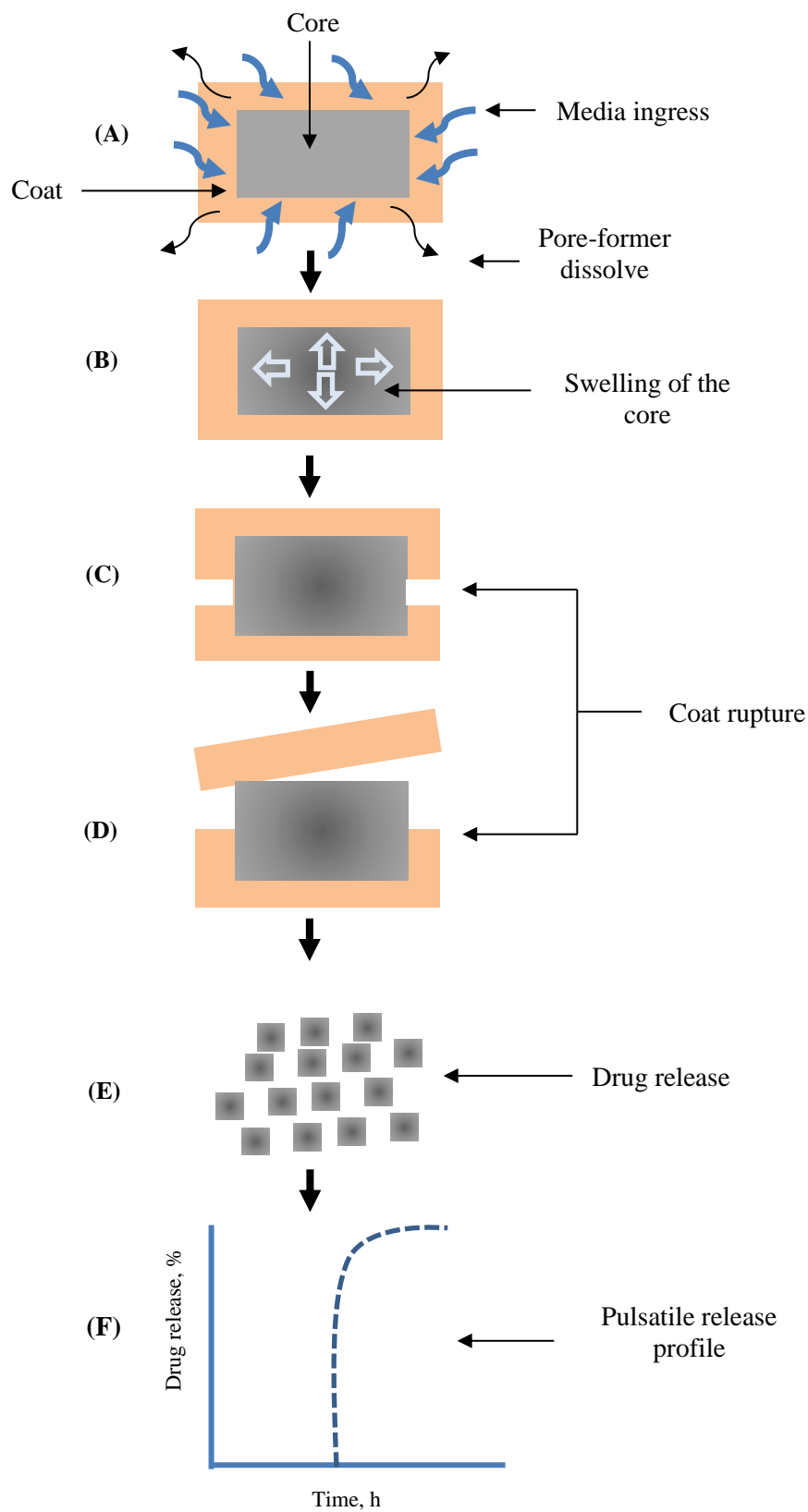
Fig. 4 Drug release from rupturable coating system.

Drug release mechanism from rupturable coating:

The mechanism of drug release from rupturable coatings in pulsatile drug delivery systems involves a series of steps that culminate in the rupture or breakage of the coating and the subsequent release of the drug.

- Lag phase: The coated dosage form, comprising a drug-containing core and a rupturable coating, is initially administered orally. The coating acts as a barrier, keeping the drug entrapped and preventing its release.

- Liquid penetration: Upon contact with fluids in the gastrointestinal tract, such as gastric or intestinal fluids, water begins to penetrate the coating. This penetration can be facilitated by the presence of pore-formers or plasticizers in the coating formulation (Fig. 4 A).

- Core swelling: As the liquid penetrates the coating, it comes into contact with the core, which is designed to be swellable. The core absorbs the liquid, causing it to swell and increase in volume. This swelling generates an outward pressure against the coating (Fig. 4 B and C).

- Coat rupture: As the swelling of the core continues, the outward pressure exerted on the coating eventually exceeds its mechanical strength. At a predetermined lag time, the coating ruptures, or breaks (Fig. 4 D), allowing the drug to be rapidly released (Fig. 4 E and F).

Materials used in rupturable coating: Rupturable coatings can be composed of various materials depending on the release mechanism and desired properties.

- **Brittle polymers:** Some polymers, such as hydroxypropyl cellulose (HPC) or ethylcellulose (EC) were combined with pore-former or plasticizer to allow penetration of liquid into the swellable core, finally leading to the breakage of the coat [23, 24].

- **pH-sensitive polymers:** pH-sensitive polymers, such as Eudragit E or Eudragit L, can be employed to design coatings that rupture when exposed to a particular pH range. The coating remains intact in the acidic environment of the stomach but ruptures in the higher pH environment of the intestines, resulting in pulsatile drug release [25, 26].

- **Lipids:** Lipid, such as waxy behenic acid was blended with lactose and compression-coated with swellable core, water was penetrated the core due to dissolution of lactose and interact with swellable core resulting pulsatile release. The lag time was decreased with increasing the pore former due to increasing the permeability [18].

1.1.1.2 Delivery system with swellable/erodible coating

Erodible coatings in pulsatile drug delivery systems are specifically designed to enable a delayed and controlled release of the drug, followed by a rapid and complete release [13, 19]. These coatings serve as a protective barrier that gradually erodes over a predetermined lag time, leading to the release of the drug in a pulsatile manner [13, 27]. To construct such systems, the drug-containing core, which can be in the form of a tablet or pellet, is coated with an erodible layer. Various techniques, including compression-coating [19], spray coating [28], or fluidized bed coating [29], can be employed to ensure uniformity and control over the coating thickness. During the lag phase, the erodible coating acts as a barrier, preventing the immediate release of the drug. The erosion process is initiated upon exposure to bodily fluids or environmental conditions, such as the pH or enzymes present in the gastrointestinal tract. As the coating gradually erodes, the drug release is triggered. Factors such as the choice of erodible polymer, its concentration, and the coating thickness can influence the erosion rate and subsequent drug release kinetics.
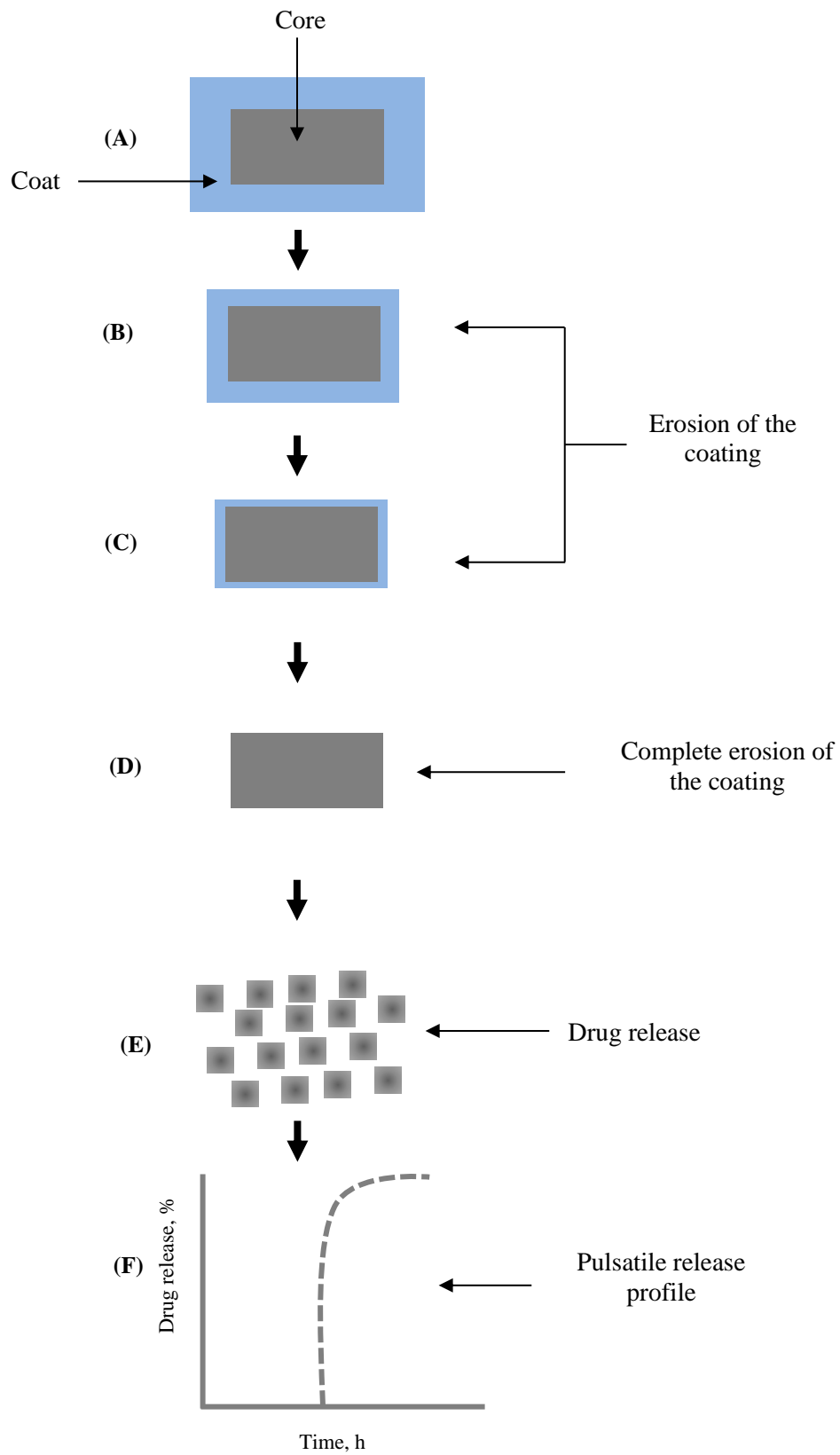
Fig. 5 Drug release from erodible coating system.

Drug release mechanism:

- Swellable/erodible coatings are typically made of water-soluble or water-dispersible polymers that gradually dissolve or erode in the presence of body fluids.
- The coating acts as a barrier, preventing drug release during the lag phase (Fig. 5 A).
- After the lag time, the barrier coating starts to dissolve or erode, resulting in a sudden and complete drug release (Fig. 5 B, C, D and E).
- The lag time can be controlled by the thickness and composition of the coating, as well as the erosion properties of the polymer [30]

Coating materials:

- **Hydrophilic polymers:** Water-soluble or water-dispersible polymers such as hydroxypropyl methylcellulose (HPMC) [33 - 32] , polyvinyl alcohol (PVA) [33], poly(lactic-co-glycolic acid) (PLGA) [34], polyethylene glycol (PEG) [34], and polyvinylpyrrolidone (PVP) [35, 36] are commonly used as erodible coating materials.
- **Enteric polymers:** Certain enteric polymers, such as cellulose acetate phthalate (CAP) [37] or hydroxypropyl methylcellulose phthalate (HPMCP) [38], have been used as erodible coatings to delay drug release until the dosage form reaches the intestines.

Available drug delivery system

Dug release from swellable/erodible coatings depends on the mechanisms that cause the coating to erode or dissolve. Various mechanisms can be employed, including pH, temperature, or enzymes.

pH-dependent: The coating can be designed to erode or dissolve in response to changes in pH. Different pH-sensitive polymers, such as Eudragit® or cellulose acetate phthalate (CAP), are commonly used. For example, the coating may be formulated to remain intact in the stomach (pH 1-3) and rapidly erode or dissolve in the intestine (pH 6-7) where pulsatile drug release is desired [37, 38].

Temperature-dependent: Temperature-sensitive coatings respond to changes in temperature, triggering the erosion or dissolution of the coating layer. Thermoresponsive polymers, such as poly(N-isopropylacrylamide) (PNIPAAm) [39]. These coatings remain intact at lower

temperatures (e.g., 37 °C) but erode rapidly at higher temperatures, such as those encountered in fevered or inflamed regions of the body.

Enzyme-dependent: Enzyme-dependent coatings utilize the presence of specific enzymes in the body to trigger erosion or dissolution. For example, coating layers can be formulated using polymers sensitive to enzymes such as esterases or proteases present in the target tissue or organ. When the enzyme comes into contact with the coating, it catalyzes the degradation process, leading to pulsatile drug release [40].

1.2   Pharmaceutical coating

Pharmaceutical coating is a process in which a thin layer of material is applied to solid dosage forms, such as tablets, capsules, or granules. Coating plays a crucial role in improving the appearance, taste, stability, and overall performance of pharmaceutical products [30].

Purpose of coating [29, 41]**:**

- **Protection:** Coating provides a protective layer to prevent degradation or damage to the drug from environmental factors such as moisture, light, or oxygen.
- **Taste masking:** Coating can mask the unpleasant taste or odor of the drug, enhancing patient acceptability and compliance.
- **Modified release:** Coating allows for controlled or delayed drug release, enabling specific release profiles such as immediate release, sustained release, delayed release or enteric release.
- **Enhanced appearance**: Coating improves the visual appeal of tablets or capsules, making them more attractive and identifiable.
- **Facilitated swallowing:** Coating can reduce tablet adhesion and provide a smooth surface, making it easier for patients to swallow.

Available coating techniques:

Sugar coating: This traditional coating technique involves layering the tablet or granule with a series of sugar-based solutions, drying each layer before applying the next. It provides a thick and smooth coating, often used for taste masking and aesthetics. However, this technique had long processing times (up to 5 d), a requirement for high level of expertise and difficulties involving the standardizing of the procedure. Also, the risk of bacterial and mold growth was high, there were

restrictions in tablet shape and lack of automation. This led to the introduction of film coating, that, consequently, led to a significant reduction in the processing time [42].

Film coating: This is the most commonly used coating technique. It involves applying a thin layer of a polymer-based solution or dispersion onto the surface of the dosage form (powder, granules, pellets, tablets, and capsules) using techniques such as spraying, dipping, or pan coating. The coating materials are solubilized or suspended in an organic and/or aqueous vehicle. Film coating offers many advantages, for example, reproducibility, can apply to different dosage forms, batch-to-batch uniformity of the product [42, 43].

However, organic solvents, despite offered shorter processing times and straightforward film formation, carry many disadvantages. The toxicity of the residual solvent in the coating, the high cost of organic solvents and its recycling, the safety hazards to operators as well as strict environmental regulation has led to a shift to the use of water as a solvent [42].

The use of water as a solvent in film coating offers several advantages and eliminates many of the disadvantages associated with the use of organic solvents are mentioned below [14, 42]:

Safety and environmental considerations:

- Water is non-toxic and non-flammable, making it a safer alternative to organic solvents, which may pose health and safety risks.
- Water-based coatings reduce the risk of fire hazards and chemical exposure during the coating process, ensuring a safer working environment.
- Water is readily available and environmentally friendly, as it does not contribute to air pollution or produce volatile organic compounds (VOCs).

Ease of handling and cleanup:

- Water-based coatings are easier to handle and clean compared to organic solvent-based systems.
- Water-based solutions or dispersions are generally less viscous, allowing for easier spraying, coating, and equipment cleaning.
- Residual water-based coatings can be easily removed from equipment and surfaces using water, simplifying cleaning procedures.

Compatibility with heat-sensitive drugs and excipients:

- Organic solvents, especially those with high volatility, can potentially degrade or interact with heat-sensitive drugs or excipients during the coating process.

- Water-based coatings offer better compatibility with heat-sensitive ingredients, minimizing the risk of degradation or undesirable chemical reactions.

It is important to note that while water-based coatings offer significant advantages, they may have certain limitations. For example, some drugs or excipients may be incompatible with water-based systems, requiring alternative coating approaches. Additionally, water-based coatings may have different requirements in terms of formulation stability, equipment compatibility, and coating process optimization [14, 42].

1.2.1 Compression coating

Compression coating, also known as double compression coating, compression coating, or dry coating, is a solvent-free coating technique that was first proposed by Parker J. Noyes in 1896. Its industrial application was introduced in the 1950s-1960s to address the formulation challenges associated with incompatible drugs [44, 30]. Over the last few decades, the use of compression coating has increased due to its advantages, including the elimination of solvents and relatively short manufacturing processes. The absence of solvents in compression coating offers several benefits. First, it reduces costs by eliminating the slow and expensive processes associated with solvent treatment and disposal. This makes compression coating a more economical option for coating pharmaceutical products.

Additionally, the solventless nature of the process contributes to environmental sustainability and compliance with regulatory guidelines. One of the notable advantages of compression coating is the significant reduction in processing times. Unlike traditional coating methods that involve drying and evaporation steps, compression coating bypasses these time-consuming stages. As a result, the overall manufacturing process is expedited, leading to improved productivity and faster turnaround times. Furthermore, compression coating can be advantageous for coating temperature-sensitive drugs. Since the process does not require heating sources in most cases, it provides an alternative method for coating drugs that are susceptible to degradation or loss of potency under high temperatures. In recent years, the utilization of compression coating has gained popularity due

to its solvent-free nature, reduced processing times, cost-effectiveness, and suitability for coating temperature-sensitive drugs.

A compression-coated tablet typically comprises an inner drug core and an outer coating shell. The outer layer plays a crucial role in determining the tablet's performance, including the mechanical strength of the coating, drug release characteristics, and overall stability [44]. The press-coated tablet consists of a core that can be either a fast-disintegrating formulation or a modified-release formulation. This core is then coated through compression with a solid barrier, typically composed of polymeric or lipid materials. The coating formulation may also include a diluent, which acts as a release modifier or pore former, as well as additional drug components for both rapid and extended-release purposes [45]. One of the key advantages of compression coating is its ability to physically separate incompatible drugs within the same dosage form. By incorporating different drugs into the core and the coat, the formulation can accommodate incompatible drug combinations. This feature allows to produce combination dosage forms in which two active substances can be targeted to different areas of the gastrointestinal tract, enhancing treatment efficacy and patient convenience. Additionally, the direct compression of both the core and the coat eliminates the need for a separate coating process, streamlining manufacturing operations and reducing production costs [44].

The compressibility of a compression-coated tablet is greatly influenced by the choice of coating materials, and sometimes the addition of excipients is necessary to optimize the compression process. Researchers have explored the use of functional polymers to achieve modified drug release profiles (Table 2) [46, 47]. Swellable hydrophilic polymers have been extensively studied for their ability to enable prolonged or pulsatile oral drug delivery systems. Among these polymers, cellulose derivatives such as HPMC [48 - 52], HPC [53] and HEC [54] have gained significant attention due to their wide availability, cost-effectiveness, and favorable compaction properties. Coating formulations based on polysaccharides like pectin [55 - 57], guar gum[58, 59], xanthan gum [59], and locust bean gum [60] have also been investigated, as they can be biodegraded by colonic bacteria. Additionally, enteric polymers like Eudragit® S, Eudragit® L, and HPMCAS have been employed in press coating techniques to achieve pH-dependent systems for targeted colonic release [61, 62]. By utilizing these diverse polymers in compression coating, researchers aim to tailor the drug release characteristics to specific requirements, such as delayed release, pulsatile release, or pH-dependent release. The selection of the appropriate polymer or polymer combination

is crucial in achieving the desired performance of the compression-coated tablets. In addition to the use of polymers, another approach in the

The development of compression-coated tablets involves the incorporation of mixed wax and brittle materials as coating agents. A notable example of this is the commercially available product Lodotra™, which contains prednisone and is specifically designed for chronopharmaceutical treatment of early-morning stiffness associated with rheumatoid arthritis [63].

Table 2 Oral pulsatile drug delivery tablets prepared by press coating technique.

Drug	Formulation of inner core	Formulation of outer layer	References
Acetaminophen, carbamazepine, propranolol HCl chlorpheniramine maleate	Drug+Ludipress, MgSt	HPMC E50, HPMC 400, HPMC K, Ludipress	Int J Pharm. 402: 72–77 (2010)
Acetaminophen, carbamazepine, chlorpheniramine maleate, Ketoprofen, diclofenac sodium	Drug+Ludipress, MgSt	Eudragit L Eudragit L/EC	Eur J Pharm Biopharm. 76: 486–492 (2010)
Ketoprofen	Drug+Na CMC, MgSt	EC, EC/glycinemax, EC/sodium alginate	Chem Pharm Bull. 57: 1213–1217 (2009)
Theophylline	Drug+Ac-Di-Sol, lactose, MgSt	Barrier granules (Compritol 888 ATO /L-HPC)	Eur J Pharm Biopharm. 67: 515–523 (2007)
Felodipine	Drug+PVP (solid dispersion) Drug+PVP/sodium docusate (solid dispersion), Ac-Di-Sol, sodium starch glycolate	PVP/HPMC K	Eur J Pharm Biopharm. 64: 115–126 (2006)
Ibuprofen	Drug+MCC, Ac-Di-Sol	Drug+HPMC K, Drug+EC	AAPS PharmSciTech. 8 (3): Article 76 (2007)
Diltiazem HCl	Drug+corn starch, PVP,	HPC-SL, HPC-L, HPC-M, HPC-H	J Control Rel. 68: 215–223 (2000)
Ibuprofen	Drug+lactose, potassium carbonate	Drug+HPMC K100/K	Int J Pharm. 189: 179–185 (1999)
Diltiazem HCl	Drug+corn starch/PVP, calcium citrate, Ca CMC, MgSt	HPC-L	Int J Pharm. 204: 7–15 (2000)
Diltiazem HCl	Drug+corn starch/PVP,	HPMCAS+plasticizer-absorbent powder	Int J Pharm. 217: 33–43 (2001)

Rosiglitazone maleate	calcium citrate, Ca CMC, MgSt Drug+Compritol 888, Drug+Precirol ATO 5, DCP, MgSt, Aerosil	HPMC K, sodium Bicarbonate	Int J Pharm Tecgnol. 1: 103–136 (2010)
Ornidazole	Drug+spray dried lactose, sodium starch glycolate, talc, MgSt	Guar gum, HPMC/starch, talc, MgSt	Drug Delivery, 10: 111–117, (2003)
Sodium diclofenac	Drug+crosslinked PVP, spray-dried lactose, talc, MgSt	Guar gum, locust bean gum, HPMC, starch, talc, MgSt	Int J Pharmtech Res. 2: 1714–1722 (2010)
Ornidazole	Drug+spray-dried lactose, sodium starch glycolate, MgSt, talc	Guar gum, HPMC, starch, MgSt, talc	Drug Delivery, 10: 111–117 (2003)
Budesonide	Drug+anhydrous lactose	Eudragit S, Eudragit L, HPMC, cellulose acetate butyrate, Pectin, guar gum	AAPS PharmSciTech. 10: 147–157 (2009)
Mesalamine	Drug+PVP K30, MgSt	Pectin, Pectin/Compritol ATO 888	Acta Pharm. 60: 39–54 (2010)
Lornoxicam	Drug, Ac-Di-Sol, MCC	Freeze-dried (drug+PVP K30)+Compritol ATO 888, MCC, MCC/lactose	Drug Dev Indus Pharm. 36: 337–349 (2010)
Lansoprazole	Drug+mannitol, lactose, cross-linked Na CMC, sodium carboxymethyl starch	β-mannanase, guar gum, β-Cyclodextrin, hydroxypropyl-β-cyclodextrin, PVP K-30, MgSt, talc/enteric coating	Drug Devel Indus Pharm. 36: 81–92 (2010)
Mesalamine	Drug+DCP, sodium starch glycolate (PVP: binder), talc, MgSt	HPMC (K, E3, E5, and E15)/enteric coating (Eudragit S100)	Acta Pharm Sciencia. 51: 251–260 (2009)

1.2.1.1 Manufacturing process of compression-coated tablets

The press-coating manufacturing process consists of several steps (Fig. 6). Traditionally, the process begins with the compression of the core tablet, followed by the compression of core-coating materials around it. The die is filled with the materials that will form the outer layer. The core tablet is positioned on top of the powder intended for the outer layer. Subsequently, the core tablet is surrounded by the outer layer-forming materials and compressed together with the powder and core inside it. One challenge associated with this method is ensuring the proper location of the

core tablet within the coating. If the core tablet is not positioned accurately in the center of the system, it can result in variations in the performance of the coating [42].
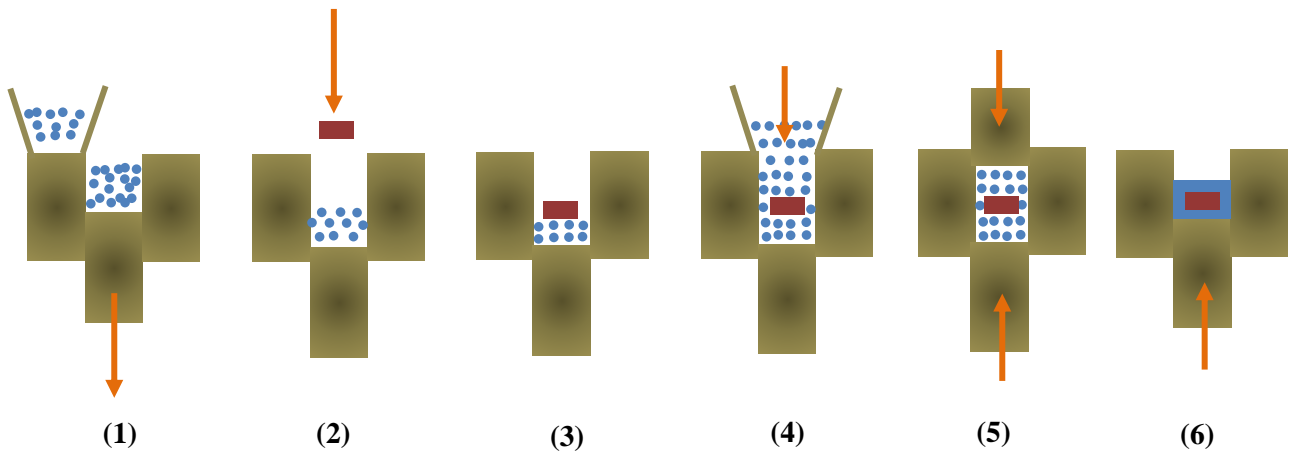

Fig. 6 Manufacturing process of compression-coated tablets.

1. Prefilling the half amounts of outer coating materials into the die
2. Putting the inner core tablet on the powder bed of outer coating materials
3. Centering
4. Filling the residual half amounts of outer coating materials
5. Compression
6. Ejection of compression-coated tablet from the die

1.2.1.2 Effect of coating formulation parameters on release

Compression coating is a technique that involves the direct compression of the inner core and the outer coating shell of a tablet. The outer coating plays a critical role in ensuring the release of the drug at the desired target site upon oral administration. The formulation of the outer coating can utilize different polymers or other materials, each providing a unique drug release mechanism. By combining hydrophilic and hydrophobic polymers, various outer coating properties such as rupturability, swellability, erodibility, or permeability can be achieved. These properties allow for controlled release by modulating the speed of media penetration.

The rate of drug release from a compression-coated tablet is influenced by several factors. Firstly, the selection of coating materials is crucial, as different polymers exhibit different release profiles. Additionally, the thickness and porosity of the outer coating can impact the drug release kinetics. Excipient particle size plays a role in determining the mechanical properties and dissolution behavior of the tablet. The compression force applied during tablet manufacturing also affects the drug release rate, as it influences the integrity and compactness of the coating. Furthermore, the position of the inner core within the tablet can introduce variability in the drug release, emphasizing the importance of accurate core placement. Considering these factors in the design and formulation of press-coated tablets allows for the optimization of drug release profiles and enhances control over the release kinetics.

Polymer particle size

In a study conducted by Lin et al. 2001, the impact of outer coating polymer particle size, specifically ethylcellulose, on drug release from press-coated tablets was investigated. The researchers observed that the drug release from these tablets exhibited an initial lag period, which was found to be dependent on the particle size of ethylcellulose. Interestingly, tablets with smaller particle sizes of ethylcellulose exhibited a longer lag time compared to those with larger particle sizes. This was attributed to the reduced porosity of the coating shell in tablets with smaller ethylcellulose particles. Based on their findings, the authors proposed that press-coated tablets prepared with an outer coating shell incorporating specific particle sizes of ethylcellulose powder could offer a programmable release profile for drug delivery at predetermined times and sites [65].

Polymers and lipids

The press coating process utilizes a wide range of pharmaceutical polymers with different functionalities. Commonly used polymers include cellulose derivatives such as ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), and hydroxypropyl methylcellulose acetate succinate (HPMCAS). Polysaccharides like guar gum, sodium alginate, and pectin, as well as water-soluble polymers like polyethylene oxide (PEO), wax (behenic acid), and methacrylate copolymers, are also employed in press coating. These polymers can be used alone or in combination to form the outer coating shell.

By categorizing these polymers based on their functions, the outer coating shell can be classified into different groups. For example, ethyl cellulose provides a water-insoluble and rupturable coating, while low molecular weight HPMC, HPC, and PEO offer erodible coatings. High molecular weight HPMC and gums can form gellable or swellable coatings, pH-dependent soluble coatings can be achieved with HPMCAS and Eudragit copolymers, and there are also waxy and bacterial digestible coatings.

Conte et al. 1993, demonstrated that the type and molecular weight of the polymer used in the outer coating shell of press-coated tablets can significantly influence the controlled and modulated drug release behavior [66]. The release of the drug from the tablet begins when the outer coating shell is completely eroded, swollen, or dissolved. When an erodible coating is used, it acts as a barrier and prevents the release of the drug from the inner core until the coating is fully removed by the dissolution medium. On the other hand, an erodible shell coating does not impact the release behavior of the inner core. In contrast, a gellable coat can delay and modify the release performance of the compression-coated tablet.

Various types of gel-forming and hydrophilic polymers have been extensively studied as outer coating materials in press-coated tablets. Among these polymers, HPMC (hydroxypropyl methylcellulose) has shown promising results as a press coating shell material for achieving sustained-release profiles [67]. The use of HPMC in the outer coating formulation allows for controlled drug release over an extended period of time. In addition to HPMC, HEC (hydroxyethyl cellulose) has also been investigated as a potential outer coating material. Matsuo et al. demonstrated that different viscosity grades of HEC could be utilized to regulate the lag time and establish a delayed release system [54]. By selecting the appropriate viscosity grade of HEC, the

release of the drug from the press-coated tablet can be delayed, providing a predetermined lag time before drug release begins. These studies highlight the versatility of gel-forming and hydrophilic polymers in press-coated tablets, offering the potential for tailoring the drug release profile based on specific therapeutic requirements. The selection of the outer coating material, such as HPMC or HEC, along with considerations of viscosity grade, allows for precise control over the release kinetics, ensuring optimal drug delivery and therapeutic outcomes [68].

Ishino et al. developed a unique press-coated tablet formulation using a waxy outer coating shell [25]. The outer coating shell was composed of low water permeable materials, specifically hydrogenated castor oil (HCO) and polyethylene glycol 6000. The inner core of the tablet contained the drug along with a disintegrating agent. This formulation exhibited time-controlled release, with the lag time varying from 4 to 10 h depending on the specific composition and thickness of the coating. By adjusting the formulation parameters, the researchers were able to achieve a desired delay in drug release, providing a controlled and predetermined release profile [25].

Pore-formers

Lin et al. conducted a comprehensive investigation on the influence of pore formers on drug release from press-coated tablets [69]. In their study, hydrophilic pore formers, namely HPMC and spray-dried lactose, were incorporated into the water-insoluble outer coating shell composed of ethylcellulose. The results of the study revealed that the choice of pore former had a significant impact on the lag time of drug release from the press-coated tablets. Tablets coated with spray-dried lactose/EC exhibited a shorter lag time compared to those coated with HPMC/ethylcellulose. This can be attributed to the higher solubility of lactose, which facilitated faster dissolution and increased the porosity of the outer coating shell. The increased shell porosity, in turn, allowed for easier penetration of the surrounding media, resulting in faster rupture of the press-coated tablet and subsequent drug release. Furthermore, the study demonstrated that the viscosity of HPMC played a crucial role in determining the lag time. As the viscosity of HPMC increased, the lag time also increased, indicating a delayed drug release. The incorporation of hydrophilic excipients in the outer coating formulation was found to be effective in modulating the lag time and achieving the desired release characteristics [69].

The investigation on drug release from press-coated tablets examined the impact of pore formers such as sodium chloride, calcium tartrate, mannitol, sucrose, and directly compressible dextrose

[70]. The study revealed that the rate of pore formation significantly affects drug release. Furthermore, the addition of hydrophobic additives, including magnesium stearate and calcium stearate, to the coating was found to impede the penetration of the dissolution solution through the pores [71, 72].

Salts

Eckman et al. conducted a study to explore the effect of salt concentration on drug release. They formulated the outer coating shell using a thermo-responsive polymer, poly (N-isopropyl acrylamide), with varying amounts of salts (Na_2SO_4 or $NaCl$). The authors noted that controlling the rate of polymer coating dissolution can be achieved by adjusting the salt concentration instead of relying solely on temperature changes. Salts have the ability to lower the critical-point solution temperature or the inverse phase transition temperature of the polymer. Therefore, by manipulating the concentration of salts, it becomes possible to modulate the temperature of the dissolution medium and achieve the desired drug release profile [73].

Compression pressure

The compression force plays a critical role in controlling the drug release from press-coated tablets. Lin et al. conducted a study to investigate the effect of compression force on drug release. They observed different lag times and drug release profiles by varying the compression force applied to the rupturable ethylcellulose coating. It was noted that for the rupturable coat, the outer coating shell breaks into two parts after the lag time, resulting in an immediate release of the drug. Therefore, the lag time and immediate release necessary for achieving time-controlled release were dependent on the applied compression force [74]. Similarly, in the case of erodible coats, similar results were observed. The lag time and drug release were found to be influenced by the compression force applied to an HPMCAS coating [71, 72].

In contrast to insoluble or erodible coating shells, the influence of compression force on drug release from swellable polymer coatings was found to be less significant. Turkoglu and Ugurlu conducted a study and demonstrated that compression force does not significantly affect the drug release profile of press-coated tablets with pectin-HPMC as the outer coating shell. Furthermore, no significant differences in drug release were observed when various compression forces were applied to pectin-HPMC K100M outer coating shells [75]. These findings suggest that the impact

of compression force on drug release may vary depending on the type of coating material used, and in the case of swellable polymer coatings, it may not be a major factor in modulating drug release behavior.

Amount of outer shell

The performance of compression-coated tablets relies on the outer coating layer, which governs erosion, swelling, disintegration, and dissolution characteristics. Achieving a uniform coating is crucial, and this can be accomplished by carefully selecting the appropriate amount of coating materials. It has been recommended that the outer coating should be approximately twice the mass of the inner core, or even more, with a volume greater than that of the inner core itself. In a study by Lin et al., the impact of the amount of coating materials on drug release was investigated. It was observed that increasing the amount of coating materials resulted in longer lag times. Specifically, compression-coated tablets prepared with 160 mg of coating exhibited a shorter lag time compared to those with 200 mg of ethylcellulose-based coating materials. The authors noted that the 160 mg ethylcellulose outer coating displayed a linear release rate up to 50% dissolution of the drug, attributed to the thinner ethylcellulose layer. Conversely, exceeding 200 mg of coating materials increased the lag time while leading to rapid disintegration and dissolution. Insufficient polymer quantity in the outer coating shell resulted in the absence of a lag time. These findings underscore the pivotal role of the amount of outer coating materials in determining the release behavior of time-dependent press-coated tablets [74]. Proper selection and optimization of the coating material quantity are crucial for achieving the desired release characteristics.

Double layered outer shell

The manufacturing process of compression-coated tablets involves multiple compression steps, offering a novel approach to develop a reliable dosage form capable of targeted drug release. In a study by Lin et al., various weight ratios of fine and coarse ethylcellulose powders, along with different excipients, were incorporated into the upper layer of the compression-coated tablets. The drug release behavior exhibited an initial lag time followed by an immediate release phase. The duration of the lag time was found to be dependent on the quantity of fine powder added, as the fine ethylcellulose powder filled the inter- and intra-particulate gaps of the coarse ethylcellulose powder. Furthermore, the addition of different excipients in the upper layer led to diverse release profiles due to their distinct physicochemical properties. The observed release profiles included

time-controlled explosion for Explotab, disruption for microcrystalline cellulose and spray-dried lactose, erosion for dibasic calcium phosphate anhydrate, and a sigmoidal profile for HPMC. The authors also highlighted that the addition of different excipients in the upper coat, along with the presence of coarse ethylcellulose powder in the lower layer, resulted in varied lag times and release profiles. Additionally, the upper part of the press-coated tablet could provide different release phases and mechanisms based on the physicochemical properties of the incorporated additives [76].

Compressibility and layer binding

The compressibility and mechanical strength of press-coated tablets are directly influenced by the choice of materials for the outer coating shell. The outer coating shell plays a crucial role in achieving proper adhesion between the core and the coating. It is recommended that the final compression force applied during tablet manufacturing should be higher than the compression force applied to the inner core. This ensures the integrity and stability of the compression-coated tablet. However, one common challenge encountered during the manufacturing process is lamination, where the two layers fail to bind effectively, resulting in separation after ejection. To address this issue, Waterman and Fergione explored a novel approach by introducing an adhesive coating applied to the core. This adhesive coating serves to enhance the adhesion between the outer coating shell and the inner core, minimizing the occurrence of lamination and improving the overall tablet integrity [75]. This innovative method provides a potential solution to overcome the challenges associated with lamination during the production of tablets, ensuring a reliable and robust dosage form.

Stability of enzymes or drugs under compression

Investigating the effect of compression is of paramount importance due to its potential impact on enzyme activity. Several studies have explored the changes in enzyme activity after compression, revealing interesting findings. D.E. Wurster et al. conducted a study on catalase activity and observed a significant loss of up to 30% when compaction pressures reached 251 MPa or higher [76]. Similarly, Teng and Groves reported a 50% decrease in the biological activity of crystalline jack bean under compaction pressures exceeding 500 MPa [77]. These studies highlight the sensitivity of certain enzymes to compression and the potential impact on their functionality.

Furthermore, Zarrintan et al. demonstrated that wheat germ lipase experienced a reduction of approximately 30% in enzymatic activity after compression [78]. However, it should be noted that not all enzymes exhibit the same level of sensitivity to tableting. For instance, the enzyme nattokinase showed successful stabilization and no significant reduction in activity following the tableting process [79].

In addition to enzymes, there have been innovative approaches to enhance the survival of probiotic bacteria during compression-coating. A novel encapsulation method utilizing a hydrogel barrier based on sodium alginate has been developed, which effectively retards the penetration of acidic media into the cells, thereby increasing the survival rate of probiotics [78]. Recent studies have also focused on the gastroprotection of probiotic bacteria such as E. coli and Lactobacillus rhamnosus, as well as pancreatic enzymes, for targeted delivery to the colon. Compression-coating technology utilizing ionic carboxylated (carboxymethyl high amylose starch, CM-HAS) and amino (chitosan) excipients has been explored for the formulation of these probiotic systems [80]. Moreover, the impact of compression force on drug-solid state polymorphic transformation has been investigated in another study [81]. This research sheds light on the potential influence of compression force on the solid-state properties and stability of drugs, which is crucial for ensuring the desired drug release profiles and therapeutic efficacy.

1.2.1.3   Effect of core formulation parameters on release

The inner core of a compression-coated tablet can be formulated using a variety of materials and compositions to achieve specific drug release characteristics. It offers flexibility in incorporating pure drug crystals, drug-excipient blends, granules, microspheres, and beads as the core matrix. Additionally, materials can be included in the core tablet to enhance disintegration or modify the drug release behavior. By incorporating different polymers into the inner core compositions, a range of drug-release mechanisms can be achieved.

The selection of core materials depends on factors such as the desired release profile, drug properties, and compatibility with the outer coating shell. Pure drug crystals or drug-excipient blends are often used when immediate or rapid drug release is desired. Granules, microspheres, and beads can provide controlled release by controlling particle size, surface area, and drug distribution within the core matrix.

Furthermore, the incorporation of different polymers into the inner core compositions allows for the modulation of drug release mechanisms. For example, hydrophilic polymers like HPMC or polyethylene oxide (PEO) can be used to create a swelling or gel-forming matrix, which controls the drug release by diffusion through the hydrated polymer network. On the other hand, hydrophobic polymers like ethylcellulose can form a water-insoluble matrix that controls drug release by erosion or dissolution of the polymer matrix over time.

Drug solubility

The solubility of a drug plays a crucial role in its absorption and influences the dissolution behavior of the drug within the gastrointestinal tract. Monitoring the dissolution behavior is important for understanding the drug's release characteristics. In a study conducted by Rujivipat and Bodmeier, HPMC-based compression-coated tablets were formulated using different drugs with varying solubilities, including carbamazepine, acetaminophen, propranolol HCl, and chlorpheniramine maleate. The results of the study demonstrated that drugs with higher solubilities exhibited a sigmoidal release profile, indicating diffusion through the gel layer prior to erosion. On the other hand, carbamazepine, a water-insoluble drug, showed a pulsatile release pattern after a lag time caused by the erosion of the HPMC outer shell. The release of more soluble drugs was not affected by an increase in HPMC molecular weight. Interestingly, the molecular weight of HPMC had a significant impact on the release behavior of carbamazepine. Increasing the molecular weight of HPMC led to a considerable increase in the lag time before the drug's release, primarily due to the erosion-based release mechanism. This finding highlights the influence of HPMC molecular weight on the dissolution behavior of water-insoluble drugs [30].

In a study conducted by Lin et al., the influence of different drugs (sodium diclofenac, theophylline anhydrate, and salbutamol sulfate) in the inner core on the release was investigated. The inner core formulations also included sodium starch glycolate as a disintegrant, while the outer coating shell consisted of fine ethylcellulose powder. When sodium starch glycolate was absent from the inner core, only salbutamol sulfate or theophylline anhydrate exhibited longer lag times (>24 h) compared to 16.4 h for sodium diclofenac alone. However, upon incorporating sodium starch glycolate into the inner core, the lag times were slightly reduced to 14.6 h for sodium diclofenac, 17.8 h for theophylline anhydrate, and 21.3 h for salbutamol sulfate. Interestingly, drugs with higher solubility in the inner core resulted in shorter lag times compared to drugs with lower

solubility. Diclofenac sodium and salbutamol sulfate exhibited rapid and complete release, while theophylline anhydrate showed fast release that slowed down after reaching 60% release [82].

Osmotic agent

Incorporating osmotic agents, such as sodium chloride, into the inner core can significantly impact the dissolution behavior of the drug. Lin conducted a study where the lag time of the tablets loaded with sodium chloride was found to be considerably shortened to less than 1 h, compared to 16.4 h for the drug alone. Moreover, the lag time decreased with increasing amounts of sodium chloride in the formulation. By incorporating sodium chloride, the inner core tablet generates a high internal osmotic pressure, which leads to the rapid rupture of the outer coating layer. Consequently, the drug is released more quickly, resulting in a shorter lag time. The use of osmotic agents provides a valuable approach to modulate the release kinetics of drugs from press-coated tablets [82].

The composition of the core has been found to influence drug release. In a study by Nuntanid et al. [83], spray-dried chitosan acetate and HPMC compression-coated tablets were prepared. The researchers discovered that drug release was enhanced when soluble diluents and super disintegrants were used. Conversely, the inclusion of sodium chloride as an osmotic agent led to a decrease in drug release [83].

Type of excipients

In addition to the findings mentioned earlier, Lin et al. 2004 [69], conducted a study where they investigated the influence of excipients present in the core on the lag time and release behavior. They formulated the inner core using different direct-compressible excipients such as spray-dried lactose, microcrystalline cellulose, or sodium starch glycolate, along with HPMC and ethylcellulose as the outer coating shell material. The researchers observed that the choice of excipients in the core had a significant impact on the lag time. When the core contained only the drug, the lag time was measured at 16.4 h. However, when spray-dried lactose, HPMC 2910 (Metolose 60 SH50), sodium starch glycolate, or microcrystalline cellulose were used as diluents in the inner core, the lag times observed were 8.5 h, 12.4 h, 14.6 h, and 15.8 h, respectively. The shorter lag time observed with spray-dried lactose compared to HPMC, sodium starch glycolate, and microcrystalline cellulose was attributed to its higher solubility. The solubility of an excipient plays a crucial role in determining the lag time and subsequent drug release behavior [69, 82].

Another study by González-Rodríguez et al. focused on the outer coating shell, which was prepared using a mixture of 50% Eudragit RSPO and 50% sodium chloride. The inner core, on the other hand, contained either lactose or polyethylene glycol 4000 (PEG 4000). They observed higher drug dissolution from the tablets containing PEG 4000, attributed to the solid dispersion of PEG 4000 with the drug, which improved the wettability and solubility of the drug [84]. Sawada et al. conducted an in vivo dog study with similar outer coating shells containing different cores. Despite observing similar in vitro release profiles, they found differences in bioavailability among these tablets. The in vivo study demonstrated that a higher core erosion ratio resulted in greater drug absorption in GIT [85].

Superdisintegrant

In a study conducted by Nuntanid et al. [83], the release of 5-aminosalicylic acid (5-ASA) from press-coated tablets was investigated. The tablets were prepared using spray-dried chitosan acetate/HPMC as the outer shell. The researchers compared different core materials, including sodium starch glycolate (superdisintegrant), α-lactose monohydrate, and dibasic calcium phosphate (as water-soluble and insoluble diluents). Their findings revealed that using a small amount of sodium starch glycolate did not establish sufficient burst release of the tablet. Additionally, no significant change in the release behavior was observed when α-lactose monohydrate or dibasic calcium phosphate were used as core materials. Based on their conclusions, the researchers suggested that drug release could be enhanced by incorporating an appropriate amount of superdisintegrant in the inner core of press-coated tablets [83].

Amounts of inner core

Rujivipat and Bodmeier conducted a study to explore the impact of inner core to outer shell ratios on the drug release behavior of press-coated tablets. They prepared tablets with different ratios: 3:1 (9 mm core in 10 mm tablet), 2:1 (9 mm core in 11 mm tablet), 1:1 (6 mm core in 8 mm tablet), and 1:2 (6 mm core in 9 mm tablet). In their study, no drug release was observed at pH 1.0 over a 20 h period. However, at pH 7.4, a lag time followed by pulsatile release was observed. Interestingly, the rate of drug release increased with an increase in the inner core to outer coat ratio. This can be attributed to the decreased thickness of the coating, which facilitated faster erosion of the coat. [30].

Core hardness

Lin et al. conducted a study to examine the impact of inner core compression force on drug release. The researchers varied the inner core compression pressure within the range of 50 to 200 kg/cm2, while maintaining a constant compression pressure of 300 kg/cm2 for the outer coating shell. Surprisingly, they found no significant difference in drug release (with a lag time of 12.5 h) when the compression pressure of the inner core was within the 50-200 kg/cm2 range. However, when the inner core compression force exceeded 200 kg/cm^2, the lag time increased to 16.3 h. This suggests that while the compression force applied to the inner core tablet has minimal influence on drug release when a constant compression force is applied to form the outer shell, higher compression forces on the inner core can prolong the lag time. This finding provides valuable insights into the relationship between compression force and drug release [82].

Position of inner core

Accurate centering of the inner core during the compression-coating process is crucial for the successful production of tablets. Any deviation from the precise centralization of the core can lead to complications and failures in the coating process. Achieving consistent drug-release performance has always been challenging due to issues such as uneven coating or off-center positioning of the core, or sometimes both. However, recent advancements have addressed this problem through the development of a novel compression tool within the OSDRC-system, along with the implementation of non-invasive X-ray computed tomography [87, 88]. These innovative approaches have proven effective in overcoming the challenges associated with centering the core during the press-coating process [65, 86].

1.3 Objectives

- To investigate the performance of pH-independent oral rupturable pulsatile drug delivery system based on compression-coated tablets as a function of core and coating formulation and process parameters for
    - lipid-based compression coatings and
    - polymer-based coatings
- To elaborate the release mechanism of the compression-coated tablets for drugs with different aqueous solubilities

2 Materials and Methods

2.1 Materials

Drugs

Metoprolol tartrate, propranolol HCl, carbamazepine (BASF SE, Ludwigshafen, Germany).

Lipid

Glyceryl behenate, (Compritol 888 ATO, Gattefosse, Lyon, France).

Polymers

Poly [ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride] 1:2:0.2 (Eudragit® RL PO), poly [ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride] 1:2:0.1, (Eudragit® RS PO, Evonik Industries AG, Darmstadt, Germany); ethylcellulose (EC) (Ethocel® Standard 4, 10 and 20 premium), hydroxypropylmethylcellulose 4000 cps, (HPMC) (Methocel® K4M Premium, Colorcon Ltd, Dartford, Kent, UK).

Pore formers and fillers

Lactose monohydrate (lactose) (GranuLac® 230, FlowLac® 100, Tablettose® 70, Meggle Wasserburg GmbH & Co. KG, Wasserburg, Germany); dicalcium phosphate dihydrate (DiCaP) (DI-CAFOS D160, Budenheim KG, Budenheim, Germany); microcrystalline cellulose (MCC) (Avicel® PH 101, FMC Biopolymer, Philadelphia, PA, USA).

Superdisintegrant

Croscarmellose sodium (AcDiSol®, FMC, Philadelphia, USA), (Primellose®, DFE Pharma, Goch, Germany), (VIVASOL®, JRS Pharma, Rosenberg, Germany); sodium starch glycolate (Primojel®, DFE Pharma, Goch, Germany); crospovidone (VIVAPHARM®, JRS Pharma, Rosenberg, Germany).

Others

Polyvinyl pyrrolidone (PVP) (Kollidon® 30, BASF SE, Ludwigshafen, Germany); colloidal silicon dioxide (Aerosil® 200, Evonik Industries AG, Essen, Germany); magnesium stearate (Baerlocher GmbH, Unterschleißheim, Germany).

2.2 Methods

2.2.1 Preparation of core tablets

Drug (10 - 60% w/w) and excipients (filler 29 - 89% w/w, superdisintegrant 0 - 20% w/w) were blended for 10 min in a Turbula®- blender (W.A Bachofen AG, Basel, Switzerland). Mg-stearate 0.5% w/w and Aerosil® 0.5% w/w were added and further blended for 1 min. The core (∅11 mm) was prepared by compressing 360 mg of the blend using a single punch tablet press (compression force - 15 kN; Korsch EK0, Korsch AG, Berlin, Germany). To investigate the effect of tablet size, 7 mm and 9 mm core tablets were prepared by compressing 200 mg and 280 mg blend with compression forces of 10 and 12 kN respectively.

2.2.2 Compression-coating of tablet cores

The tablet cores were compression-coated into 15 mm diameter tablets using lipid (glyceryl behenate 30 - 50% w/w), pore-former (dicalcium phosphate 50% w/w or lactose 9 - 59% w/w), binder (PVP 0 - 20% w/w), lubricant (magnesium stearate 0.5 % w/w), and glidant (Aerosil® 0.5 % w/w). The compression-coated tablets were prepared by first filling 40% of powders in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining 60% of the powder on top and then by compression at 20 kN unless otherwise mentioned. To study the effect of the tablet size on the release, 7, 9 and 11mm tablet cores were compression-coated to 11, 13, and 15mm tablets respectively. A similar procedure was also applied to polymer-based compression-coated tablets.

2.2.3 Drug release

The drug release was investigated in a USP type II paddle apparatus (Vankel® VK 300, Vankel Industries, Edison, NJ, USA) [0-150 rpm, 37 °C, 900 mL 0.1N HCl (pH 1.2), phosphate buffer pH 6.8, n=3]. Samples were withdrawn at a predetermined time intervals, and drug concentrations were measured by UV-spectrophotometer (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at a wavelength of 286, 270, and 274 nm for carbamazepine, propranolol HCl and metoprolol tartrate respectively. The lag time (t_{10}) and release time (t_{80-10}) are defined as the times in h of 10% and 80–10% of the drug released, respectively.

2.2.4 Water uptake and dry mass loss study

The tablets were weighed and then separately placed into 100 mL glass bottles filled with 40 mL 0.1 N HCl and phosphate buffer pH 6.8 (n = 3), followed by horizontally shaking (37 °C, 80 rpm; GFL 3033, Gesellschaft für Labortechnik, Burgwedel, Germany). At predetermined time intervals, samples were withdrawn, accurately weighed (wet mass (t), and dried to constant weight at 40 °C (dry mass (t)). The media uptake (%) and dry mass loss at the time t were calculated as follows:

$$\text{Media uptake, \% (t)} = \frac{\text{wet mass (t)} - \text{dry mass (t)}}{\text{wet mass (t)}} \times 100$$

$$\text{Dry mass loss, \% (t)} = \frac{\text{initial mass} - \text{dry mass (t)}}{\text{initial mass}} \times 100$$

2.2.5 Leaching of pore-former

To assess the leaching rate of the pore-former, compression-coated tablets were prepared using lactose particles of varying sizes (50 to 500 µm). The concentration of the pore-former was maintained at 30 - 50% w/w, while the core of the tablets remained constant. To calculate the leaching of the pore-former, a dry mass loss study was conducted. The leaching rate was determined by analyzing the slope of the dry mass loss over time.

2.2.6 Pore surface area

The leaching of lactose during dissolution process resulted in the formation of pores within the coat. To quantify the extent of pore formation, the leaching rate of the pore-former was used to calculate the total surface area of the pores.

First, the total volume of lactose present in the coating was determined for each particle size. This was achieved by dividing the mass of lactose by its tapped density, yielding the volume of lactose within the coating.

Next, the volume of a single lactose particle was calculated using the formula for the volume of a sphere: $V = 4/3 \ \pi r^3$, where r represents the radius of the particle. This calculation provided an estimation of the volume occupied by an individual lactose particle.

Additionally, the surface area of a single particle was determined using the formula for the surface area of a sphere: $A = 4\pi r^2$, where r represents the radius of the particle. This calculation enabled the estimation of the surface area associated with each lactose particle.

The leaching rate of the pore-former permitted for the estimation of the total surface area of the pores formed within the tablets. The calculation of the volume of lactose in the coating allowed for a quantitative assessment of the amount of lactose leached and thus the size and number of pores generated. By considering the individual volume and surface area of a single lactose particle, the surface area of the entire pore network within the compression-coated tablets were estimated.

2.2.7 Mechanical properties of the coating in the dry and wet state

Tablets prepared from coating formulations (11mm diameter with different thickness) were fixed in a self-designed Teflon holder with several holes (diameter 10 mm). The mechanical properties of the coats were measured using a texture analyzer (TA.XT. Plus texture analyzer, Stable Micro Systems Ltd., UK). A metal probe with a hemispherical end (diameter 5mm, length 15 cm) was driven through the dry coat at a speed of 5mm/min. Force (N) versus displacement (mm) curves were recorded with a 5 kg load cell (n = 3). Then, the holder with the fixed coat was immersed into 0.1 N HCl at horizontally shaking for 5 h (37 °C, 80 rpm), and rupturing tests were performed on the wet tablets at predetermined time intervals (n = 3). The following parameters were calculated:

$$\text{Breaking strength} = \frac{\text{Force at coat break}}{\text{Area of the cross section of the coat within the holder}}$$

Strain at the coat break was calculated as follows:

$$\text{Strain/elongation, \%} = \frac{\Delta l}{r} * 100 = \frac{\sqrt{r^2 + D^2} - r}{r} * 100$$

where Δl is the linear expansion of the coat, r is the radius of the hole in the holder and D is the displacement of the probe.

2.2.8 Moisture treatment of the coating

Tablets prepared from coating formulations (11mm diameter with 2 mm thickness) were stored at different humidities [0% RH (silica gel); 75% RH (saturated NaCl); 84% RH (saturated KCl)] at room temperature for 2 months for moisture-equilibrated samples. The moisture content of the samples was determined by weighing samples before and after moisture treatment and was

calculated as a percentage based on the initial weight. The mechanical properties of the coat were measured based on section 2.2.7.

2.2.9 Stability test

Tablets were packaged into blisters on a blister machine (Sepha EZ Blister, Dundonald Belfast, Northern Ireland). The settings were used to form (pressure 0.6 MPa, time 2.0 sec), seal (pressure 0.6 MPa, time 2.0 sec, temperature 160 °C), and cut (pressure 0.4 MPa, time 1.0 sec) the blister. No forming temperature is used for aluminum foil as this material is formed by physical deformation (cold-forming). For base 150 micron ALU/ALU and lidding 20 micron hard were used (Constantia Patz GmbH, Loipersbach, Austria). To assess the long-term stability of the tablets, a stability test was conducted. The samples were placed in a stability chamber (Sanyo Gallenkamp PLC, Leichter, UK) and exposed to 25 ± 2 °C and a relative humidity of 60 ± 5% for 7 to 30 d.

2.2.10 Core swelling force

Core swelling force experiments were conducted using a custom-built swelling device. The core tablets were positioned within a Plexiglas cylinder and placed on top of a glass filter with porosity grade #1 (Fig. 7). A texture analyzer probe was then carefully positioned on the top of the tablet and maintained in a fixed position throughout the experiment (n=3). To measure the core swelling force, buffer pH 6.8 was used. During the experiment, the swelling force exerted by the core tablets was recorded using the texture analyzer. The device measured the force required to resist the swelling of the tablets as they absorbed the media.
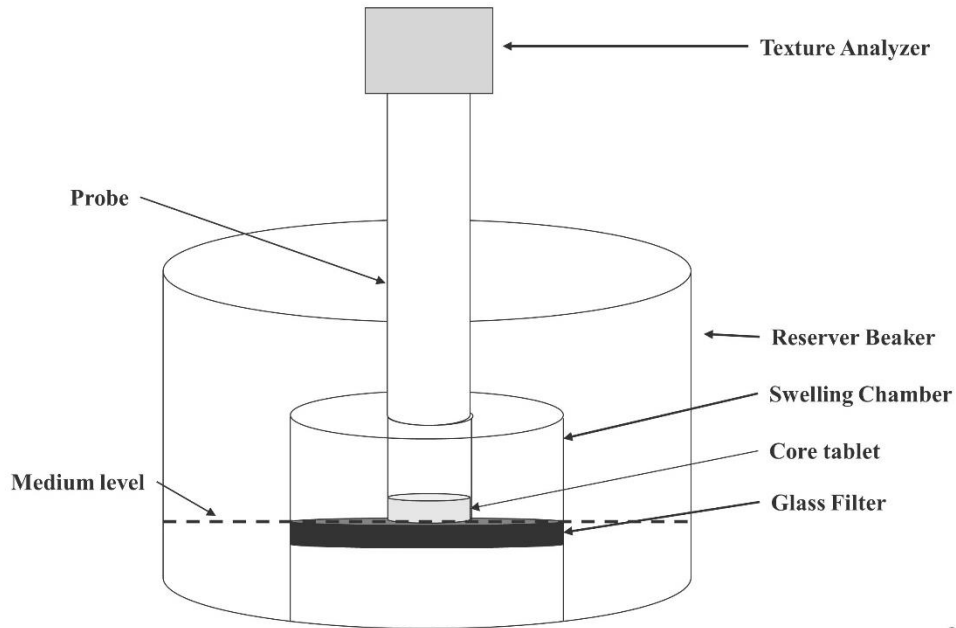
Fig. 7 Swelling device for measuring the core swelling force by using texture analyzer.

2.2.11 Core water uptake and swelling energy

Water uptake and swelling energy experiments (n = 3) were conducted using a self-built device. The setup involved placing 11 mm core tablets inside a Plexiglas cylinder on a glass filter with porosity grade #1 (Fig. 8). The core tablets were positioned on the glass filter, and a predetermined weight load punch was placed on top of each tablet. To initiate the experiment, a medium with a pH 6.8 at room temperature was added to the device. The medium was carefully poured into the device, filling it up to the level of the glass filter. As the medium penetrated through the filter, it triggered the swelling process of the core tablets. Throughout the experiment, the displacement of the weight load punch was closely monitored and recorded over time. The punch was pushed upward as the tablets swelled, indicating the extent of swelling and the associated mechanical forces.

The swelling energy (E) was calculated as:

$$E = F_{weight} \cdot d$$

where E represents the swelling force in millijoules (mJ), Weight is the predetermined weight force applied by the punch, and d is the displacement of the punch, measured using a scale.

Simultaneously, the water flux resulting from the medium uptake by the core tablets was automatically replaced from a reservoir via a tube system. The weight change of the reservoir beaker was continuously recorded using a digital balance as a function of time. This enabled the measurement of the water uptake kinetics of the tablets.

The medium uptake was calculated as:

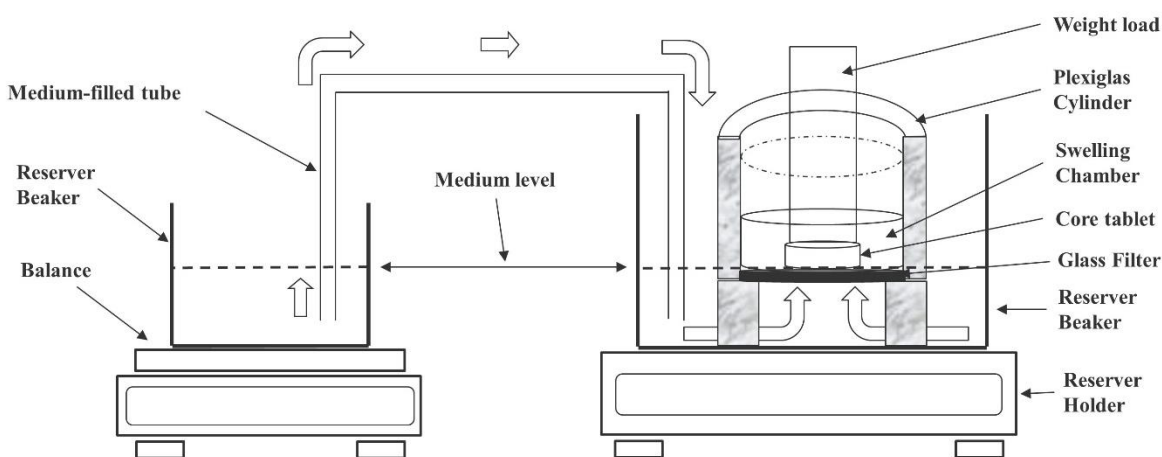$$\text{Media uptake } (\%) = \frac{\text{Amount of water uptake}}{\text{Initial weight of the core}} \times 100$$

Fig. 8 Swelling-device for the simultaneous measurement of the water uptake and the swelling energy developed by the core tablet.

2.2.12 Visual observation

Video monitoring of drug release was carried out using a light macroscope equipped with image analysis software (IC Capture), The Image Source Europe GmbH, Bremen, Germany). The experimental setup involved several steps to enable clear visualization and recording of the drug release process.

Initially, the upper part of the compression-coated tablets was removed using sandpaper. This step allowed for the visualization of the core tablet, which is the area of interest for drug release observation. The tablet was carefully clamped between two transparent plexiglass plates using screws, ensuring a tight seal to prevent any leakage during the experiment.

The clamped tablet was then placed within the media, ensuring that the removed side (the visualized core side) was positioned facing the camera. This arrangement enabled clear imaging of the drug release process. To enhance the visibility of the tablet, a white background was used, and top lighting was employed to ensure adequate illumination. Using the light macroscope and the image analyzing software, pictures were captured at regular intervals to monitor the drug release from the compression-coated tablets. The software facilitated analysis and processing of the acquired images, allowing for precise evaluation of the drug release behavior. By employing this video monitoring approach, it was possible to directly observe and record the drug release process in real-time.

3 Results and Discussion

3.1 Effect of coating formulation parameters on pulsatile release based on lipid-based compression -coated tablets

3.1.1 Background

Pulsatile drug delivery systems are characterized by a lag time and generally a rapid release phase. They are frequently formulated as rupturable [88] or erodible [27] coating systems. Many techniques are used to prepare this system such as traditional coating with tablets [23, 49], capsules [89, 90], or pellets [91] and compression coating technology [49]. The compression-coating technique is a solvent-free process for tablets with thick coatings with a shorter processing time than traditional spray coating. The compression-coated tablet consists of an inner core and an outer coating. The outer coat allows the ingress of water and hydrates/swells the core and develops a swelling pressure, resulting in rupturing of the coating and pulsatile release [83, 92]. By utilizing compression-coating technology, pulsatile drug delivery systems can achieve precise control over drug release profiles, potentially mimicking the natural circadian rhythm of certain diseases. Additionally, this approach allows for the targeted delivery of drugs to specific regions of the gastrointestinal tract, maximizing their therapeutic potential [23, 49].

Various lipids and polymers, such as glyceryl behenate [49], hydrogenated castor oil [25], ethylcellulose [65], and HPMC [93], have been extensively studied as coating materials in compression-coated tablets. These materials play a crucial role in providing the necessary physical strength to the coat, ensuring its integrity during drug release. The lag time of drug release from compression-coated tablets can be effectively controlled by incorporating pore-formers of different solubilities into the coating layer. Hydrophilic pore-formers like HPMC or lactose were utilized in the water-insoluble ethylcellulose outer coating. Lactose showed shorter lag time compared to HPMC [69]. Other pore-formers, including sodium chloride, calcium tartrate, mannitol, sucrose, and directly compressible dextrose, have also been investigated for their impact on drug release from compression-coated tablets [69, 70]. Additionally, factors such as polymer particle size [65], compression force [71, 72], and coating thickness [74] can influence the lag time. Variations in these factors can lead to different release profiles. For instance, low compression force combined

with higher coating thickness resulted in immediate release after the lag time, whereas high compression force and low thickness led to a slower release profile. These effects can be attributed to changes in the density of the coat, which directly impact the drug release kinetics [94 - 96].

The objective of this study was to develop a pH-independent compression-coated tablet for potential colonic drug delivery and to evaluate the effect of coating formulation parameters on pulsatile release. The proposed system consists of core tablets composed of drug (propranolol HCl) with superdisintegrant (crosscarmellose sodium) and filler (lactose). The coating layer contains lipid (glyceryl behenate), pore former (dicalcium phosphate or lactose), and binder (polyvinyl pyrrolidone).

3.1.2   Results and discussion

This study aimed to develop a time-controlled pulsatile release tablet system utilizing compression-coating technology. To achieve this, croscarmellose sodium was chosen as the swelling agent in the core tablet due to its high swelling capacity, as reported in previous studies [88]. Glyceryl behenate was selected as the main coating material and lipid component for its hydrophobic nature. Glyceryl behenate, being hydrophobic, contributes to the formation of a mechanically weak coating when water enters the system and dissolves the pore-former. This weak coating exhibits low breaking strength and low strain. As the core tablet containing croscarmellose sodium absorbs water, it swells and generates a swelling pressure within the tablet. This swelling pressure ultimately leads to the rupture of the coating layer. The rupture of the coat enables the pulsatile release of the drug from the core tablet.

To investigate the effect of the pore-former on drug release, dicalcium phosphate was compared to lactose. Dicalcium phosphate showed pH-dependent drug release due to pH-dependent solubility [97] (Fig. 9 A). A pH-independent release was achieved using lactose as the pore former (Fig. 9 B). In addition, dicalcium phosphate showed higher water uptake and dry mass loss in pH 1.2 than pH 6.8 (Fig. 10 A and B). In contrast, pH independent water uptake and dry mass loss were observed from lactose (Fig. 10 A and B). The lactose coat had much more water uptake and dry mass loss than dicalcium phosphate due to a higher solubility.

In this study, the impact of the pore-former on the mechanical properties of the coat in wet state was investigated. A blend of coating material was compressed into tablets with dimensions of 11

mm diameter and 2 mm thickness. The mechanical properties of the coat were evaluated over time, considering the dissolution of the pore-former and the resulting changes in the coat structure. The breaking strength of the coat containing dicalcium phosphate was higher in pH 6.8 compared to pH 1.2 (Table 3). This can be attributed to the pH-dependent solubility of dicalcium phosphate, resulting in a stronger coat in pH 6.8. In contrast, the pH of the medium had no significant effect on the breaking strength of the coat containing lactose. Furthermore, the breaking strain of the coat, which indicates its elasticity, was not affected by the pH of the medium (Table 3). This suggests that the mechanical flexibility of the coat remained constant regardless of the pH conditions. Lactose is a more favorable pore-former for the development of rupturable pulsatile release systems. Lactose exhibited stable mechanical properties and did not show dependence on the pH of the medium. Lactose can maintain the structural integrity of the coat while allowing for controlled rupture upon swelling, making it a suitable choice for achieving pulsatile drug release.
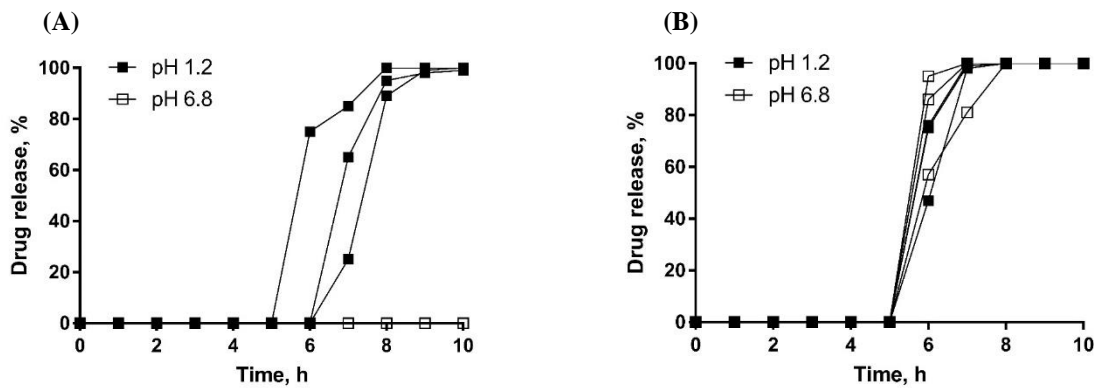
Fig. 9 Effect of the pore-former (A) dicalcium phosphate and (B) lactose on release, coat containing 40%, (w/w) glyceryl behenate, 50% (w/w) dicalcium phosphate or lactose, 10% (w/w) PVP.
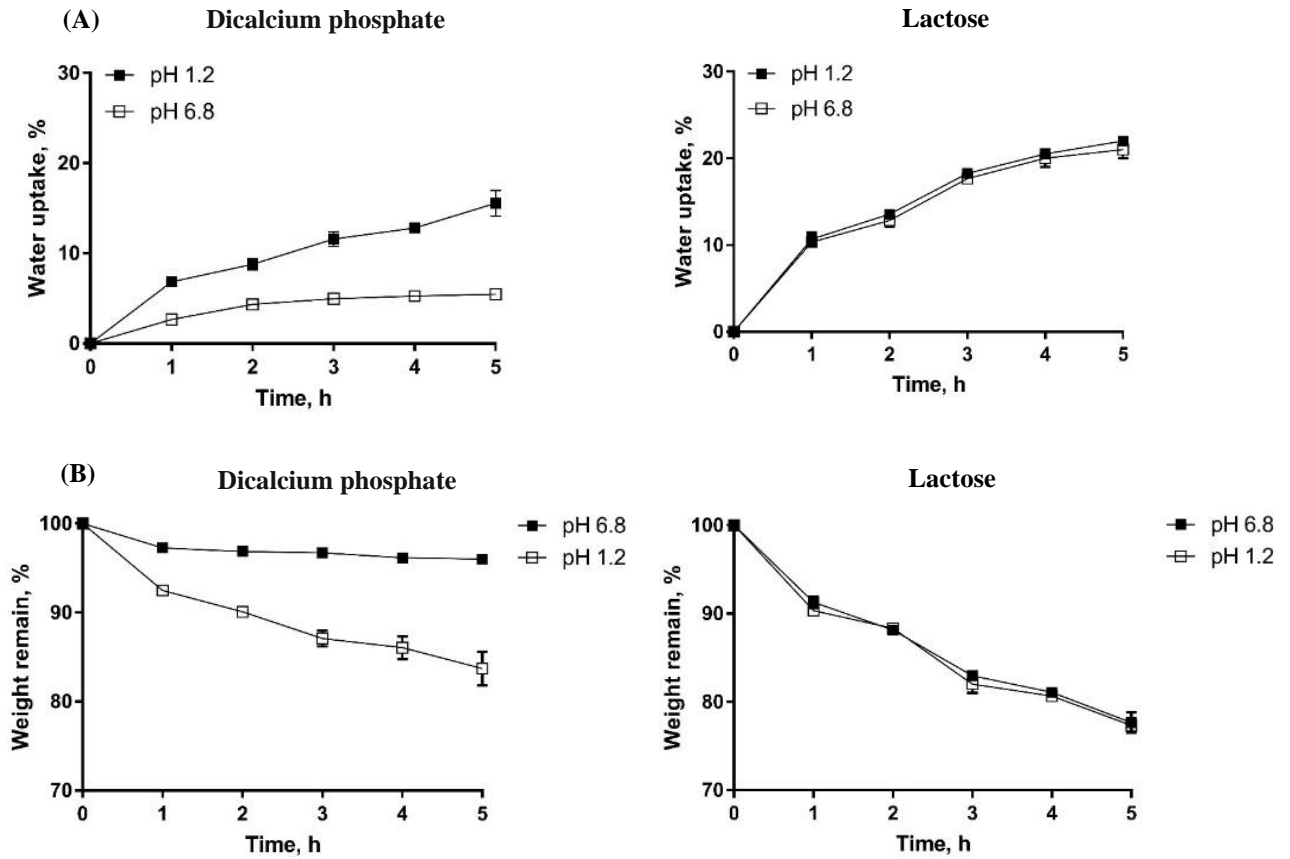
Fig. 10 Effect of pore-former on (A) water uptake and (B) dry mass loss, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) dicalcium phosphate or lactose, 10% (w/w) PVP.

Table 3 Effect of pH and pore-former type on the wet mechanical properties of the coating after 5h incubation

Pore-former	Medium	Breaking strength (MPa)	Strain (%)	Energy (MJ)
Dicalcium phosphate	pH 1.2	0.21 ± 0.02	0.16 ± 0.04	0.34 ± 0.05
	pH 6.8	0.45 ± 0.05	0.20 ± 0.02	0.70 ± 0.03
Lactose	pH 1.2	0.18 ± 0.05	0.14 ± 0.03	0.27 ± 0.05
	pH 6.8	0.20 ± 0.03	0.15 ± 0.04	0.29 ± 0.04

The control of lag time can be achieved by varying the composition (lipid/pore-former ratio) and thickness (upper and lower) of the compression-coating, in addition to the choice of pore-former. Variations in the coating composition and thickness can influence the lag time (Fig 11 A). Regardless of the coating thickness, an increase in the amount of pore-former leads to a decrease

in the lag time (Fig. 11 B). This is attributed to the enhanced permeability of the coat resulting from the higher pore-former content. On the other hand, increasing the coating thickness extends the lag time due to the increased mechanical strength of the coat. Interestingly, there was little difference in the release profiles between 2 mm and 3 mm coated tablets (Fig. 11 C). The crack in the tablets appeared at the powder interface in the middle of the tablet during the coating process (Fig. 11 D). This crack acted as a weak point in the structure, allowing for the rupture of the tablets into two halves upon swelling. After rupturing, the drug was rapidly released while the coat remained intact. However, longer release time (t_{80-10}) was observed in 1 mm coat due to detachment of small fragments from the edge of the tablets and core exposed to dissolution medium slowly resulting slow release after lag time (Fig. 11 C and D). It's inferred that at least 2 mm coating thickness is required to obtain pulsatile release. This ensures the formation of a crack at the desired location and facilitates the rapid release of the drug upon swelling while maintaining the structural integrity of the coat.
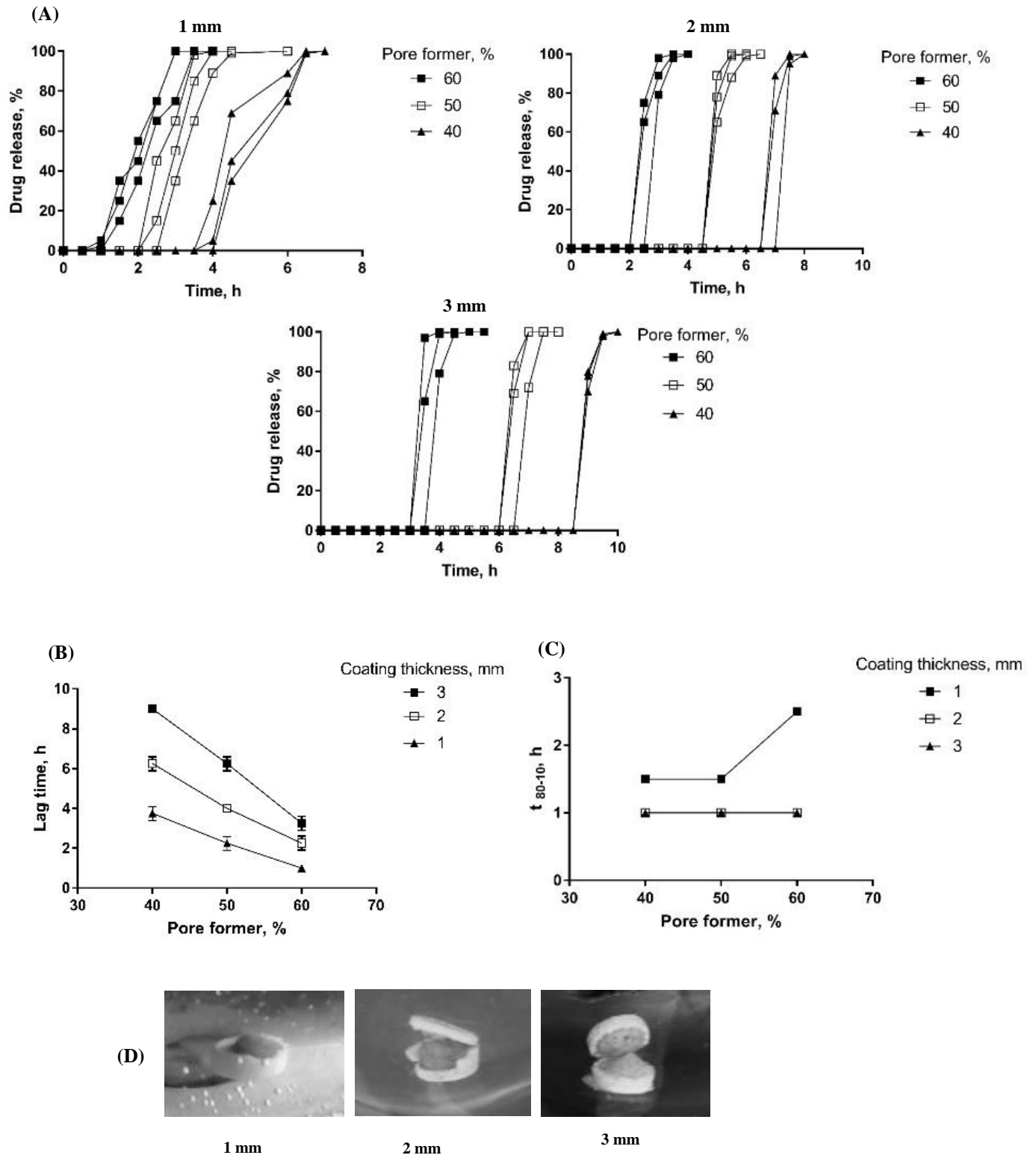
(A)

(B)

(C)

(D)

Fig. 11 Effect of lactose concentration on the drug release (A) different coating thickness (B) lag time (C) release time (D) rupture profile, coat containing 30 - 50% (w/w) glyceryl behenate, 40 - 60% (w/w) lactose, 10% (w/w) PVP.

Simultaneously with the investigation of drug release, the study also examined the uptake of release media by the compression-coated tablet. This analysis provided valuable insights into the behavior of the coating in response to the surrounding environment. The media uptake exhibited a nearly linear trend until the coat ruptured (Fig. 12 A). The rate of media uptake decreased with increasing coating thickness. However, the extent of water uptake at the rupture point remained relatively consistent across different coating thicknesses, ranging from 23.7% to 25.0% (w/w). The trend of decreasing media uptake with increasing coating thickness can be attributed to the higher mechanical resistance of the thicker coating. The thicker coating layer restricts the ingress of the release media, resulting in a slower rate of water uptake compared to thinner coatings and maximum water uptake values were slightly higher for the thicker coatings due to their enhanced mechanical strength (Fig. 12 B).
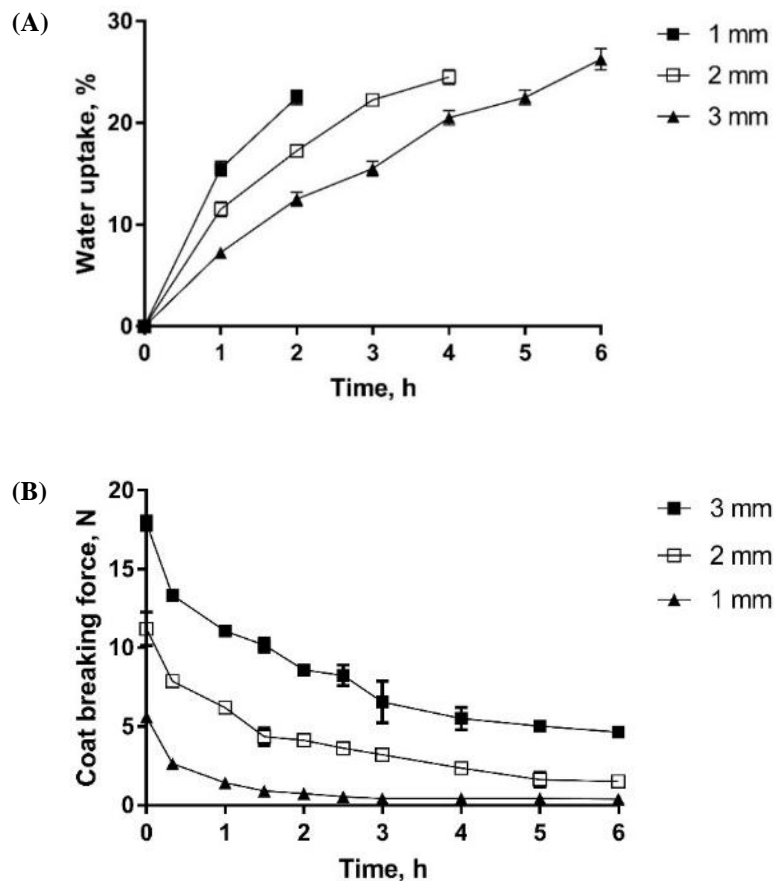
Fig. 12 Effect of coating thickness on (A) water uptake and (B) wet mechanical property, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.

The addition of soluble additives, known as porosity modifiers, to the insoluble coat plays a significant role in altering the permeability and influencing the release rate of the drug [70]. To study the effect of particle size of lactose on drug release, compression-coated tablets were prepared with different size lactose. The lag time increased with increasing the particle size (Fig. 13 A). This is due to the slow leaching of lactose from larger particles (Fig. 13 B). This observation is further supported by erosion/dry mass loss studies (Fig. 14), which demonstrate that tablets containing smaller lactose particles promote faster erosion and dry mass loss, confirming the shorter lag time. Furthermore, a correlation can be observed between the pore surface area and both lactose leaching rate and lag time (Fig. 13 C and D). The surface area of the pores directly influences the leaching rate of lactose and, subsequently, the lag time of drug release. It is important to note that the coating formulation included a fixed concentration of binder (PVP) at 10% (w/w). To ensure no leaching of binder, additional experiments were conducted by preparing compression-coated tablets without lactose. The results confirmed that there was no significant dry mass loss in the tablets, indicating that the binder remained intact within the coat and did not dissolve or leach out during the dissolution process. Additionally, the water uptake data showed no significant increase, further supporting the absence of binder leaching (Fig. 15).
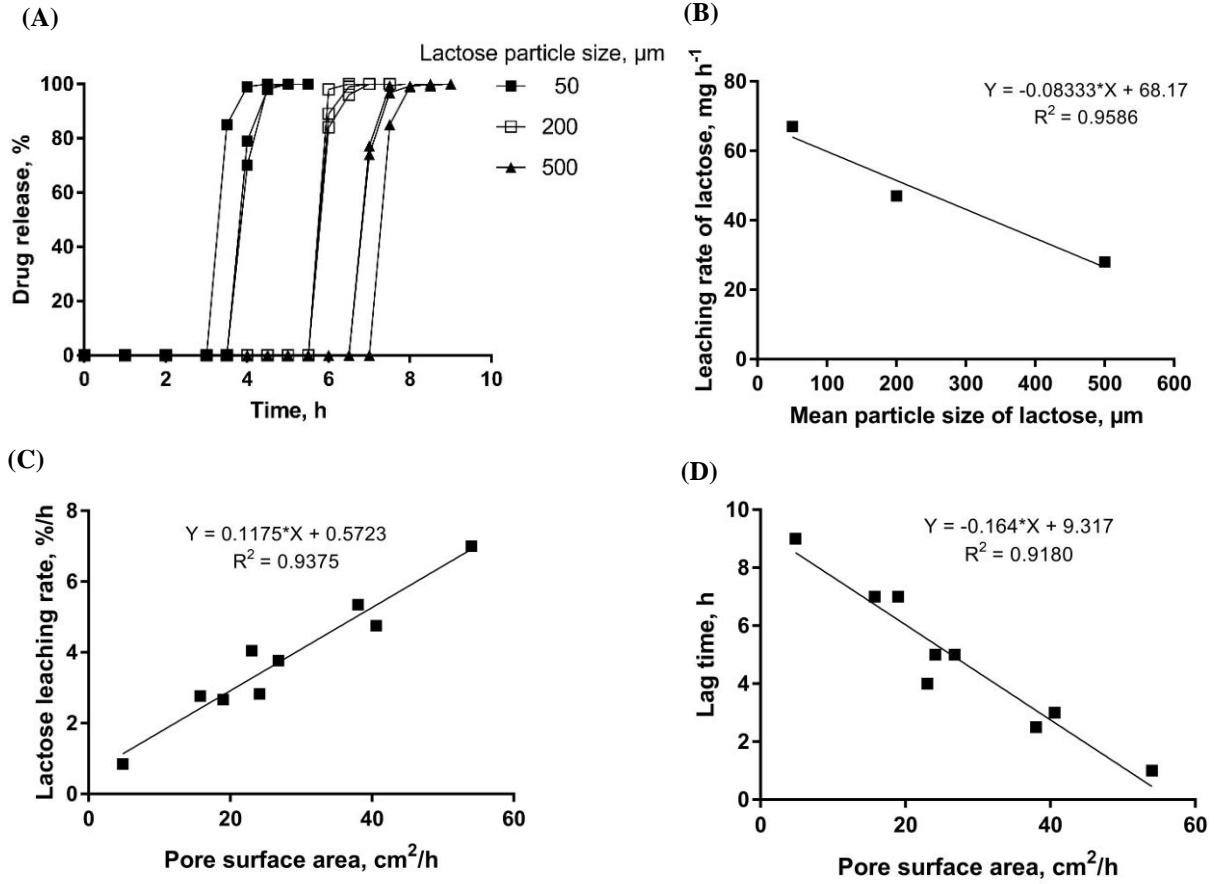
(A)

(B)

(C)

(D)

Fig. 13 Effect of lactose particle size on (A) drug release (B) leaching rate, and relationship of pore surface area with (C) leaching rate and (D) lag time, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.
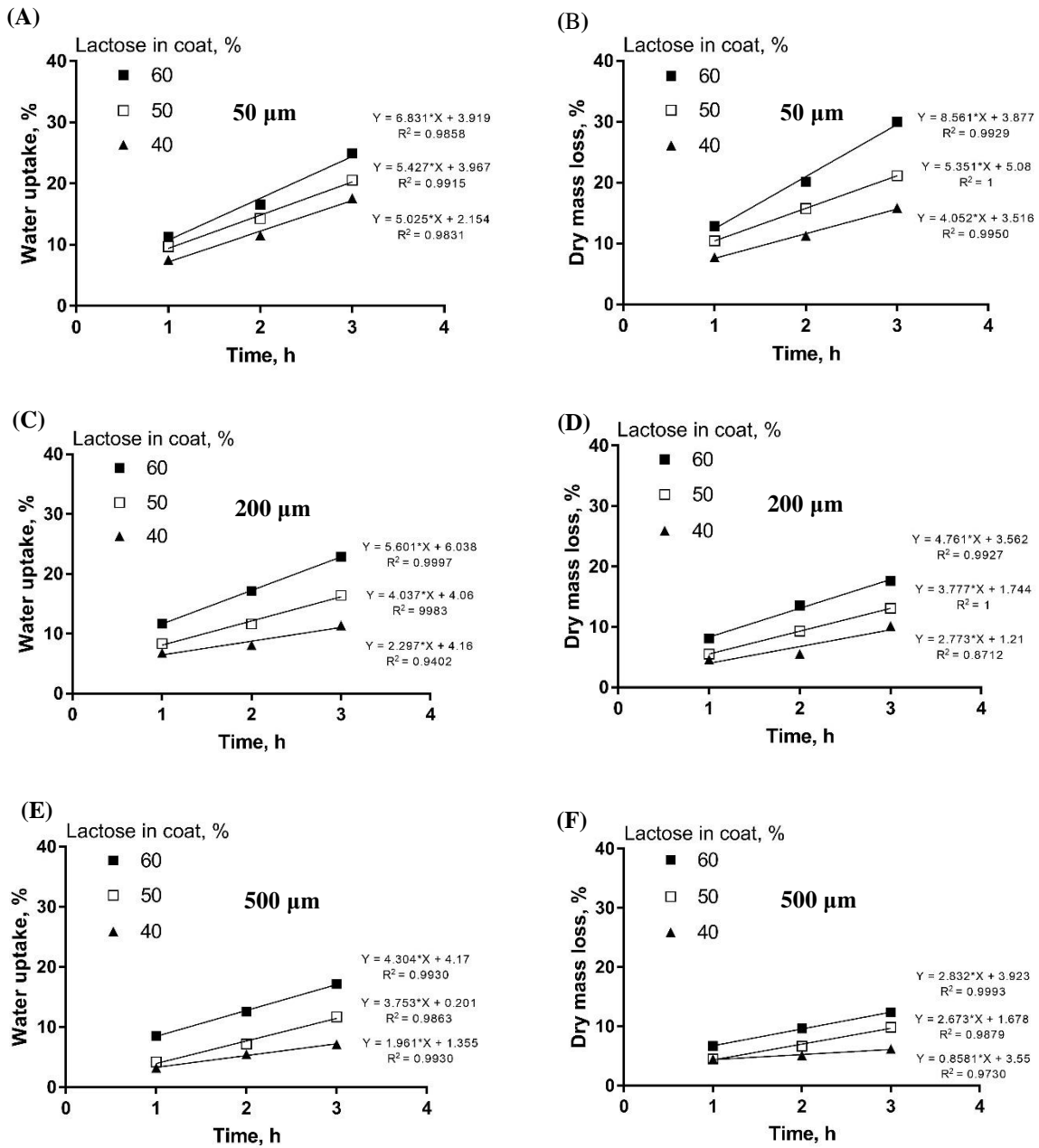
Fig. 14 Effect of lactose content on coat water uptake from (A) 50 μm, (C) 200 μm and (E) 500 μm, and dry mass loss from (B) 50 μm, (D) 200 μm, and (F) 500 μm. (coat containing 30 – 50% (w/w) glyceryl behenate, 40 – 60% (w/w) lactose and 10% (w/w) PVP.
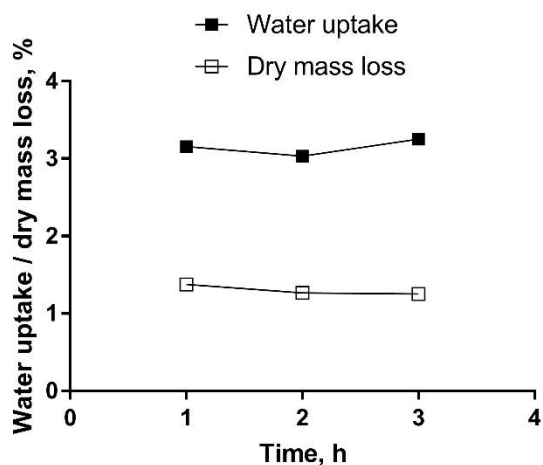
Fig. 15 Water uptake and dry mass loss study from the coat containing 90% (w/w) glyceryl behenate and 10% (w/w) PVP.

Binders play a crucial role in the compression-coating process by promoting the adhesion and cohesion of the powder particles, thereby ensuring the formation of robust tablets with desirable mechanical properties [99].

In this study, coating without binder (PVP) showed immediate drug release because of poor interparticle bonding, leading to rapid disintegration of the coat upon contact with the dissolution medium (Fig. 16 A). However, with 5-10% binder, a distinct lag time followed by a rapid drug release was observed (Fig. 16 B). The inclusion of the binder improved the mechanical properties of the coat, enhancing its integrity and resistance to immediate disintegration.
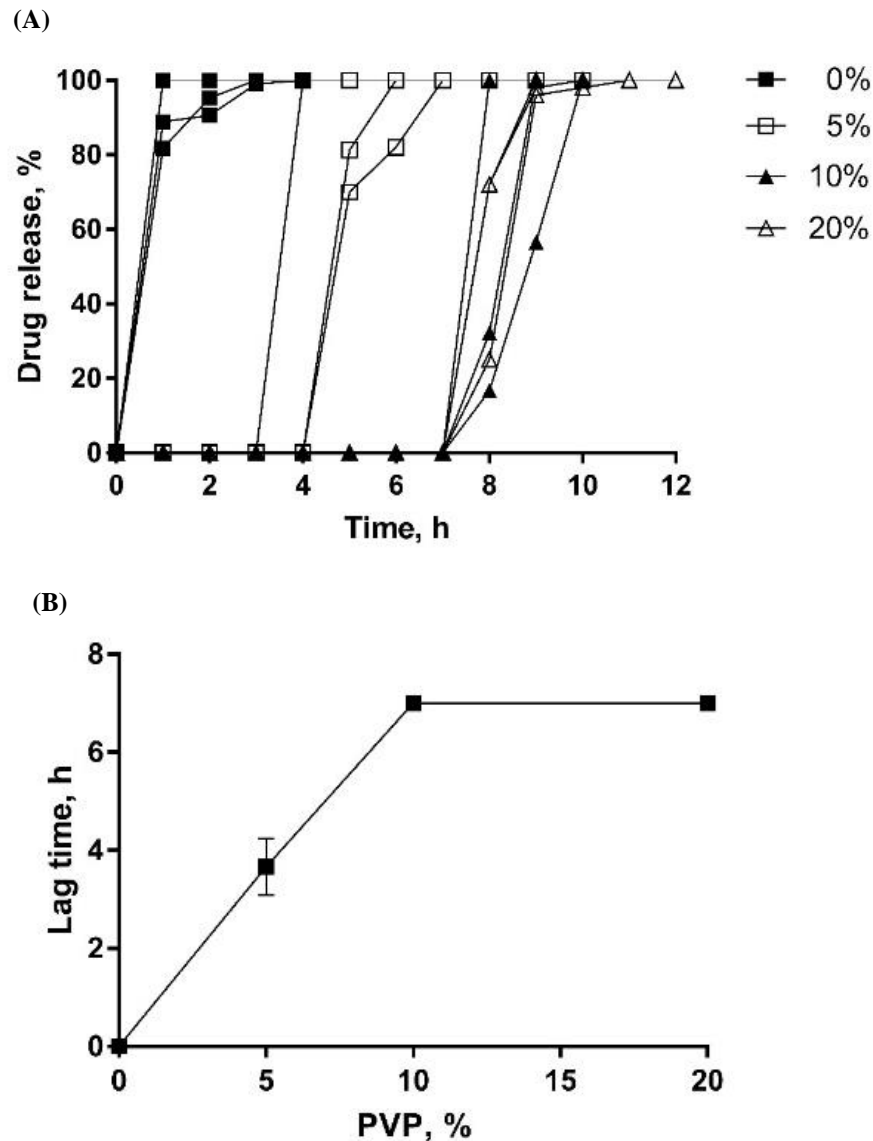
(A)

(B)

Fig. 16 Effect of PVP content on (A) drug release and (B) lag time, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.

The impact of compression force on the lag time depends on the composition of the coating formulation. HPMC K4M, which forms a gel layer on the tablet surface, is not significantly affected by compression force [30]. However, for ethylcellulose-based coatings, the compression force plays a significant role in modulating the lag time.

As expected, increasing the compression force within the range of 10-25 kN resulted in a corresponding increase in the lag time (Fig. 17 A and B). This can be attributed to the reduction in porosity and the simultaneous increase in the density of the coating. Higher compression forces lead to tighter compaction of the coating layer with high mechanical property (Fig. 17 C), reducing its permeability and delaying the ingress of water into the core tablet. Interestingly, despite the increased lag time with higher compression forces, the release profile remained unchanged, and immediate drug release was observed. The lag time can thus be controlled by changing the compression force without, significantly affecting the subsequent pulsatile release.
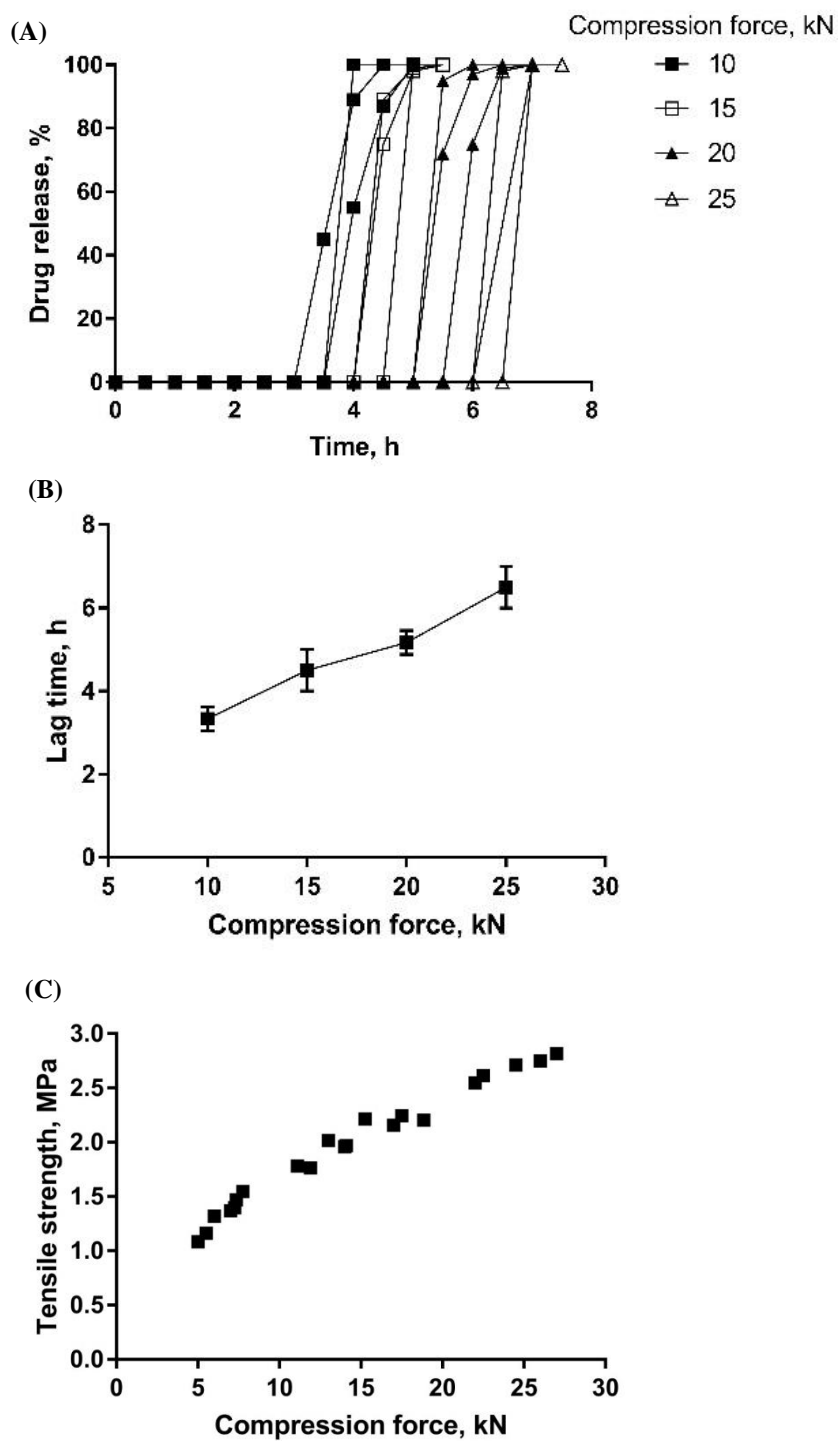
Fig. 17 Effect of compression force on (A) drug release, (B) lag time and (C) tensile strength, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.

The gastrointestinal tract (GIT) exhibits different contractile activities along its various segments. For instance, the colon has lower contractile frequencies compared to the stomach [100]. Therefore, when developing a dosage form targeting the colon, it is crucial for the formulation to withstand the mechanical stresses encountered during its passage through the GIT. Compression-coated tablets are designed to maintain their mechanical integrity until they reach the desired site of release.

To assess the robustness of the tablets under mechanical stress, core tablets loaded with propranolol HCl were prepared and coated with a 2 mm thick layer. The drug release behavior was then evaluated under various agitation speeds from 0 to 150 rpm. Surprisingly, similar lag times were observed (Fig. 18). The independence of the lag time from the agitation speed suggests that the tablets possess a consistent mechanical strength that can withstand the peristaltic forces encountered throughout the GIT. This is an essential characteristic for a dosage form targeting the colon, as it ensures the integrity and functionality of the coat until it reaches the desired site of drug release.
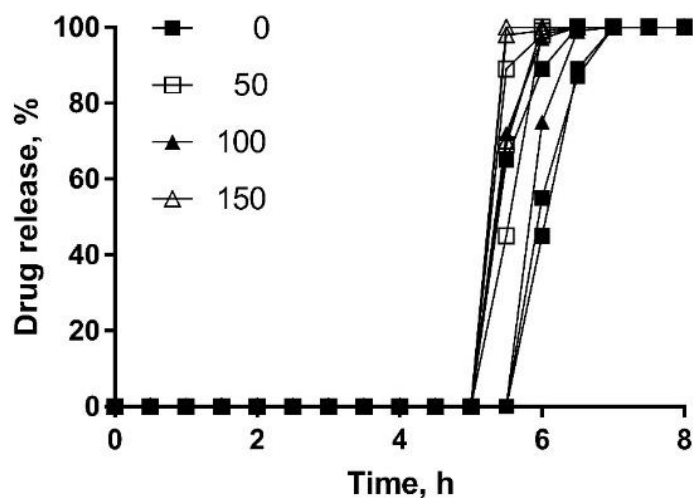

Fig. 18 Effect of paddle rotation speed on drug release, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.

Achieving high drug doses in compression-coated tablets poses a challenge due to the increased amount of coating materials required and the larger size of the dosage form. To evaluate the impact of dosage form size on the drug release, a 2 mm coating thickness were prepared using different sizes of core tablets. The formulations included an 11 mm core in a 15 mm tablet, a 9 mm core in a 13 mm tablet, and a 7 mm core in an 11 mm tablet. Surprisingly, all formulations exhibited pulsatile release with nearly identical lag times (Fig. 19). The size of the tablet does not significantly affect the release behavior. Despite the variation in core tablet size, the compression-coated tablets demonstrated consistent and predictable drug release kinetics, indicating that the pulsatile release mechanism is independent of the tablet sizes.
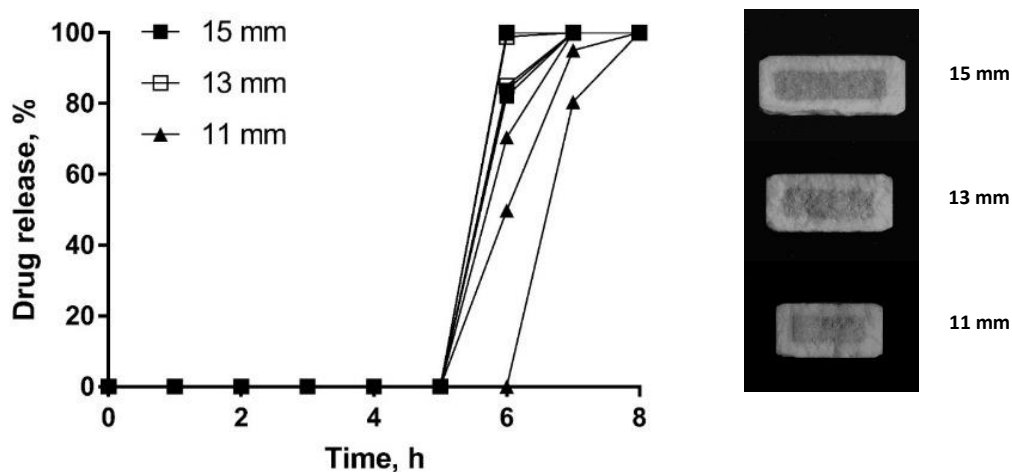

Fig. 19 Effect of tablet size on drug release, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP, compression-coated tablet: core, mm (15 : 11, 13 : 9, 11 : 7)

Thermal treatment is a commonly employed technique to modify the drug release from different coats [103]. The impact of curing temperature and time on the drug release profile was investigated using propranolol HCl loaded core tablets coated with a blend comprising 40% w/w glyceryl behenate, 50% w/w lactose, and 10% w/w PVP, with a coating thickness of 2 mm. Curing at 60 °C for 1 h and 70 °C did not significantly affect the release of propranolol HCl (Fig. 20 A, B and C). However, when the curing time was extended to 1 h at 70 °C, a noticeable increase in the lag time was observed. This may be attributed to the enhanced mechanical properties of the coating resulting from prolonged exposure to higher temperatures. Despite the prolonged lag time, the release profile

57

remained unchanged. Interestingly, during the rupture of tablets cured at 70 °C for 1 h, detachment of a fragment of the coating was observed (Fig. 20 D).
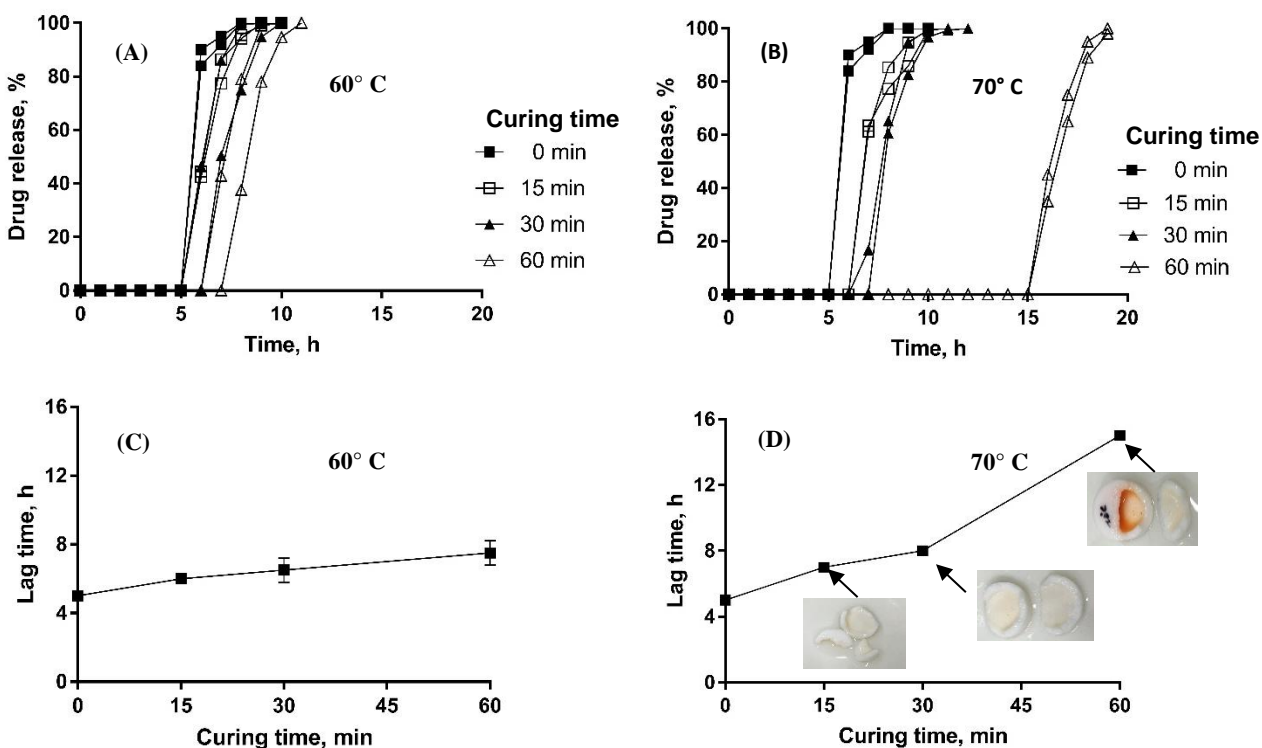

Fig. 20 Effect of curing temperature and time on drug release (A) 60 °C (B) 70 °C and lag time (C) 60 °C and (D) 70 °C, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.

Ensuring the stability of a dosage form is crucial to maintain consistent drug release over its shelf life. According to the current ICH guidelines (2009), long-term stability testing is typically conducted at 25 °C / 60% RH. The drug release was assessed over a period of 12 weeks under the recommended stability testing conditions (25 °C / 60% RH). The drug release profile remained unchanged throughout the entire testing period (Fig. 21). The consistent drug release observed over the 12-week testing period indicates that the coating formulation is robust and capable of maintaining its functional properties under the specified storage conditions.
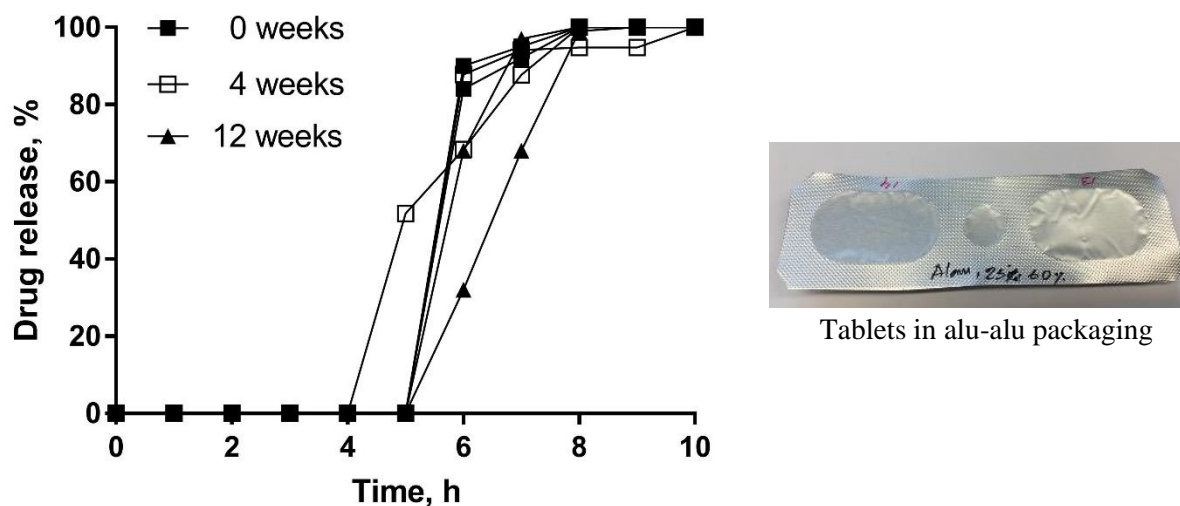
Tablets in alu-alu packaging

Fig. 21 Effect of the storage condition on propranolol HCl release from compression-coated tablets, coat
containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.

Spray dried lactose is widely used as an excipient in direct compression due to its favorable binding and flow properties [101]. However, it exhibits moisture sorption behavior compared to other types of lactose [102]. Understanding the mechanical properties of the coating is crucial for ensuring the stability and functionality of compression-coated tablets. To investigate the impact of moisture uptake on the mechanical properties of the coat, tablets composed solely of coating materials were prepared with a diameter of 11 mm and a thickness of 2 mm. These tablets were then subjected to elevated humidity conditions, specifically 75% RH and 84% RH, as the humidity increased, the tablets exhibited higher moisture uptake (Fig. 22 A). This increase in moisture content led to a decrease in the mechanical properties of the coat because of the plasticizing effect of absorbed water within the amorphous regions of spray dried lactose (Fig. 22 B) [103]. Interestingly, despite the changes in mechanical properties, the elongation of the coat remained unchanged (Fig. 22 C).
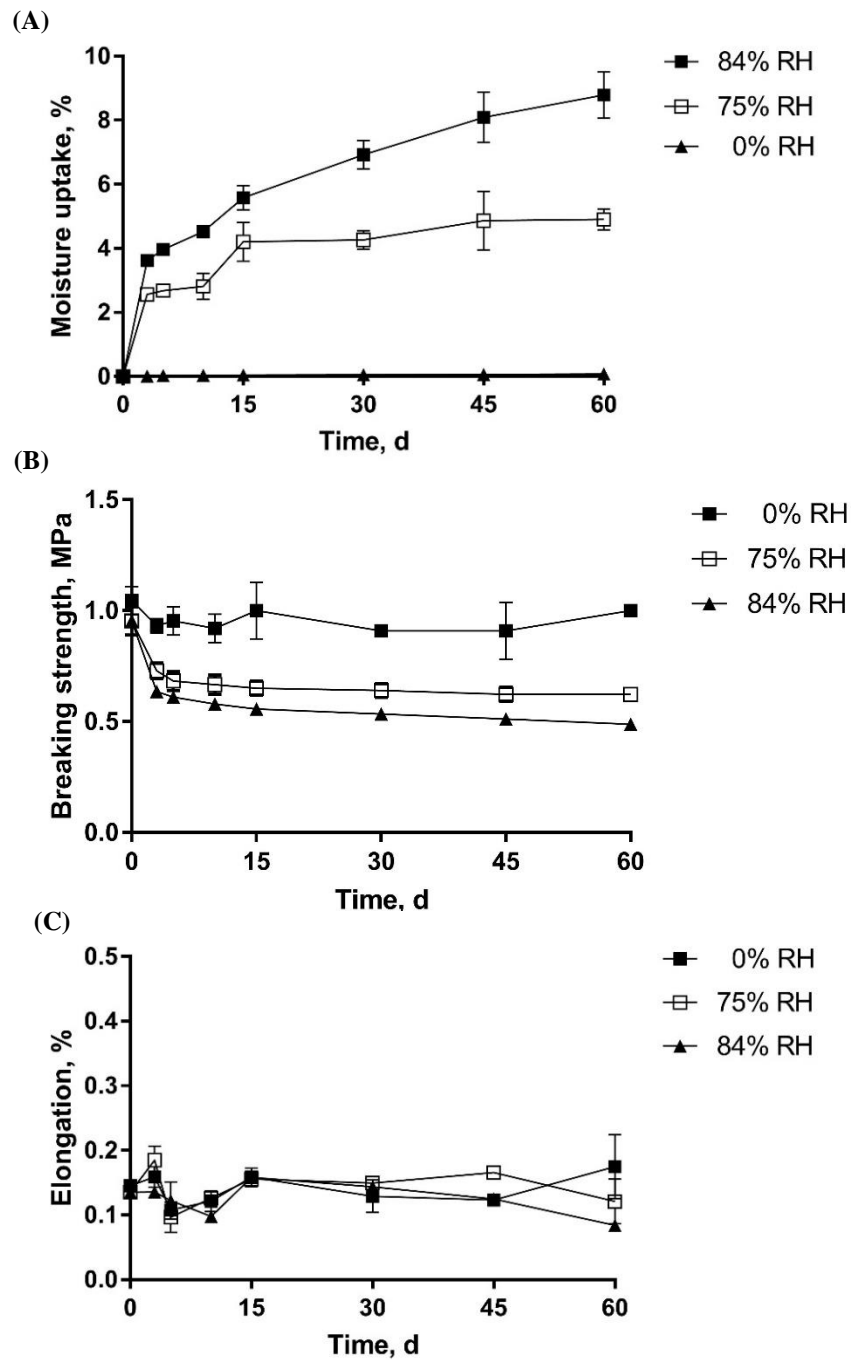
Fig. 22 Effect of storage time (0 – 60 d) and relative humidity (RH) on coat (A) moisture uptake, (B) breaking strength and (C) elongation, coat containing 40% (w/w) glyceryl behenate, 50% (w/w) lactose, 10% (w/w) PVP.

Lodotra[®] is a commercially available compression-coated tablet with pulsatile drug release. The drug release profile of Lodotra[®] 5 mg tablet has a distinct lag time of 4.5 ± 0.5 h, followed by rapid drug release (Fig. 23 A). Notably, the lag time (t_{10}) and release time (t_{80-10}) were slightly longer at pH 6.8 compared to pH 1.2, because of the presence of dicalcium phosphate in the coating. To gain further insights, additional investigations were conducted. A lower mechanical property, higher water uptake, and greater dry mass loss was observed at pH 1.2 compared to pH 6.8 due to higher solubility of dicalcium phosphate in pH 1.2 than pH 6.8 (Fig. 23 B, C, and D).
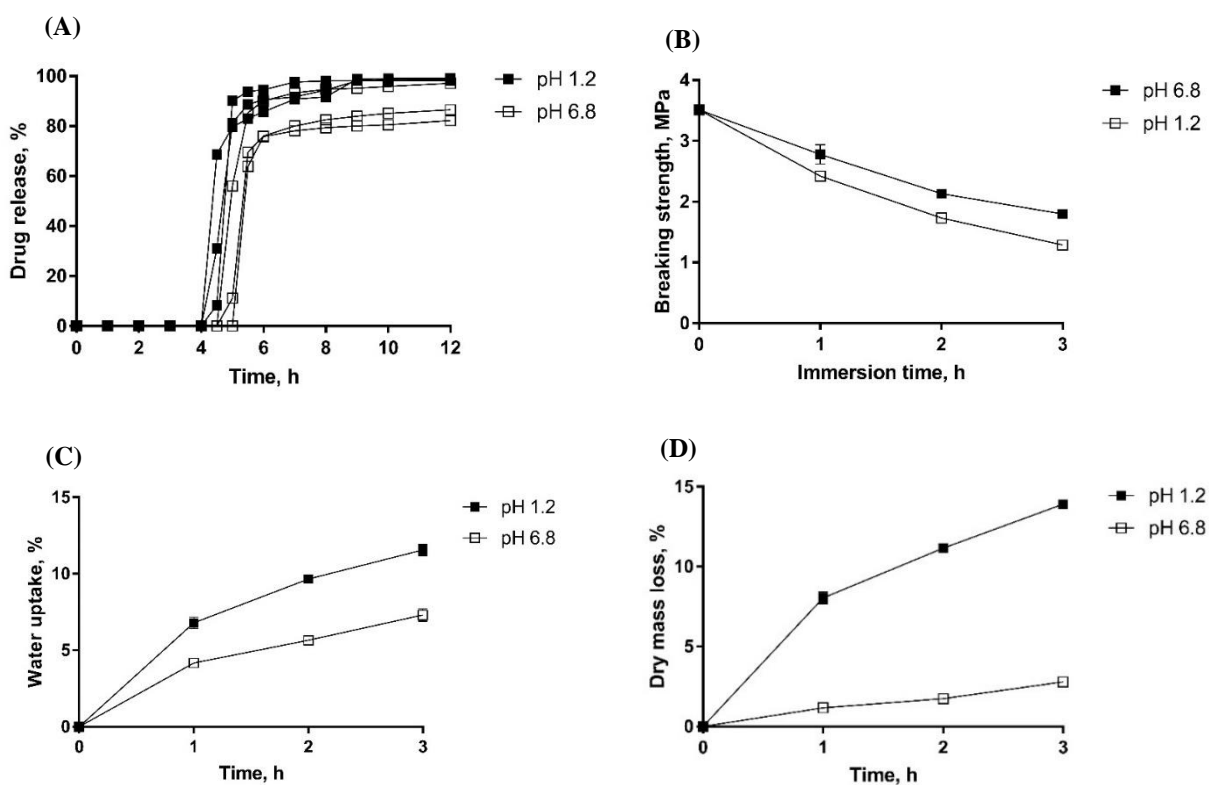

Fig. 23 (A) Drug release (B) wet mechanical properties (C) water uptake and (D) dry mass loss study from commercially available formulation, Lodotra[®] 5 mg.

3.1.3 Conclusion

The development of pH-independent lag times in rupturable pulsatile compression-coated tablets can be achieved by incorporating lactose as a pore-former in a lipid-based coating layer. This pore-former effectively influenced the pulsatile release profile by controlling the water permeability and mechanical properties of the coat. Furthermore, the inclusion of a binder, such as 5-10% PVP, in the coating layer plays a crucial role in determining the lag time of the tablets. Notably, with the presence of the binder, a distinct lag phase is observed in the dissolution profile, followed by rapid drug release after the lag time has elapsed. Additionally, the pulsatile release profile can be further modulated by adjusting factors such as the amount and particle size of the pore-former, the thickness of the coating layer, and the compression force. These parameters directly impact the water permeability and mechanical strength of the coating, thereby influencing the lag time and subsequent drug release behavior. A minimum coating thickness of 2 mm was required to achieve pulsatile release characteristics. This ensured the formation of a crack at the middle of the tablet and facilitates the rapid release of the drug upon swelling while maintaining the structural integrity of the coat. Tablet size, agitation rate (0 rpm to 150 rpm) and log time storage (25°C / 60% RH) did not affect drug release. The mechanical properties of the coating decreased with increasing storage humidity (0% RH to 84% RH) and storage time (0 d to 60 d), as indicated by increasing moisture uptake. Despite the changes in mechanical properties, the elongation of the coating remained unchanged.

3.2 Effect of core formulation parameters on pulsatile release based on lipid-based compression-coated tablets

3.2.1 Results and discussion

The aim of this study was to investigate how core formulation parameters influence pulsatile release in compression-coated tablets. Drugs with varying solubility levels were selected, including carbamazepine, propranolol HCl, and metoprolol tartrate, with solubility values of 0.2, 250, and 1000 mg/ml, respectively. In addition to the drug selection, different loading levels (10 - 60% w/w) were employed, along with the incorporation of various superdisintegrants and fillers, within the tablet core. By investigating the effect of solubility, loading level, superdisintegrants, and fillers on the pulsatile release profile, the study aimed to provide insights into the adaptability and performance of the compression-coated tablets.

Compression-coated tablets were prepared using a core formulation consisting of 60% w/w drug with varying solubility and 40% w/w lactose. The release behavior of the drugs was evaluated, with metoprolol tartrate, the most water-soluble drug, exhibiting zero-order release kinetics after an 11 h lag time (Fig. 24 A). This release pattern could be attributed to the high osmotic pressure generated within the core. Subsequently, the drug diffused through the coat in a zero-order manner. Conversely, minimal release was observed from the less water-soluble drugs, propranolol HCl and carbamazepine (Fig. 24 A). However, as the drug solubility increased (metoprolol tartrate > propranolol HCl > carbamazepine), the drug release also increased, indicating a direct correlation between drug solubility and osmotic pressure. Particularly, even after 24 h of dissolution testing, no rupture of the coat was observed for all drugs. The observations from the cross-section analysis provide valuable insights (Fig 24 B). The empty coating shell observed with metoprolol tartrate formulation confirms the successful release of the drug. In contrast, the wet core observed in the propranolol HCl formulation suggests partial drug release, while the dry core in the carbamazepine formulation indicates limited drug release. This suggests that a core formulation consisting solely of drug and filler was insufficient to rupture the coat. A core formulation consisting of only drug and filler is thus inadequate to achieve efficient coat rupturing and pulsatile drug release.
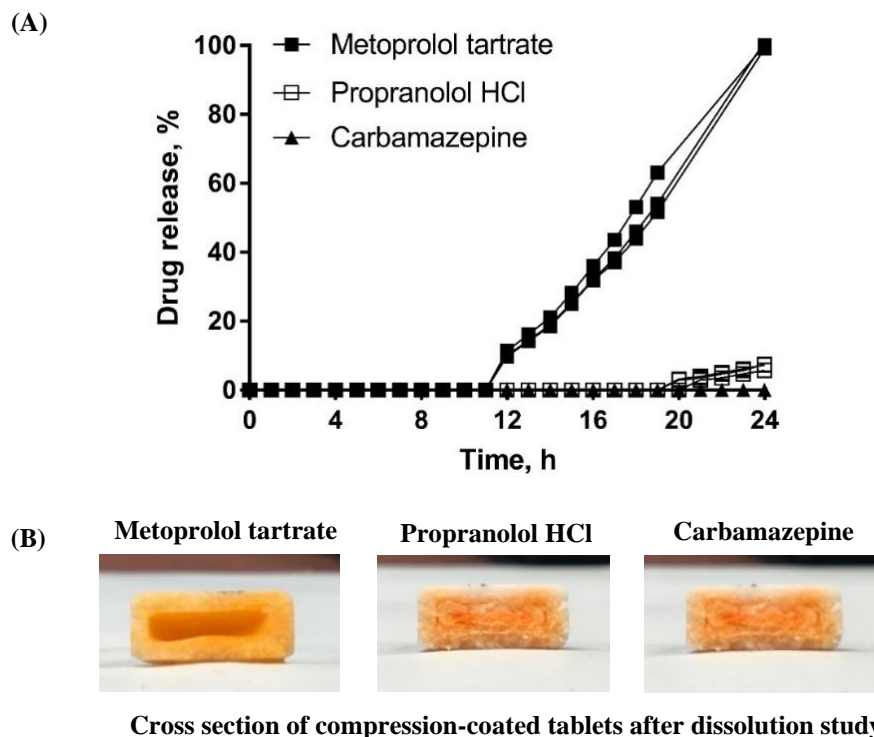
(A)

(B) **Metoprolol tartrate** **Propranolol HCl** **Carbamazepine**

Cross section of compression-coated tablets after dissolution study

Fig. 24 Effect drug solubility on (A) drug release (B) cross-section of tablets after 24 h dissolution study, core containing 60% (w/w) drug, 40% (w/w) lactose.

To facilitate the rupture of the coat, the core tablet needs to generate sufficient swelling pressure upon contact with water. AcDiSol (croscarmellose sodium) was incorporated into the core tablets due to its high swelling capacity [89]. The addition of AcDiSol resulted in a distinct lag time followed by rapid and complete drug release. Notably, the lag time was longer for metoprolol tartrate compared to propranolol HCl and carbamazepine (Fig. 25 A), which can be attributed to the reduced swelling of the core (Fig. 25 B). The decrease in swelling with increasing drug solubility can be explained by the highly soluble components competing for available water within the core. This competition leads to an increase in ionic strength and osmotic pressure, thereby diminishing the effectiveness of the superdisintegrant (AcDiSol) [104]. Visual observation of the swelling behavior of AcDiSol powder in saturated solutions of different drugs further confirmed these findings (Fig. 26). AcDiSol exhibited complete swelling within 15 minutes in saturated solutions of carbamazepine and propranolol HCl, while no swelling was observed in the saturated solution of metoprolol tartrate until 3 h. Similar results were obtained with core tablets prepared using a formulation of 10% AcDiSol and 90% lactose (Fig. 27).

The visual observations of AcDiSol swelling in saturated solutions of different drugs provide additional evidence for its solubility-dependent swelling. The rapid and complete swelling of AcDiSol in the solutions of carbamazepine and propranolol HCl confirms its ability to generate swelling pressure and facilitate coat rupture. However, the absence of swelling in the saturated solution of metoprolol tartrate until 3 h suggests a delayed onset of swelling, potentially contributing to the longer lag time observed with this highly soluble drug. These results clearly indicate that AcDiSol exhibits reduced swelling in the presence of highly soluble components.
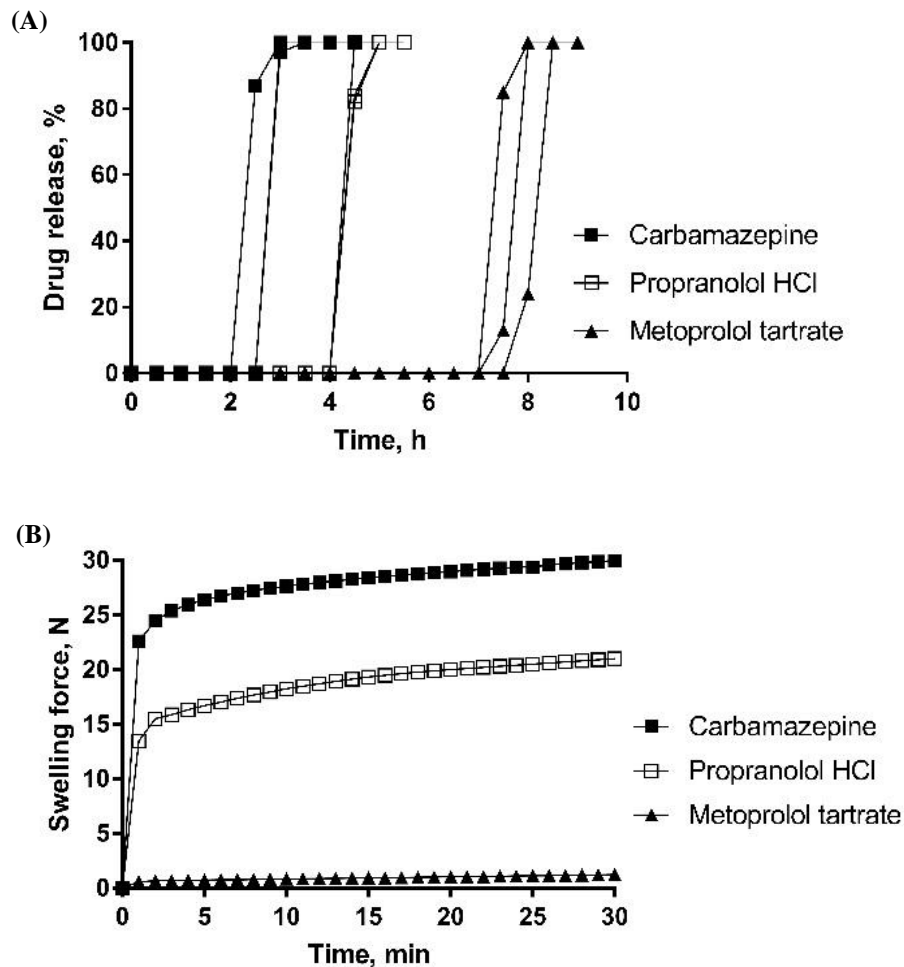

Fig. 25 Effect of drug solubility on (A) drug release (B) swelling force, core containing 60% (w/w) drug, 30% (w/w) lactose and 10% /w/w) AcDiSol.
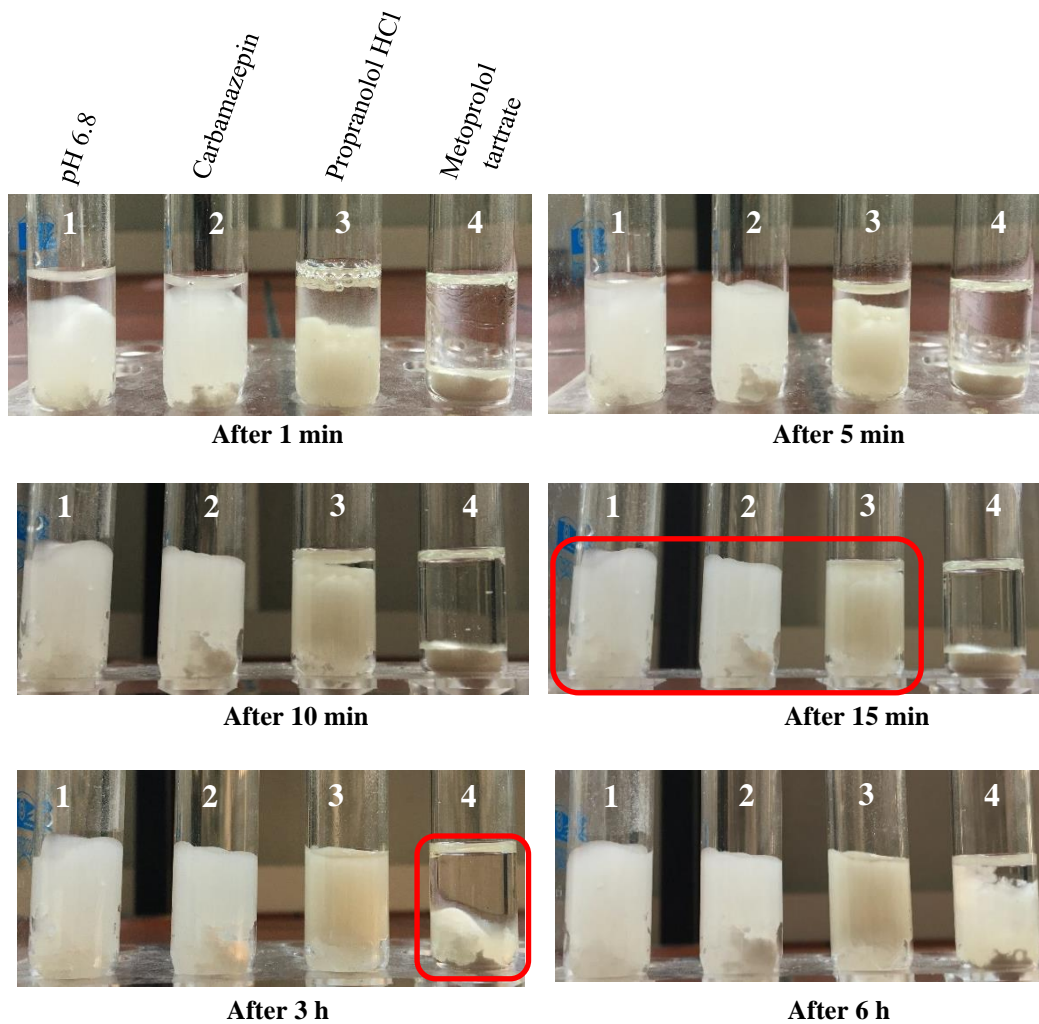
Fig. 26 Swelling of AcDiSol powder in saturated drug solutions.

Saturated drug solution

	Metoprolol tartrate	Propranolol HCl	Carbamazepine

Time

5 s

15 s

30 s

60 s ← Core disintegrated

15 min

30 min

60 min ← Core remain intact
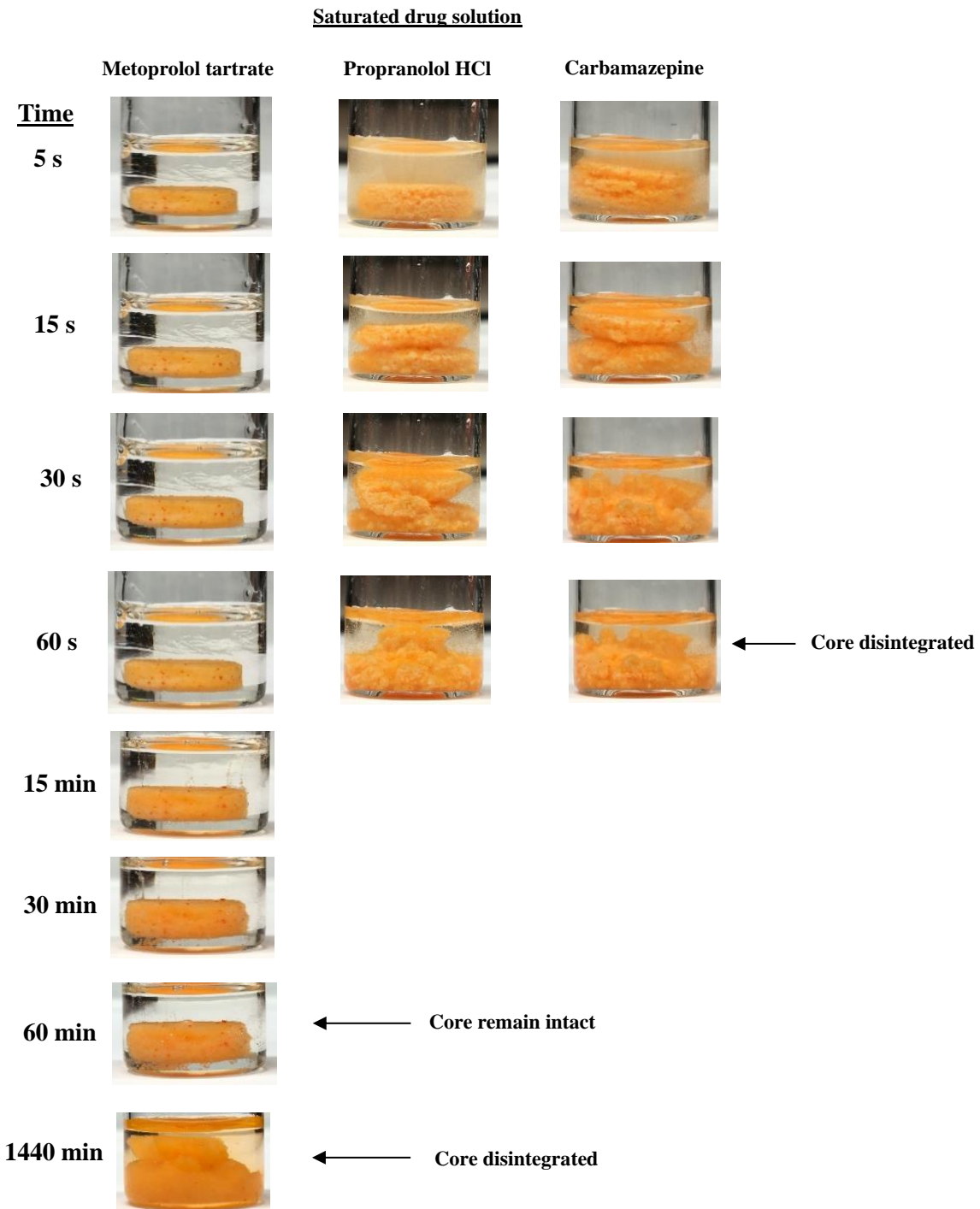
1440 min ← Core disintegrated

Fig. 27 Effect of saturated drug solution on core swelling, core containing 90% (w/w) lactose and 10% (w/w) AcDiSol.

Moreover, the critical water uptake, which is the point at which coat rupture occurs, is influenced by the solubility of the drug. As the drug solubility increased, the water uptake capacity of the compression-coated tablet also increased (metoprolol tartrate > propranolol HCl > carbamazepine) (Fig. 28 A). Furthermore, it was observed that the rate of water uptake and dry mass loss (Fig. 28 B) exhibited a similar pattern for all drugs.
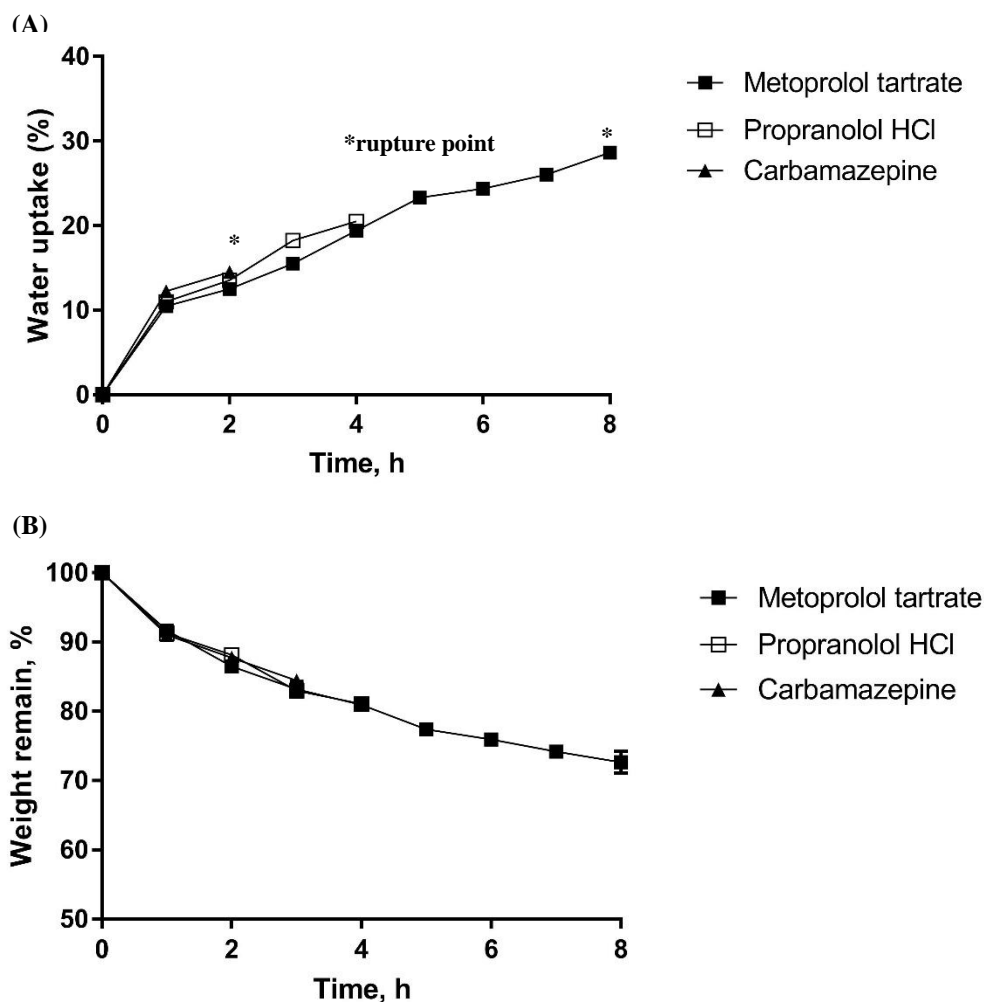
(A)

(B)

Fig. 28 Effect of drug solubility on **(A)** water uptake **(B)** dry mass loss, core containing 60% (w/w) drug, 30% (w/w) lactose and 10% /w/w) AcDiSol.

The drug release mechanism in pulsatile release systems has been explained by several authors [17, 87, 103]. In these systems, water enters through the coat and evenly distributes throughout the core, resulting in the generation of swelling pressure. Subsequently, the coat ruptures, leading to drug

release. The lag time before coat rupture is influenced by the permeability and mechanical properties of the coat, as well as the swelling properties of the core [17, 88, 89]. However, previous studies have primarily focused on a single drug in the core with varying concentrations of swelling agents [20, 107]. Only a limited studies have explored the effects of drug solubility, core fillers, and osmotic agents on drug release [30, 82]. To investigate the impact of drug solubility on core water uptake and swelling, cores containing drugs with different solubilities were placed on a swelling device, and the water uptake and swelling pressure were measured (Fig. 29 A and B). When water reached the core, a high swelling pressure was observed in the case of carbamazepine and propranolol HCl, indicating that a relatively small amount of water was sufficient to reach the critical pressure due to their low solubility (Fig. 29 C and D). This indicates that the low solubility of these drugs allowed for efficient generation of the required pressure within the core. On the other hand, metoprolol tartrate, with its higher solubility, required a larger amount of water to reach the critical pressure for coat rupture.
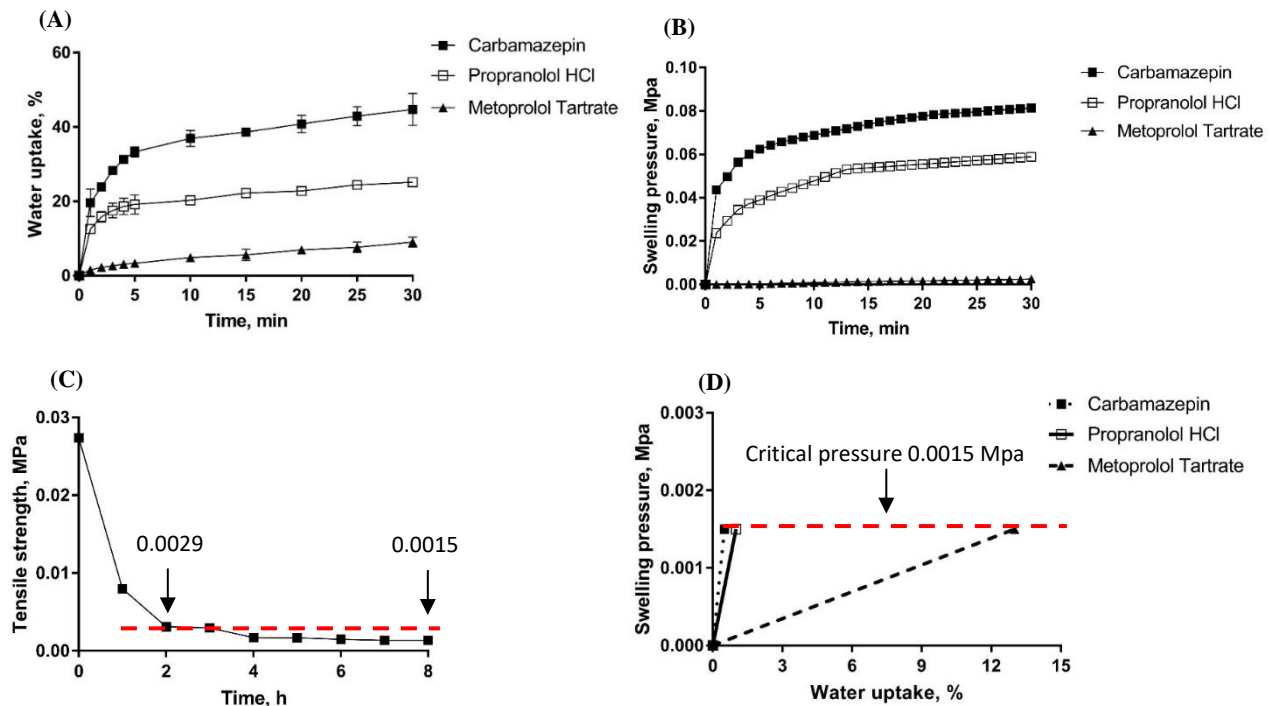

Fig. 29 Effect of drug solubility on core (A) water uptake (B) core swelling energy, and (C) wet mechanical properties of the coat, (D) water uptake to reach the critical pressure, core containing 60% (w/w) drug, 30% (w/w) lactose and 10% /w/w) AcDiSol.

The increased water uptake with higher core solubility was confirmed through a macroscopic evaluation of compression-coated tablets (Fig. 30). This visual assessment provided valuable insights into the release mechanisms of these different drugs. In the case of carbamazepine and propranolol HCl, as water penetrated the core during the initial stage, localized swelling occurred at weak points, leading to a rapid rise in swelling pressure. This pressure was directed towards the coating at the weak point, resulting in coat rupture (Fig. 30 A and B). These findings established that carbamazepine and propranolol HCl required only a small amount of water to trigger rupture.

In contrast, the core containing highly soluble metoprolol tartrate exhibited a different behavior. Upon contact with water, metoprolol tartrate dissolved, generating minimal mechanical resistance and pressure. Consequently, the coat remained intact during the initial stage of water penetration. To reach the critical pressure necessary for coat rupture, a greater amount of water had to permeate the core, leading to a higher volume of core swelling (Fig. 30 C). Metoprolol tartrate required a significantly larger amount of water compared to propranolol HCl and carbamazepine due to its higher solubility.
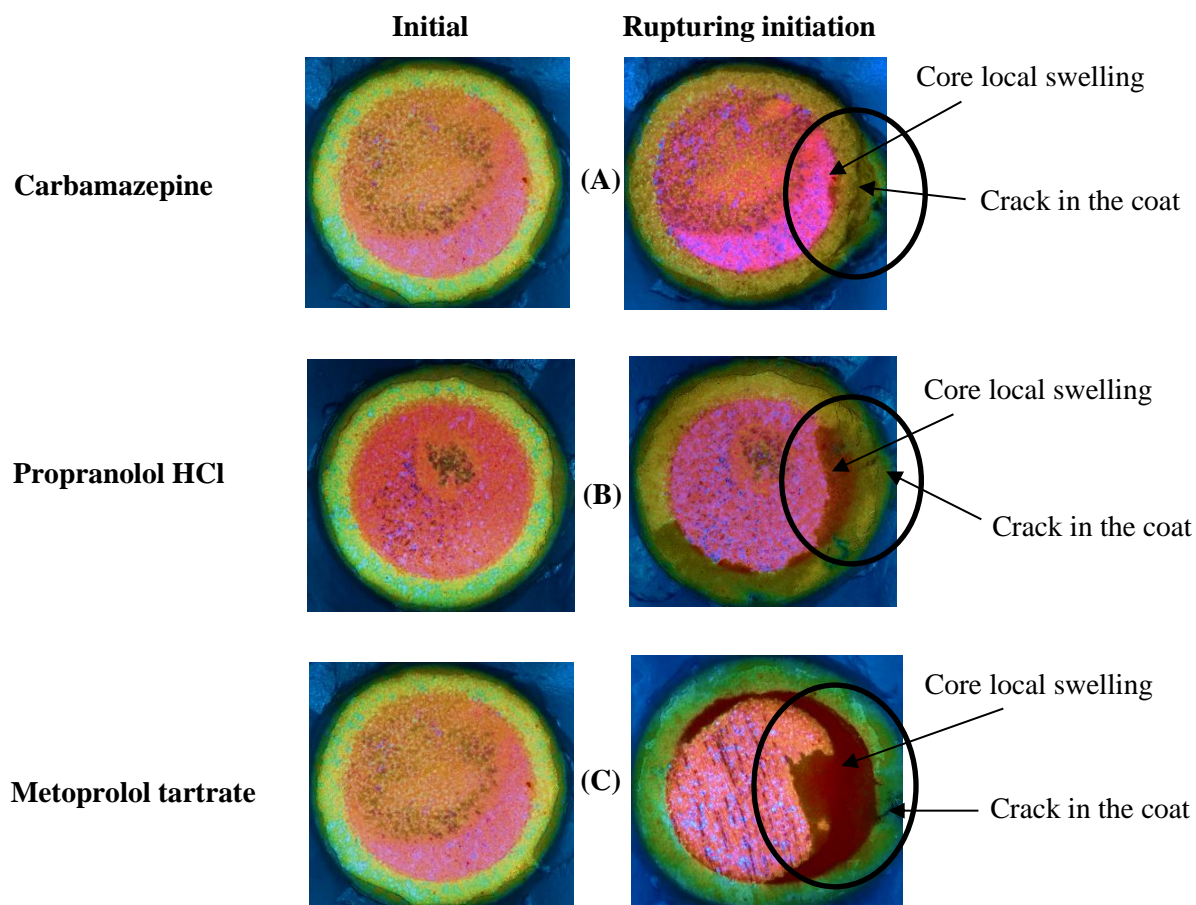
Fig. 30 Photographs of compression-coated tablets with different drug solubility (A) carbamazepine, (B) propranolol HCl, (C) metoprolol tartrate, core containing 60% (w/w) drug, 30% (w/w) lactose and 10% /w/w) AcDiSol.

Next, a 2 mm core was compressed into a 4 mm tablet. Surprisingly, similar lag times were observed across various drug solubilities indicating the same mechanism at play (Table 4). Local swelling occurred, with water permeating the entire core and exerting pressure on the coating. This pressure ultimately led to the rupture of the coat and subsequent drug release.

Table 4 Effect of core volume and drug solubility on lag time

Core tablet, mm	Core volume, mm^3	T_{lag}, h		
		Carbamazepine	Propranolol HCl	Metoprolol tartrate
11	285.1	2.5 ± 0.5	4.5 ± 0.5	8.0 ± 0.5
2	4.71	3.0 ± 0.5	3.5 ± 0.5	4.0 ± 0.5
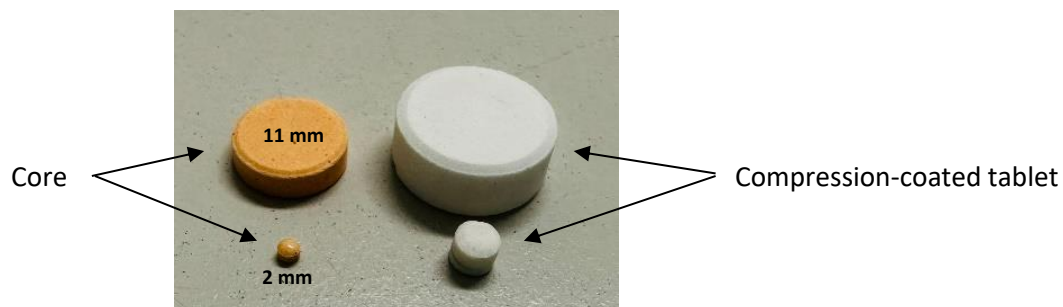
To quantify the relationship between lag time and core balanced solubility, a linear correlation was observed (Fig. 31). The core balanced solubility was calculated using the following equation:

Core balanced solubility = $S_1 * D_1/100 + S_2*D_2/100$

S_1 = Solubility of first component (mg/mL)
D_1 = Dose of first component (%)
S_2 = Solubility of second component (mg/mL)
D_2 = Dose of second component (%)

The core balanced solubility represents the solubility of the core independent of specific drugs and excipients. It was found that as the core balanced solubility increased, the lag time also increased, indicating a decrease in core swelling [20, 88]. Interestingly, varying the concentration of AcDiSol (ranging from 5% to 20%) had no significant effect on the lag time for core solubilities up to 250 mg/mL (Fig. 31). This suggests that within this range of core balanced solubility, the concentration of AcDiSol does not impact the lag time.
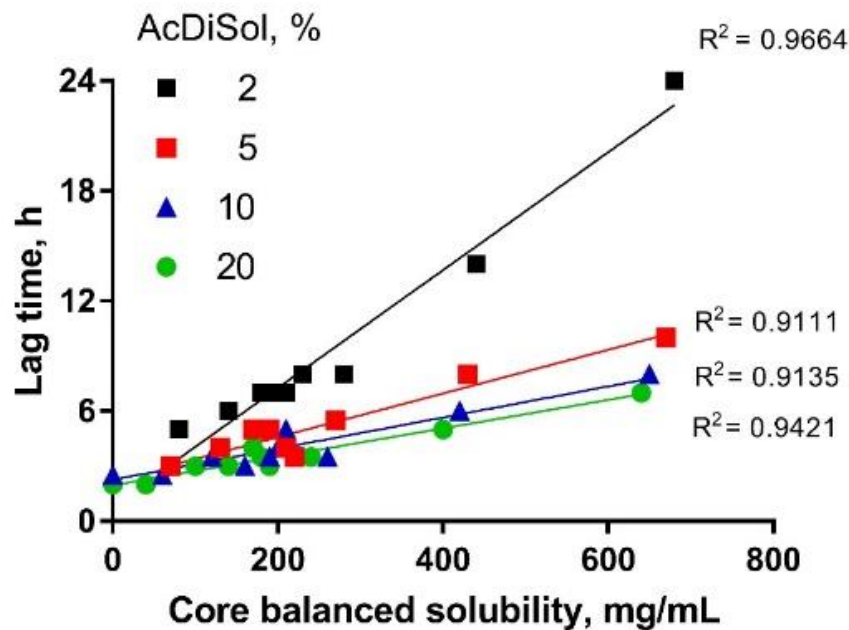
Fig. 31 Effect of AcDiSol concentration and core balanced solubility on lag time.

To gain a better understanding of the factors influencing the lag time in compression-coated tablets, the relationship between core balanced solubility, coating thickness, and lag time was investigated (Fig. 32). The lag time increased as the core solubility increased, primarily attributed to a decrease in core swelling. Additionally, an increase in coating thickness led to a longer lag time, which can be attributed to the enhanced mechanical properties of the coat.
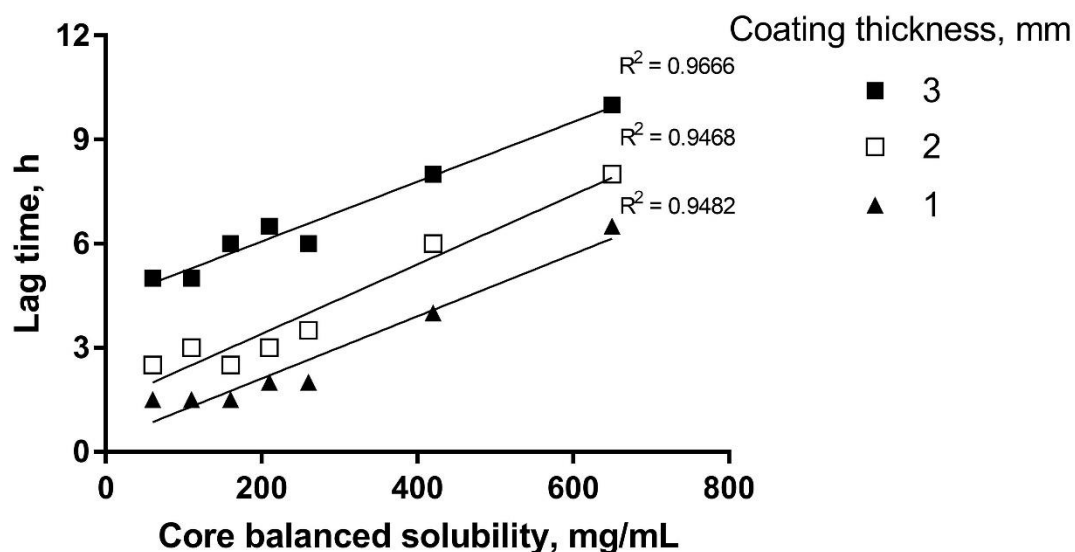
Fig. 32 Effect of coating thickness and core balanced solubility on lag time.

In order to achieve pulsatile drug release, it is crucial to ensure rapid swelling and expansion of the core upon contact with the medium. To investigate this phenomenon, croscarmellose sodium, sodium starch glycolate, and crospovidone were evaluated as superdisintegrants in the core containing propranolol HCl. The tablets were coated with a formulation consisting of 40% (w/w) glyceryl behenate, 50% (w/w) lactose, and 10% (w/w) PVP. The study aimed to assess the impact of the three superdisintegrants on drug release, core swelling, and core volume increase. Surprisingly, similar lag times were observed for all the superdisintegrants indicating that they generated comparable critical swelling forces upon contact with the media (Fig. 33 A). However, during the initial 30 min of the swelling study, the core containing croscarmellose sodium exhibited higher swelling force compared to those containing sodium starch glycolate and crospovidone (Fig. 33 B). This variation in swelling force can be attributed to the presence of a higher degree of cross-linked ester groups in the core containing croscarmellose sodium, leading to greater swelling and volume increase (Fig. 33 C) [20, 108]. Based on these findings, croscarmellose sodium was selected as the preferred superdisintegrant.
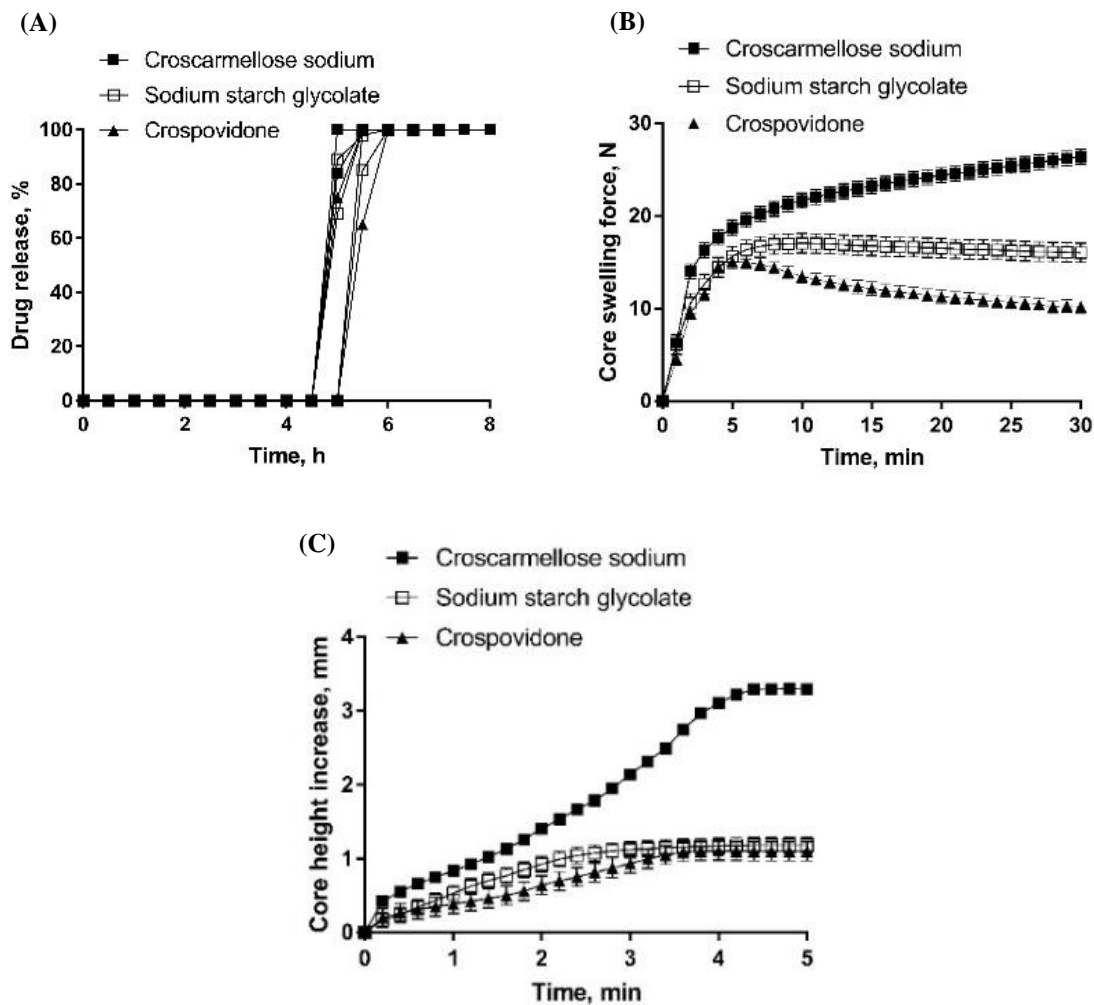
Fig. 33 Effect of superdisintegrant type on (A) drug release (B) core swelling force and (C) core height increase, core containing 60% (w/w) propranolol HCl, 30% (w/w) lactose, 10% (w/w) superdisintegrant.

To investigate the impact of croscarmellose sodium, core tablets containing propranolol HCl were prepared using Primellose®, Vivasol®, and AcDiSol®. These core tablets were then compression-coated with a formulation consisting of 40% (w/w) glyceryl behenate, 50% (w/w) lactose, and 10% (w/w) PVP. Interestingly, all the formulations exhibited almost identical lag times due to similar swelling force (Fig. 34 A and B).
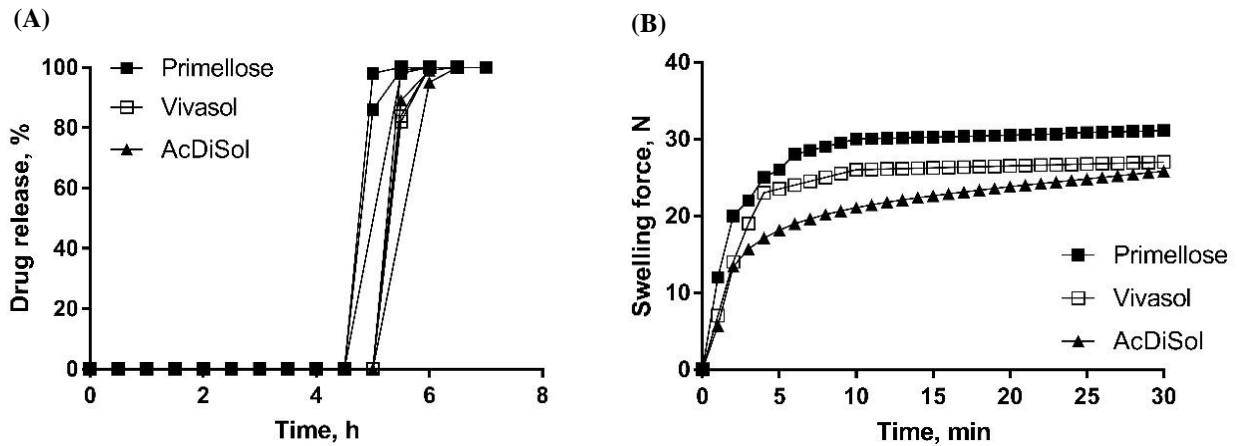
Fig. 34 Effect of croscarmellose sodium type on (A) drug release and (B) core swelling, core containing 60% (w/w) propranolol HCl, 30% (w/w) lactose, 10% (w/w) superdisintegrant.

When the core tablet comes in contact with the medium, the medium enters through the pores and causes the core to swell. The extent of core swelling is influenced by the rate at which water is absorbed, which is in turn associated with the porosity of the tablets. The higher compression forces during tablet manufacturing lead to decreased porosity and increased hardness [109]. Interestingly, no significant difference was observed in lag time based on core hardness (Fig. 35). This finding is consistent with previous research [110].
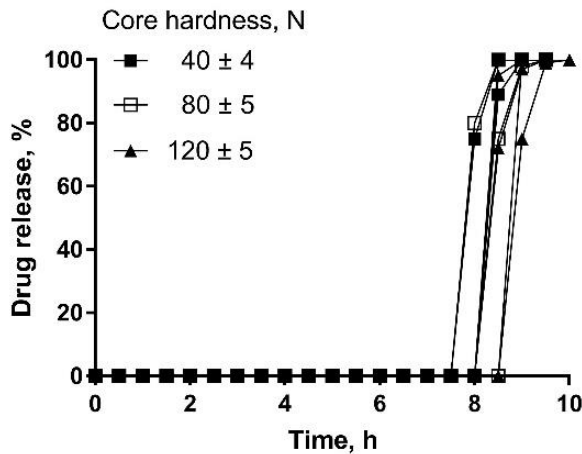

Fig. 35 Effect of core hardness on drug release, core containing 60% (w/w) metoprolol tartrate, 30% (w/w) lactose, 10% (w/w) AcDiSol.

One of the critical formulation factors that significantly affects drug release in pulsatile delivery systems is drug loading. With metoprolol tartrate, the lag time increased as the drug loading was increased (Fig. 36 A). This can be attributed to the increase in osmotic pressure and the simultaneous decrease in swelling pressure. Furthermore, higher metoprolol tartrate loading led to a reduction in core water uptake, energy, and volume (Fig. 36 B, C and D). Similar findings have been reported in previous studies, highlighting the inhibitory effect of soluble components on tablet swelling [111, 112]. Soluble component starts to dissolve upon contact with the liquid, leading to a decrease in the efficiency of tablet swelling. Additionally, the dissolution of the soluble component can increase the viscosity of the medium, resulting in slower liquid penetration.
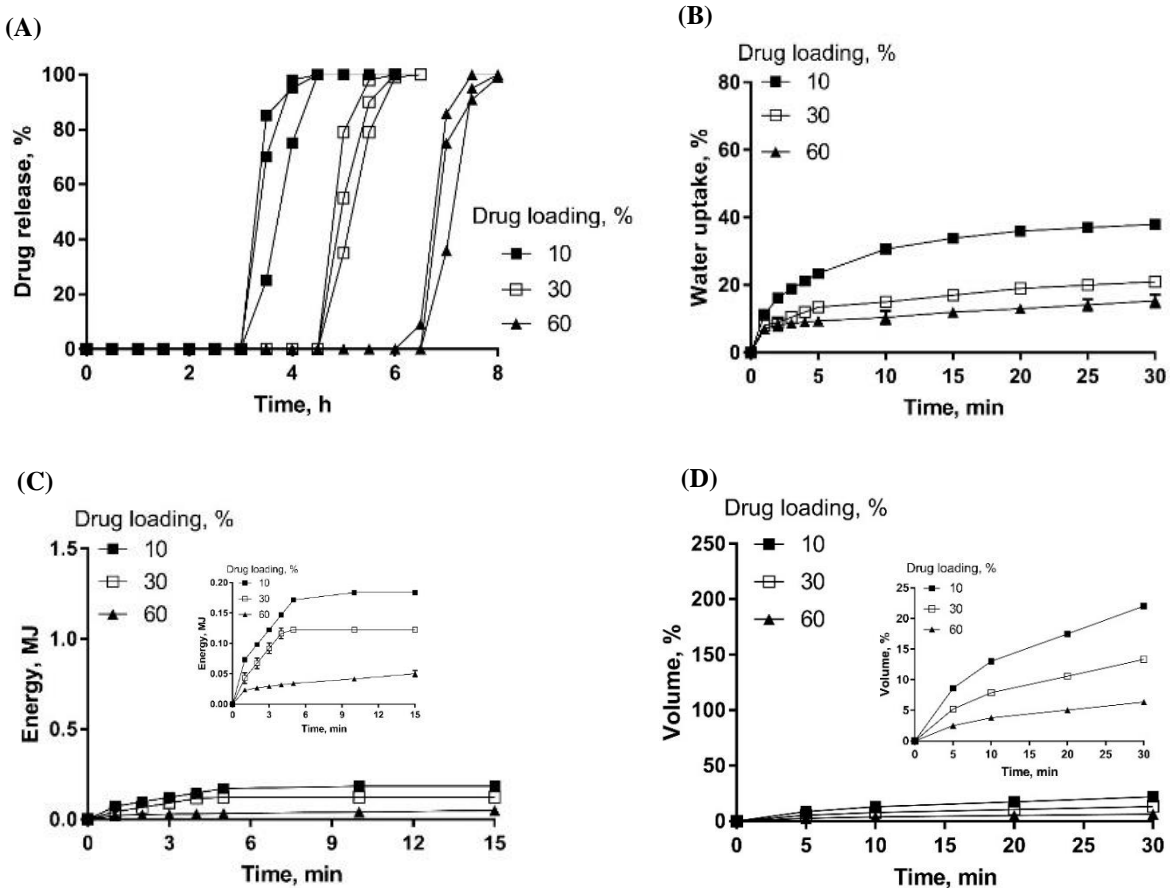

Fig. 36 Effect of metoprolol tartrate loading on (A) release (B) water uptake (C) swelling energy, and (D) volume change, core containing 10 - 60% (w/w) drug, 20 - 70% (w/w) lactose, 20% (w/w) AcDiSol.

Next, the propranolol HCl loading was also investigated. Increasing the drug loading resulted in a decrease in lag time due to the corresponding increase in core water uptake, energy, and volume (Fig. 37 A, B, C and D).

It is worth mentioning that lactose, which has a higher solubility compared to propranolol HCl, was present in the formulation. Therefore, as the loading of propranolol HCl increased, the amount of lactose decreased, consequently reducing the overall solubility of the core. This decrease in solubility contributed to a decrease in lag time. These findings align with the observations reported by Rubinstein et al. in 1977, which demonstrated that a higher expansion of the superdisintegrant leads to greater swelling in the presence of a low soluble component [113].
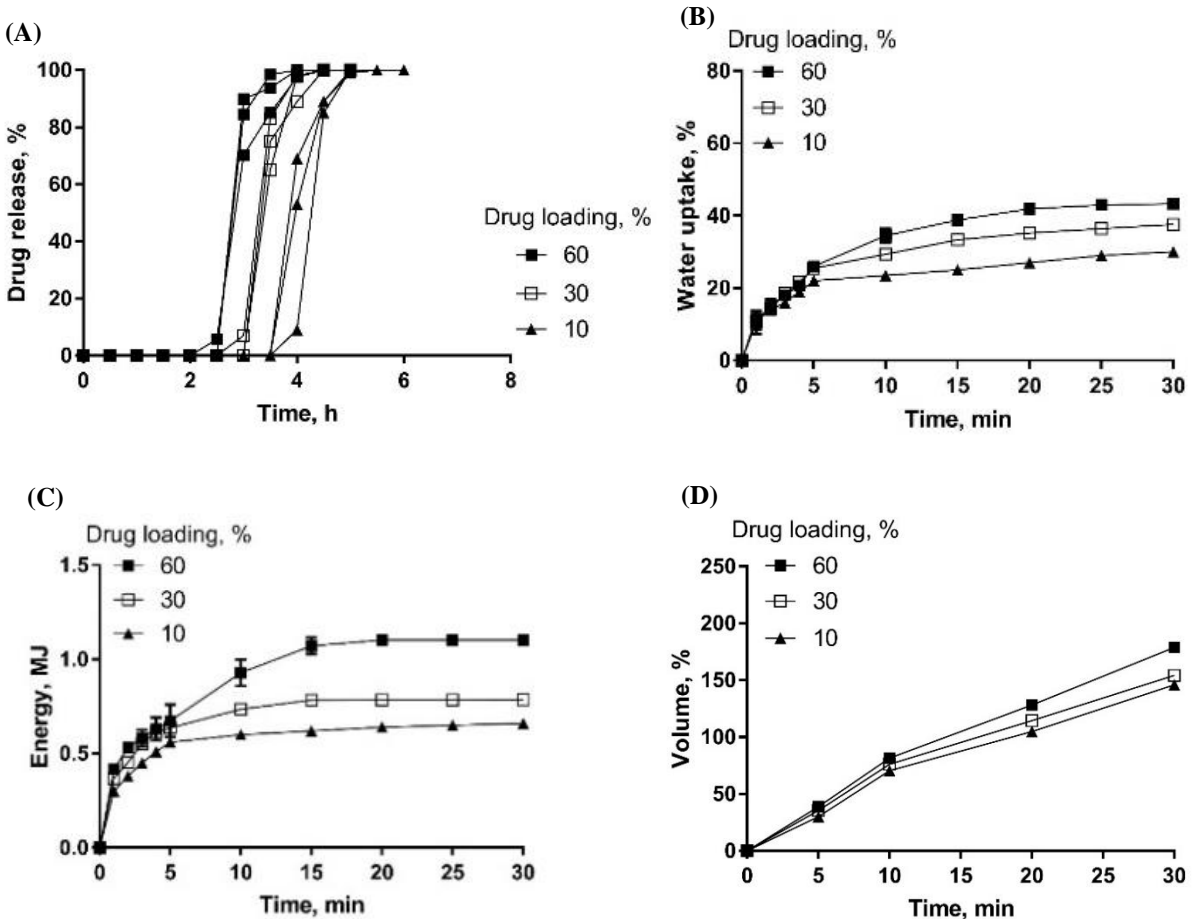

Fig. 37 Effect of propranolol HCl loading on (A) release (B) water uptake (C) swelling energy, and (D) volume change, core containing 10 - 60% (w/w) drug, 20 - 70% (w/w) lactose, 20% (w/w) AcDiSol.

Finally, the carbamazepine loading was investigated. Increasing the drug loading led to a shorter lag time, which can be attributed to a decrease in core solubility (Fig. 38 A). This decrease in solubility was achieved by reducing the amount of drug and increasing the amount of lactose in the core formulation, thus enhancing the overall solubility of the core.

Furthermore, in line with expectations, the water uptake, energy, and volume of the core exhibited an increasing trend with higher drug loading (Fig. 38 B, C and D). This can be attributed to the decreased solubility of the core resulting from the higher drug loading. Consequently, the insoluble drug enabled more water to be available for the superdisintegrant, leading to increased water uptake and enhanced swelling behavior [114].
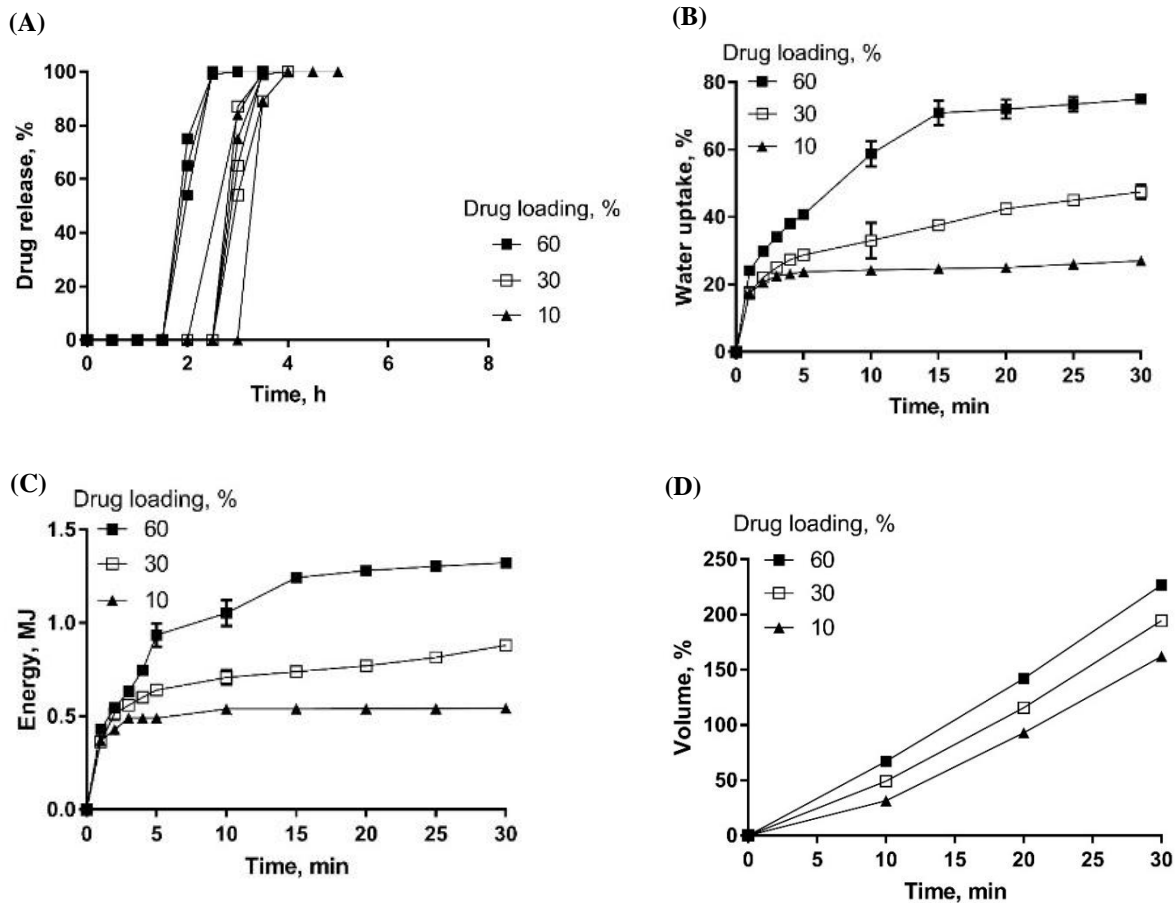

Fig. 38 Effect of carbamazepine loading on (A) release (B) water uptake (C) swelling energy, and (D) volume change, core containing 10 - 60% (w/w) drug, 20 - 70% (w/w) lactose, 20% (w/w) AcDiSol.

Superdisintegrants, such as AcDiSol, play a crucial role in facilitating the swelling of core tablets and ensuring the rupture of the coating by generating internal forces. Previous studies have explored the concept of pulsatile drug release using a capsule-based system, where hard or soft gelatin capsules were coated with a swelling layer, followed by a water-insoluble but permeable polymer layer [20]. The swelling layer, containing a high concentration of AcDiSol, was responsible for the rupture of the coating upon contact with water [20].

In this study, a core formulation containing the low water-soluble drug carbamazepine was prepared, and different concentrations of AcDiSol were incorporated. The compression-coated tablets were formulated using a fixed coating composition comprising 40% (w/w) glyceryl behenate, 50% (w/w) lactose, and 10% (w/w) PVP. The lag time decreased with increasing concentrations of AcDiSol (Fig. 39 A). This is due to the enhanced swelling force generated by the higher AcDiSol content, leading to increased water uptake and swelling pressure and energy (Fig. 39 B, C, and D). Interestingly, despite the decreased lag time, the release profile remained unchanged, and the drug release was immediate. The AcDiSol concentration influenced the lag time but did not affect the overall release time of the formulation.
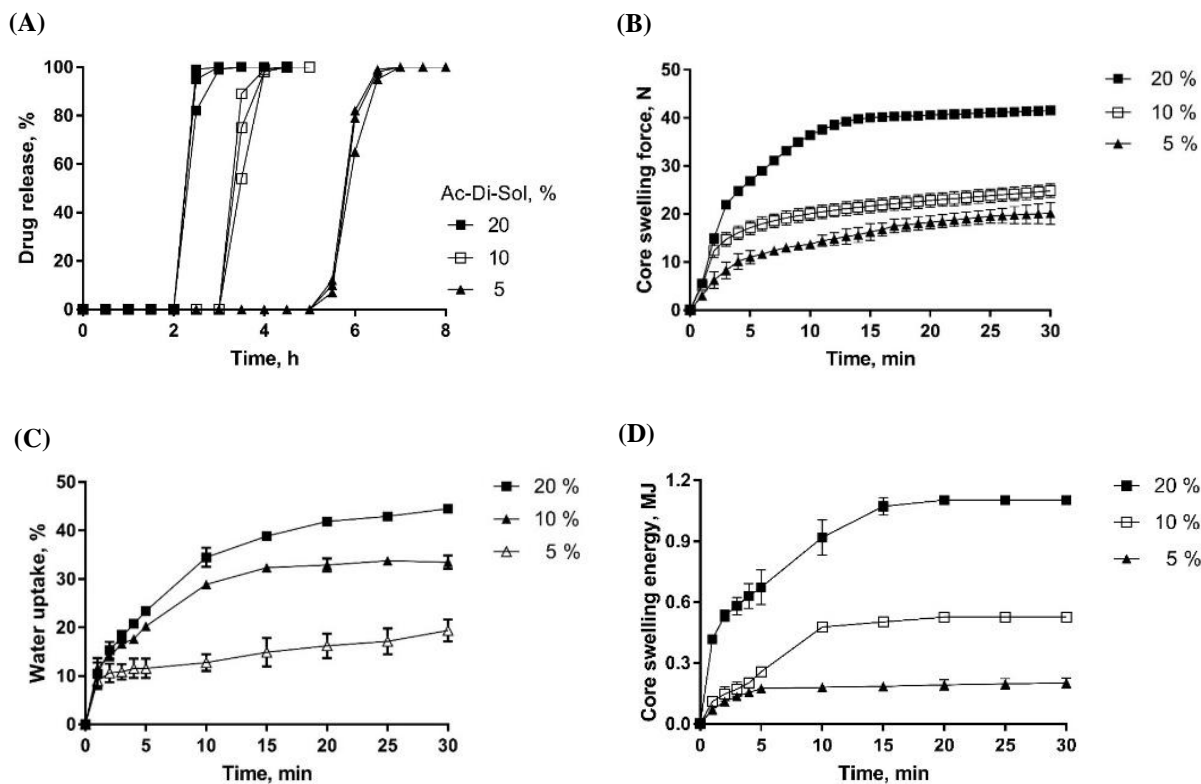
Fig. 39 Effect of AcDiSol concentration on (A) drug release and (B) core swelling force (C) core water uptake and (D) swelling energy, core containing 10% (w/w) carbamazepine, 70 - 85% (w/w) lactose, 5 - 20% (w/w) AcDiSol.

Accurate determination of the swelling behavior of the core is of utmost importance in understanding the underlying mechanisms of drug release. In this study, the swelling energy and water uptake of the core were evaluated using a swelling device. The swelling energy was calculated by measuring the displacement of the punch and using the predetermined weight force applied to the punch. To normalize the swelling energy, it was divided by the amount of AcDiSol (g) present in the core (Fig. 40 C).

The swelling energy increased with increasing load (Fig. 40 A). This can be attributed to the higher compression of the AcDiSol under higher loads, resulting in more mechanical work or swelling energy being exerted. Furthermore, water uptake was observed in the same experiment. The highest amount of water uptake occurred with a 2.5g load (Fig. 40 B). Under low loads, AcDiSol is able to swell more freely, leading to a lower mechanical work/energy requirement.

Interestingly, the ratio of swelling energy to the amount of water uptake remained constant over time. The observed swelling energy in the core, under a certain load, is directly related to the amount of water uptake. Specifically, a higher water uptake corresponded to a higher observed swelling energy. These findings are consistent with previously published studies [20].
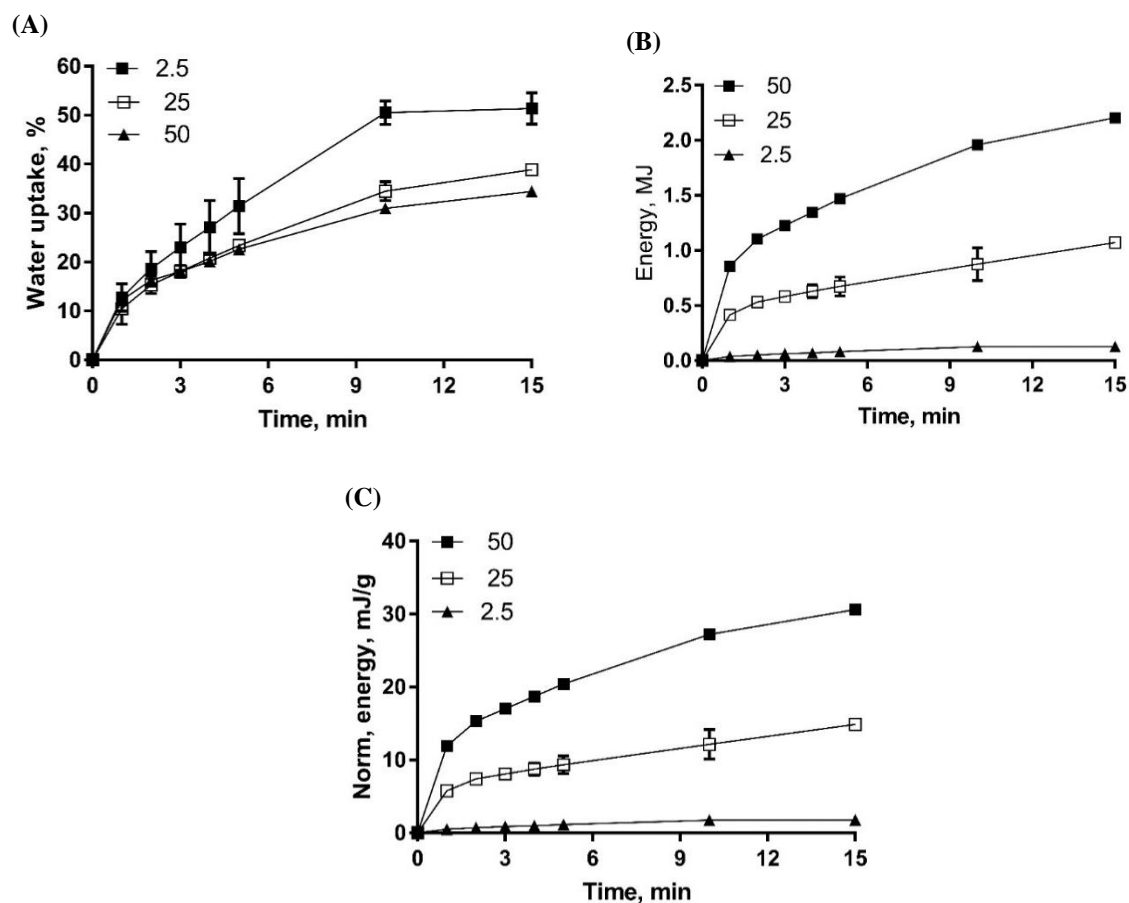
Fig. 40 Effect of weight load on core (A) water uptake, (B) energy (C) normalized energy, core containing 60% (w/w) propranolol HCl, 20% (w/w) lactose, 20% (w/w) AcDiSol

To investigate the impact of core fillers on drug release, a comparison was made between a water-soluble filler (lactose) and two alternative fillers, a water swellable filler (microcrystalline cellulose) and a water-insoluble filler (dicalcium phosphate). Notable differences in lag time among the formulations were observed. Specifically, the formulation of the core with lactose exhibited a longer lag time compared to the formulations containing dicalcium phosphate and microcrystalline cellulose (Fig. 41).

This observation can be attributed to the effect of fillers on the swelling behavior of the core. The use of a soluble filler, such as lactose, decreases the overall swelling of the core. This is likely due to the dissolution of the soluble filler when the medium penetrates the core, leading to a reduction in swelling and subsequently an increased lag time. This phenomenon has been documented in previous studies [112].

On the other hand, the incorporation of an insoluble filler, like dicalcium phosphate, resulted in an increased swelling of the core. The presence of an insoluble filler allows for a larger amount of water to be available for the superdisintegrant, facilitating enhanced swelling of the core. Consequently, this leads to a shorter lag time [111].
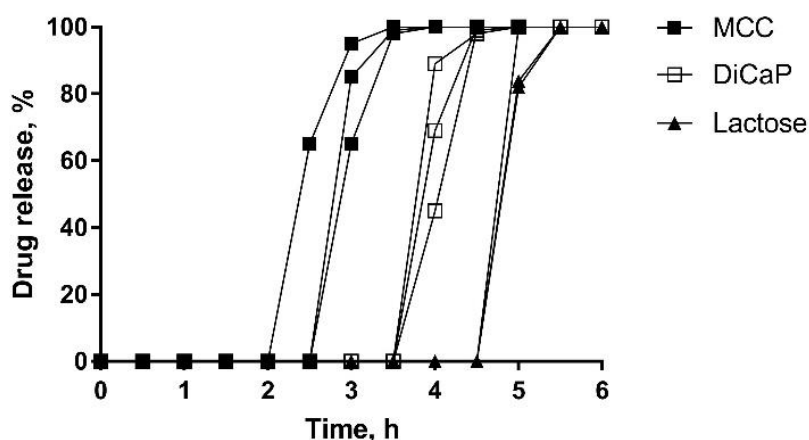
Fig. 41 Effect of core fillers on drug release, core containing 60% (w/w) propranolol HCl, 30% (w/w) filler, 10% (w/w) AcDiSol.

In the case of soluble filler (lactose), the water uptake and swelling decreased with increasing the metoprolol tartrate loading (Fig. 42 A and C). This can be attributed to the higher solubility of the core resulting from an increase in the amount of drug present. These findings are in line with a previous study [115]. Since metoprolol tartrate has higher solubility than lactose, increasing the drug loading led to an increase in the overall solubility of the core.

Furthermore, when lactose was replaced with microcrystalline cellulose, even higher water uptake and swelling were observed (Fig. 42 B and D). This can be explained by the further decrease in the solubility of the core with microcrystalline cellulose as filler. The lower solubility of microcrystalline cellulose compared to lactose contributed to increased water uptake and enhanced swelling.

Fig. 42 Effect of metoprolol tartrate loading on core water uptake (A) lactose, (B) microcrystalline cellulose and swelling (C) lactose (D) microcrystalline cellulose, core containing metoprolol tartrate 10 – 60% (w/w), 30 – 80% (w/w) filler, and 10% (w/w) AcDiSol.
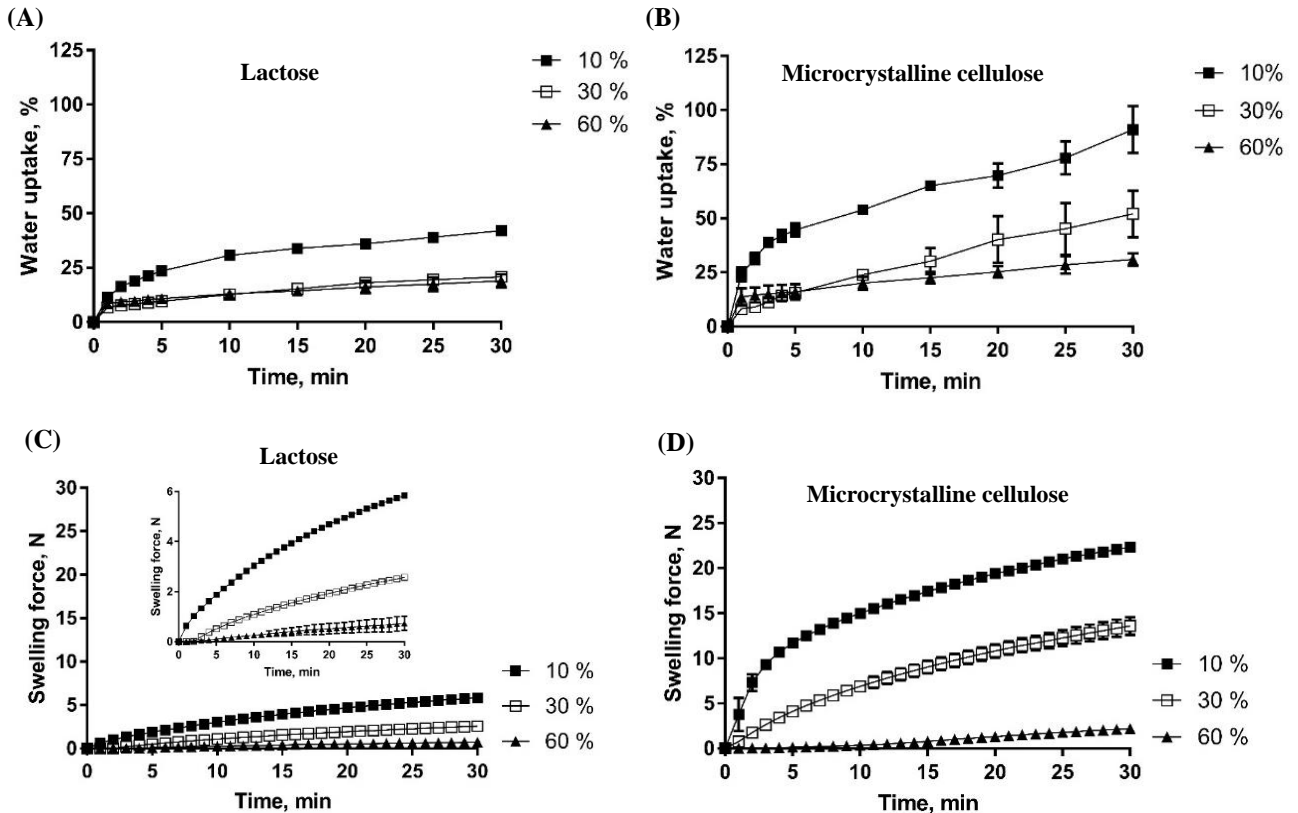
3.2.2 Conclusion

Pulsatile release compression-coated tablets were developed using core tablets containing model drugs with different solubilities (carbamazepine, propranolol HCl, and metoprolol tartrate), various fillers (lactose, dicalcium phosphate, and microcrystalline cellulose), and different superdisintegrants (croscarmellose sodium, sodium starch glycolate, and crospovidone). These core formulations were compression-coated with a fixed coating blend consisting of lipid, pore-former, and binder materials to explore the impact of core formulation parameters on pulsatile drug release. The inclusion of a superdisintegrant was essential for achieving pulsatile release.

The rupture of the coating and subsequent lag time was strongly influenced by the drug solubility and loading, which affected the swelling properties of the core. Higher solubility of the drug led to increased lag time due to reduced swelling of the core (metoprolol > propranolol > carbamazepine). Furthermore, a small amount of water was needed to reach the critical pressure for carbamazepine and propranolol HCl. In contrast, metoprolol tartrate required a larger quantity of water due to its higher solubility. Macroscopic observation confirmed the localized swelling at the weak point, resulting in coat rupture.

Among the superdisintegrants, AcDiSol exhibited a high degree of swelling, resulting in a decreased lag time with increasing concentration. The ratio of water uptake to energy remained constant, indicating that water uptake was the driving force behind the generation of swelling force.

The addition of a highly soluble filler in the core increased the lag time by enhancing the solubility and decreasing the overall swelling behavior (lactose > dicalcium phosphate > microcrystalline cellulose). Core hardness had no effect on lag time.

3.3 Preparation and characterize of polymer-based compression-coated tablets with pulsatile drug release

3.3.1 Background

Ethylcellulose (EC) is a widely used water-insoluble polymer in various drug delivery applications, including controlled-release matrix systems and pulsatile release systems [62, 121, 122]. The selection of ethylcellulose with different particle sizes as a coating material in compression-coated tablets has been shown to impact the drug release behavior [65]. This highlights the importance of considering the particle size of the ethylcellulose powder during formulation development. Furthermore, the choice of hydrophilic polymers in compression-coated tablets can significantly influence the release profile of the drug. For instance, hydroxypropyl methylcellulose (HPMC) has been associated with sustained release profiles [67], while hydroxyethyl cellulose (HEC) has been found to induce delayed drug release [54]. Additionally, non-cellulosic polymers such as alginate/chitosan combinations have demonstrated time-controlled release capabilities [120].

The objective of this study was to develop and evaluate a compression-coated tablet system for achieving pulsatile release. The system comprised a core tablet containing a model drug with different solubilities, superdisintegrant, and fillers, while the coating layer consisted of ethylcellulose with release modifying Eudragit® RL, RS, HPMC, lactose, dicalcium phosphate.

3.3.2 Results and discussion

The compression-coated tablet is a type of reservoir system characterized by a drug-containing core surrounded by a release-rate controlling polymer(s). In this study, ethylcellulose, a water-insoluble and directly compressible polymer powder, was incorporated with Eudragit® RL, RS, and HPMC polymers or pore-former, lactose, dicalcium phosphate and PVP to investigate their effect on pulsatile drug release and mechanical properties.

The effect of increasing Eudragit® RL content in ethylcellulose (10 - 40%) on pulsatile drug release was investigated in this study. A higher Eudragit® RL content resulted in a decrease in the lag time (Fig. 43 A and C). This decrease in lag time can be explained by the increased water uptake caused by the higher permeability of the coating (Fig. 43 B). The presence of Eudragit® RL, which is known for its hydrophilic properties, enhances the water penetration into the coating layer. This

increased water uptake leads to faster swelling of the core tablet, resulting in the rupture of the coating and subsequent drug release.

Interestingly, despite the shorter lag time, a prolonged release time (t_{80-10}) was observed with higher Eudragit® RL content (Fig. 43 D). This can be explained by the higher plasticization effect of Eudragit® RL, which leads to a slower opening of the coating (Fig. 43 E). The plasticization effect reduces the rigidity of the coating, resulting in a controlled and sustained drug release over a longer period. However, incomplete rupturing of the coating was observed in the formulations containing 20-40% Eudragit® RL. This suggested that the critical concentration (10%) of Eudragit® RL beyond which the coating's rigidity is compromised, leading to incomplete rupturing.

Fig. 43 Effect of ethylcellulose and Eudragit[®] RL ration on (A) drug release, (B) water uptake, (C) lag time, (D) release time (E) coat rupturing.

The effect of Eudragit[®] RL content on the mechanical properties of the coat was investigated in this study. To assess these properties, a blend of the coating material was compressed into tablets with a diameter of 11 mm and a thickness of 2 mm.

Additionally, the elongation of the coat in dry and wet state increased with increasing Eudragit[®] RL content (Fig. 44 A and B). This increase in elongation indicates a slower opening of the coat

and a sustained drug release after the lag time. The higher concentration of Eudragit® RL imparts more flexibility and elongation to the coat, resulting in controlled and prolonged drug release.

s
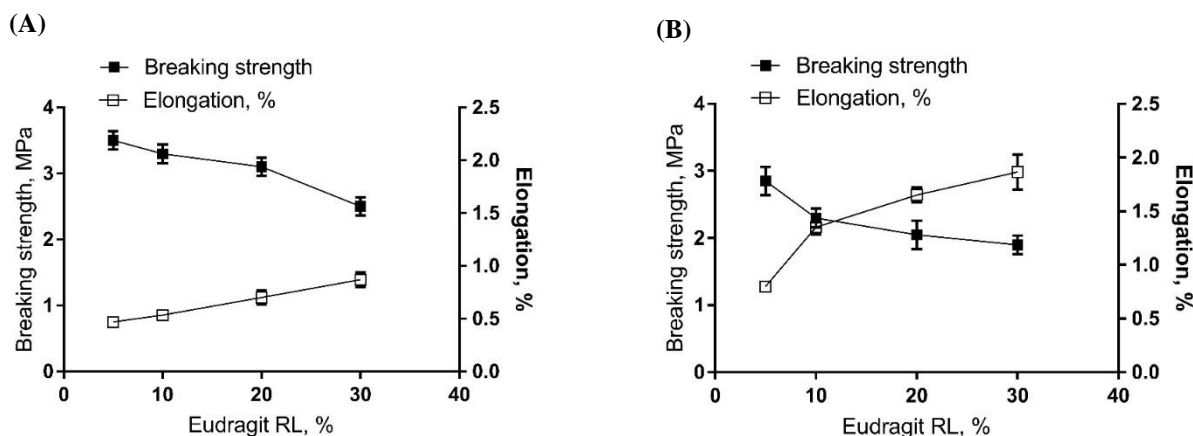
Fig. 44 Effect of EC and RL ration on coat mechanical properties on (A) dry state and (B) wet state.

Next, Eudragit® RL was substituted with Eudragit® RS. As anticipated, an increase in Eudragit® RS content (ranging from 10% to 40%) in the coat led to a reduction in the lag time (Fig. 45 A and C). This reduction was attributed to the enhanced water uptake by the coating material (Fig. 45 B).

Interestingly, contrary to the findings with Eudragit® RL, a prolonged release time (t $_{80-10}$) was not observed with higher Eudragit® RS content (Fig. 45 D). This discrepancy may be attributed to the lower water uptake and increased brittleness of the coat associated with higher concentrations of Eudragit® RS.

In all formulations, after the lag time, the coats ruptured and split into two halves, facilitating the immediate release of the drug (Fig. 45 E). The coating system effectively fulfilled its role in achieving pulsatile drug release. Based on these findings, it can be concluded that Eudragit® RS exhibits favorable characteristics as a permeable polymer in a rupturable pulsatile release system.
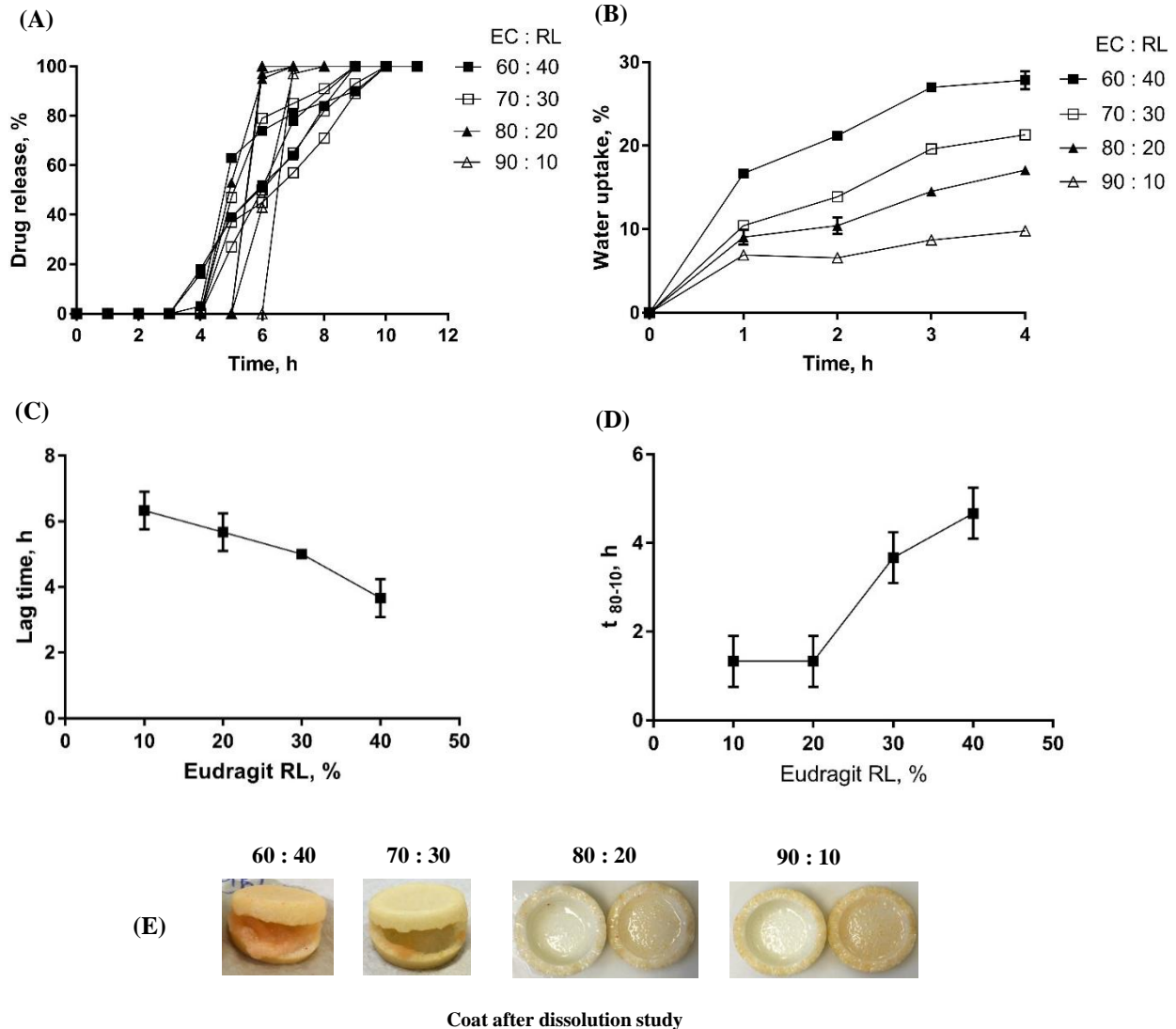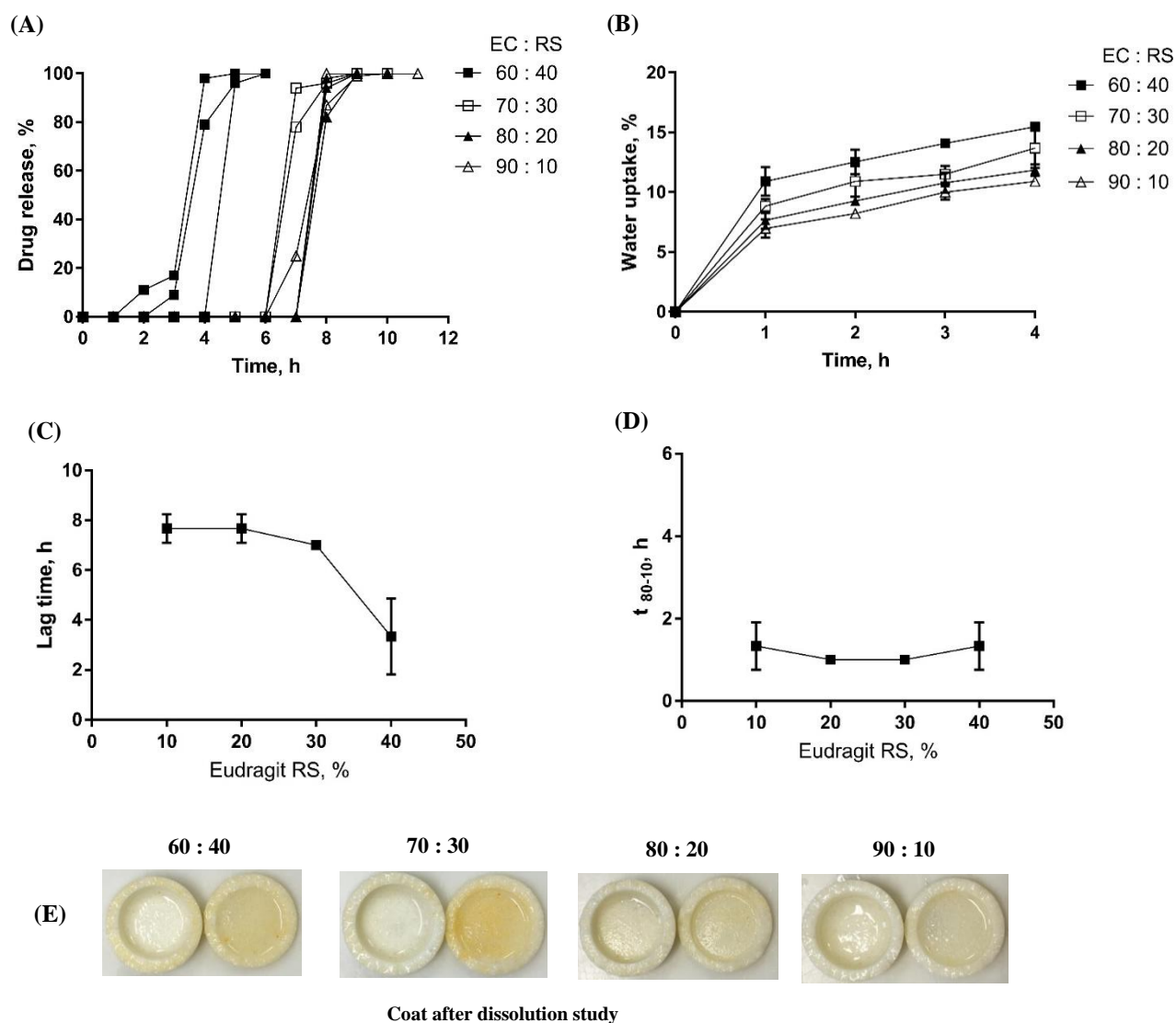
Fig. 45 Effect of ethylcellulose and Eudragit® RS ratio on (A) drug release, (B) water uptake, (C) lag time, and (D) release time, and (E) coat rupturing.

To assess the impact of Eudragit® RS content on the mechanical properties of the coat in both dry and wet states, a blend of the coating materials was compressed into tablets with a diameter of 11 mm and a thickness of 2 mm. In the dry state, the mechanical properties of the coat exhibited a slight decrease with increasing Eudragit® RS content (Fig. 46 A). This can be attributed to the increased flexibility of the coat resulting from the incorporation of Eudragit® RS.

On the other hand, in the wet state, the mechanical properties of the coat did not show significant changes (Fig. 46 B). Importantly, no elongation of the coat was observed in the wet state, indicating that the coat ruptured and led to immediate drug release after the lag time in all formulations. This finding highlights the suitability of Eudragit® RS, owing to its high brittleness, which facilitates the rapid rupture of the coat.
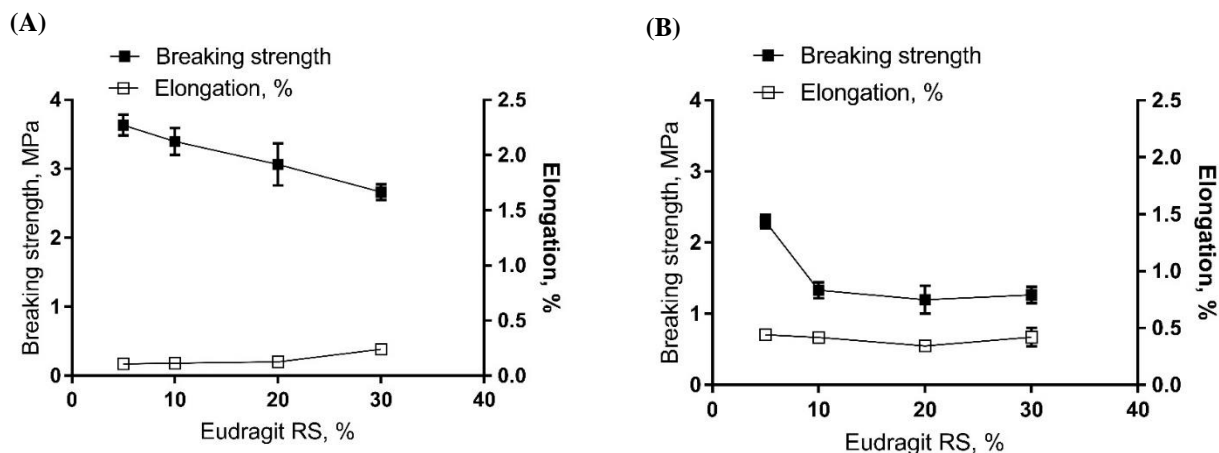
Fig. 46 Effect of ethylcellulose and Eudragit® RS ratio on coat mechanical properties on (A) dry state and (B) wet state

Furthermore, the suitability of incorporating HPMC into the EC-based coat was examined, focusing on its impact on drug release and coat mechanical properties. Initially, a lag time of 9 ± 1 h was observed with 10% HPMC, and a further increase in HPMC content resulted in minimal drug release (Fig. 47 A). This phenomenon can be attributed to the formation of a gel layer by HPMC, which hinders drug release (Fig. 47 B).

Subsequently, the effect of HPMC content on the mechanical properties of the coat in both dry and wet states was investigated. In the dry state, no significant impact on the mechanical properties or elongation of the coat was observed (Fig. 47 C). However, in the wet state, the mechanical properties of the coat were reduced, and the elongation of the coat was significantly increased with higher HPMC content (Fig. 47 D). This can be attributed to the formation of a gel layer, which not only inhibits drug release but also alters the mechanical behavior of the coat.

Based on these observations, ethylcellulose combined with high molecular weight HPMC is not suitable for a pulsatile release system based on compression-coated tablets.
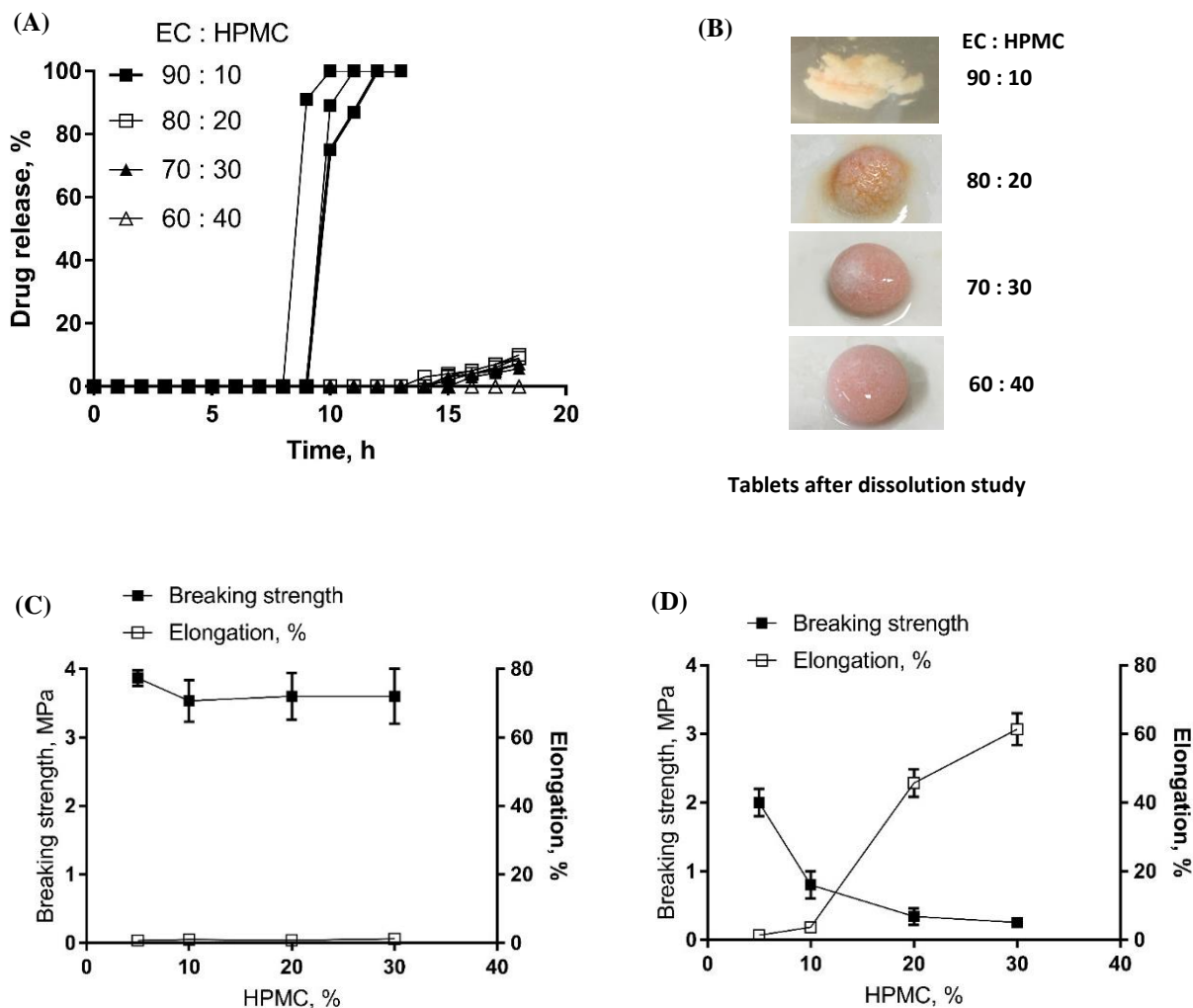
Fig. 47 Effect of ethylcellulose and HPMC ratio on (A) drug release (B) gel formation, and coat mechanical properties on (C) dry state (D) wet state

The use of hydrophilic excipients in the insoluble outer shell of compression-coated tablets has been previously explored as pore-forming agents to facilitate water penetration. Increasing the content of water-soluble excipients in the coating shell has been shown to decrease the lag time. Notably, different drug release behaviors were observed when various hydrophilic excipients were incorporated into press-coated tablets, suggesting the influence of their physicochemical properties [68]. To investigate the effect of pore-former, a coating blend consisting of 60% ethylcellulose and 40% pore-former (either lactose, dicalcium phosphate, or PVP) was prepared, and drug release studies were conducted (Fig. 48). Immediate release happened from the coating containing lactose

and dicalcium phosphate, probably due to the low mechanical properties of the coat. However, a pulsatile release with a 4 h lag time was observed from the coating containing PVP. This can be explained by the dual role of PVP, as it not only enhanced the mechanical properties of the coat but also served as a pore-former, facilitating the desired pulsatile drug release.
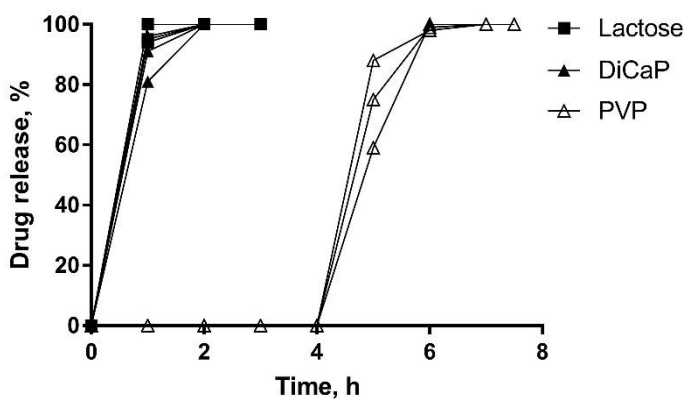
Fig. 48 Effect pore-former on drug release, coat containing 60% (w/w) ethylcellulose and 40% (w/w) pore-former.

To gain further insights into the impact of PVP concentration on drug release, an additional study was undertaken. The results confirmed the anticipated trend, as the lag time decreased with increasing PVP content in the coating (Fig. 49). This decrease in lag time can be attributed to the reduction in the porosity of the coat, leading to an increase in permeability. Thus, the concentration of PVP can be effectively utilized to control the lag time.
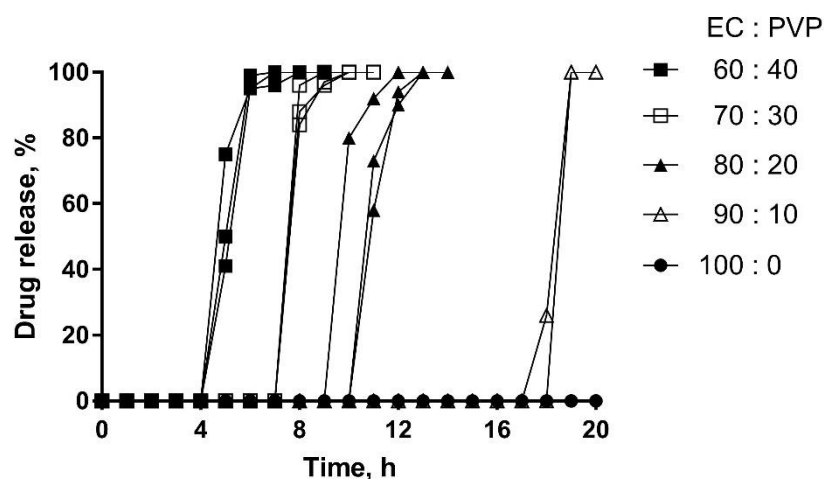
Fig. 49 Effect of ethylcellulose and PVP ratio on drug release.

The addition of superdisintegrants, such as AcDiSol, in the core formulation is essential for promoting core tablet swelling and facilitating the rupture of the coating through the generation of internal forces. Previous studies have explored the concept of pulsatile drug release using capsule-based systems, where a swelling layer containing a high concentration of AcDiSol was responsible for the rupture of the coating upon contact with water [20].

In this investigation, a core formulation containing propranolol HCl as the model drug was prepared, and various concentrations of AcDiSol (5 - 20%, w/w) were incorporated. The compression-coated tablets were formulated using a fixed coating composition consisting of 90% (w/w) ethylcellulose and 10% (w/w) Eudragit RS®. Notably, it was observed that as the concentration of AcDiSol decreased, the lag time increased (Fig. 50). This can be explained that a higher content of AcDiSol leads to increased swelling of the core, thereby reducing the lag time before drug release.

Interestingly, despite the variation in the lag time, the release profile of the drug remained unchanged, and an immediate drug release was observed. This finding suggested that the drug release mechanism is primarily dependent on the rupture of the coating rather than the concentration of AcDiSol in the core.
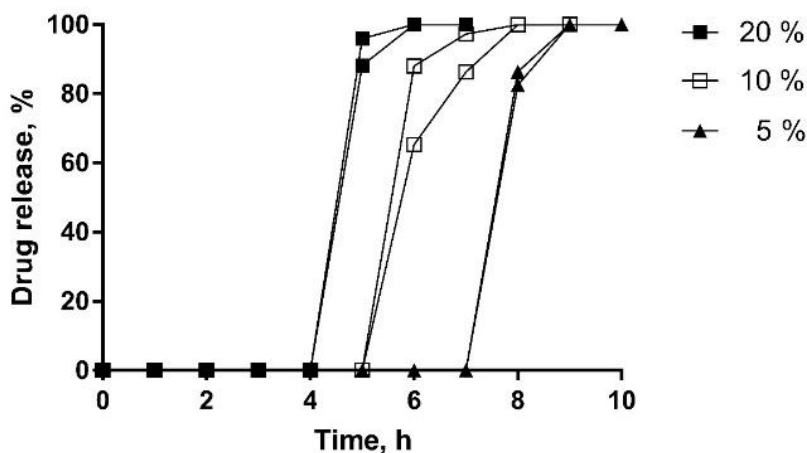
Fig. 50 Effect of superdisintegrant concentration on release, core containing 60% (w/w) propranolol HCl, 20 – 35% (w/w) lactose, 5 – 20% (w/w) AcDiSol, and cot containing 90% (w/w) ethylcellulose and 10% (w/w) Eudragit RS®.

To investigate the impact of drug solubility on the release, different cores were prepared using drug with varying solubilities, namely metoprolol tartrate, propranolol HCl, and carbamazepine. These cores were then compression coated with a blend consisting of 90% (w/w) ethylcellulose and 10% (w/w) Eudragit RS®. Surprisingly, no release was observed from the metoprolol tartrate formulation, while lag times of 7 and 5 h were observed for the propranolol HCl and carbamazepine, respectively (Fig. 51). The highly soluble drug metoprolol tartrate decreased the swelling capacity of the core. Since the ethylcellulose coat has higher mechanical properties, the metoprolol tartrate core was unable to generate sufficient pressure to rupture the coat and facilitate drug release. The decrease in core swelling with increasing drug solubility can be explained by the competition between highly soluble drug components and available water within the core. This competition leads to an elevation in ionic strength and osmotic pressure, thereby diminishing the effectiveness of the AcDiSol [103].
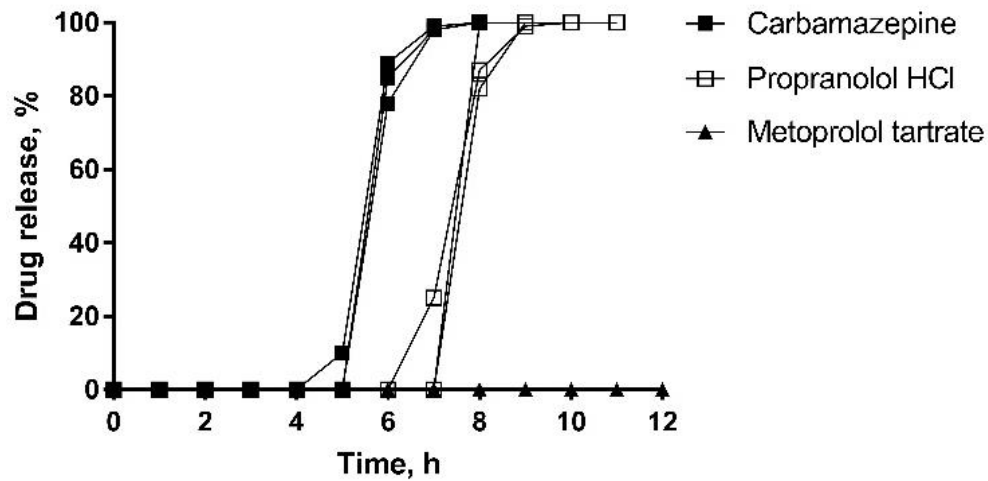
Fig. 51 Effect of drug solubility on release, core containing 60% (w/w) drug, 30% (w/w) lactose and 10% (w/w) AcDiSol, coat containing 90% (w/w) ethylcellulose and 10% (w/w) Eudragit RS®.

To investigate the impact of core fillers on drug release, soluble filler (lactose) was compared with swellable microcrystalline cellulose and a water insoluble dicalcium phosphate. Lactose showed longer lag time than dicalcium phosphate and microcrystalline cellulose because lactose dissolves upon contact with water and decreased the swelling of the core, resulting in longer lag time (Fig. 52).
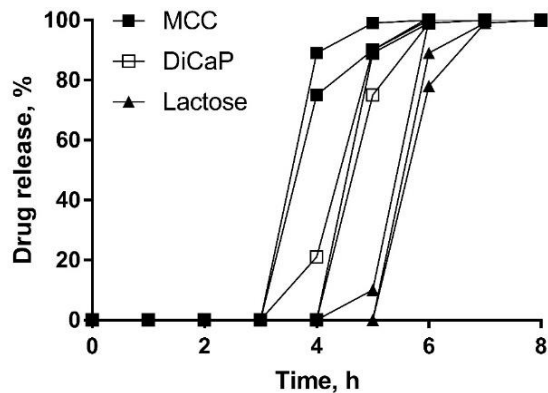
Fig. 52 Effect of core fillers on release, core containing 60% (w/w) propranolol HCl, 30% (w/w) filler and 10% (w/w) AcDiSol, coat containing 90% (w/w) ethylcellulose and 10% (w/w) Eudragit RS®

The influence of ethylcellulose particle size on drug release has been previously investigated [64], wherein smaller particle sizes were associated with longer lag times. This can be explained by the more efficient consolidation of the polymer powder, resulting in reduced residual porosity of the coat and decreased permeability. In this study, particle sizes of different ethylcellulose powders were measured (Fig. 54), and consistent with the literature, smaller particles showed longer lag time (Fig. 53), particularly with ethylcellulose Std 4. Furthermore, the choice of Eudragit polymer, specifically Eudragit RL® and Eudragit RS®, had an impact on the drug release behavior. Eudragit RL® showed a slow release after the lag time (Fig. 53 A), whereas Eudragit RS® showed immediate release (Fig. 53 B) following the lag time. This difference can be attributed to the higher flexibility and plasticization of Eudragit RL® in the wet state. Moreover, a longer lag time was observed with Eudragit RS® compared to Eudragit RL® due to its higher permeability.

Additionally, when the core containing metoprolol tartrate, a highly soluble drug, was compression-coated with a coat consisting of smaller-sized particles (90% (w/w) ethylcellulose Std 4 with 10% (w/w) Eudragit RS®, no release was observed (Fig. 53 B). However, lag time decreased with increasing the particle size of the polymer. This finding suggested that for highly soluble drugs, a higher particle size of EC is more suitable to achieve the desired pulsatile drug release.
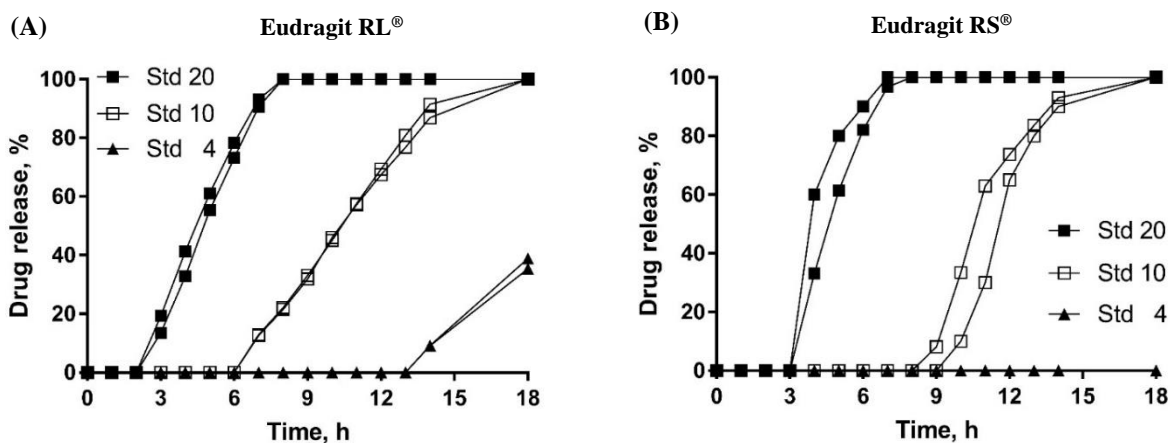
Fig. 53 Effect of ethylcellulose grade on release (A) 90% (w/w) ethylcellulose with 10% (w/w) Eudragit® RL and (B) 90% (w/w) ethylcellulose with 10% (w/w) RS, core containing 60% (w/w) metoprolol tartrate, 30% (w/w) lactose and 10% (w/w) AcDiSol.
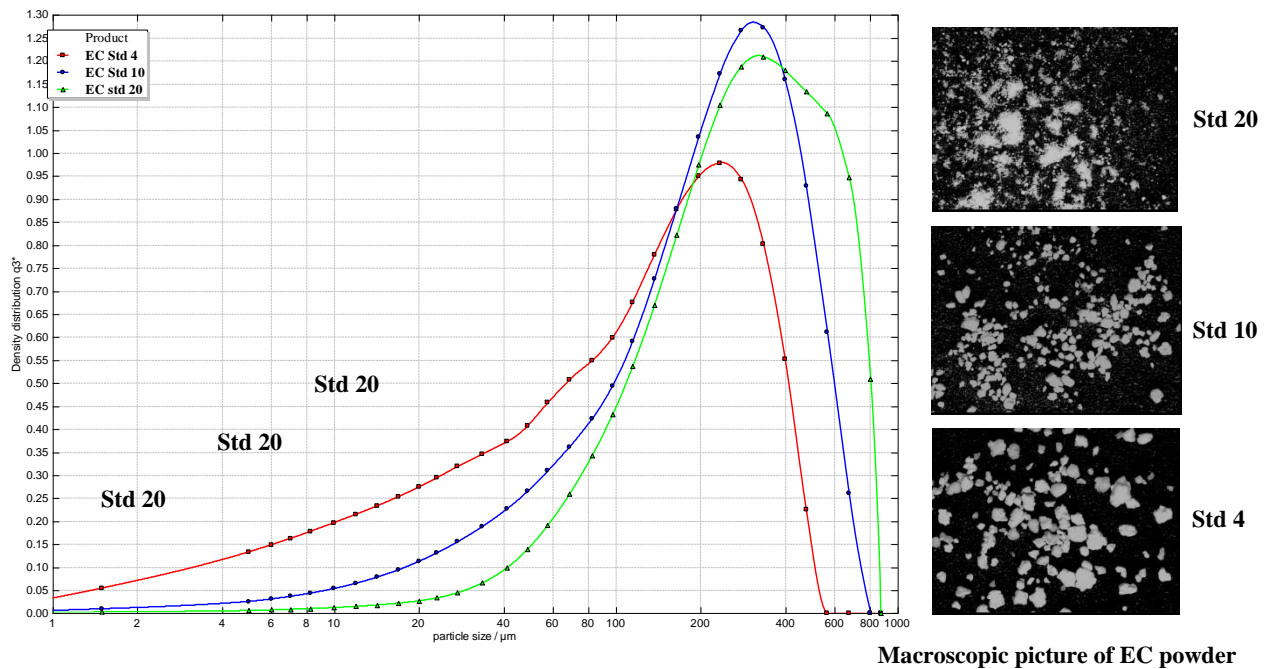
Fig. 54 Particle size distribution of different grade ethylcellulose.

A coating blend with Eudragit RS® and ethylcellulose showed promising mechanical properties with pulsatile release. To investigate further, ethylcellulose and Eudragit RS® were incorporated in the upper coat, while utilizing only ethylcellulose powder in the lower coat. Initially, when the tablets were compressed with a force of 10kN, showed immediate release of the drug from all the formulations, which could be due to insufficient binding between the two layers (Fig. 55 A). Surprisingly, higher compression force (20kN) led to the establishment of pulsatile drug release with a consistent lag time of approximately 5 ± 1 h across almost all the formulations (Fig. 55 B).
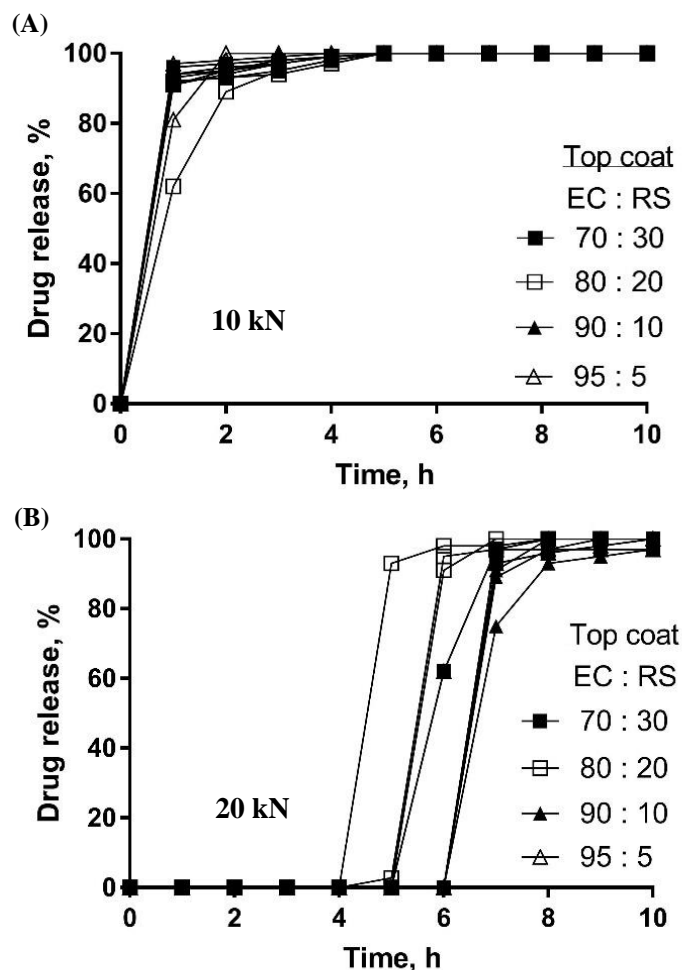
Fig. 55 Effect of ethylcellulose and Eudragit RS® ration on drug release (**A**) 10 kN and (**B**) 20 kN.

Next, the top layer was replaced with 100% (w)w) HPMC while lower layer retaining the 100% (w/w) ethylcellulose. Interestingly, this modification led to an immediate release of the drug due to the presence of different materials in the two layers, resulting in low layer binding (Fig. 56 A). After release, the formation of an HPMC gel layer and an intact ethylcellulose coat was observed (Fig. 56 B).

Upon further investigation, varying amounts of HPMC with ethylcellulose was used in the top layer; the lag time increased with increasing the ethylcellulose content due to decreasing the permeability of the coat (Fig. 56 C). This finding highlighted the tunable nature of the pulsatile drug release mechanism when HPMC is incorporated into the upper layer of the coat. By adjusting

the HPMC content, it was possible to modulate the lag time and achieve the desired pulsatile drug release profile.

(A)

(B)

Coat after dissolution study

(C)
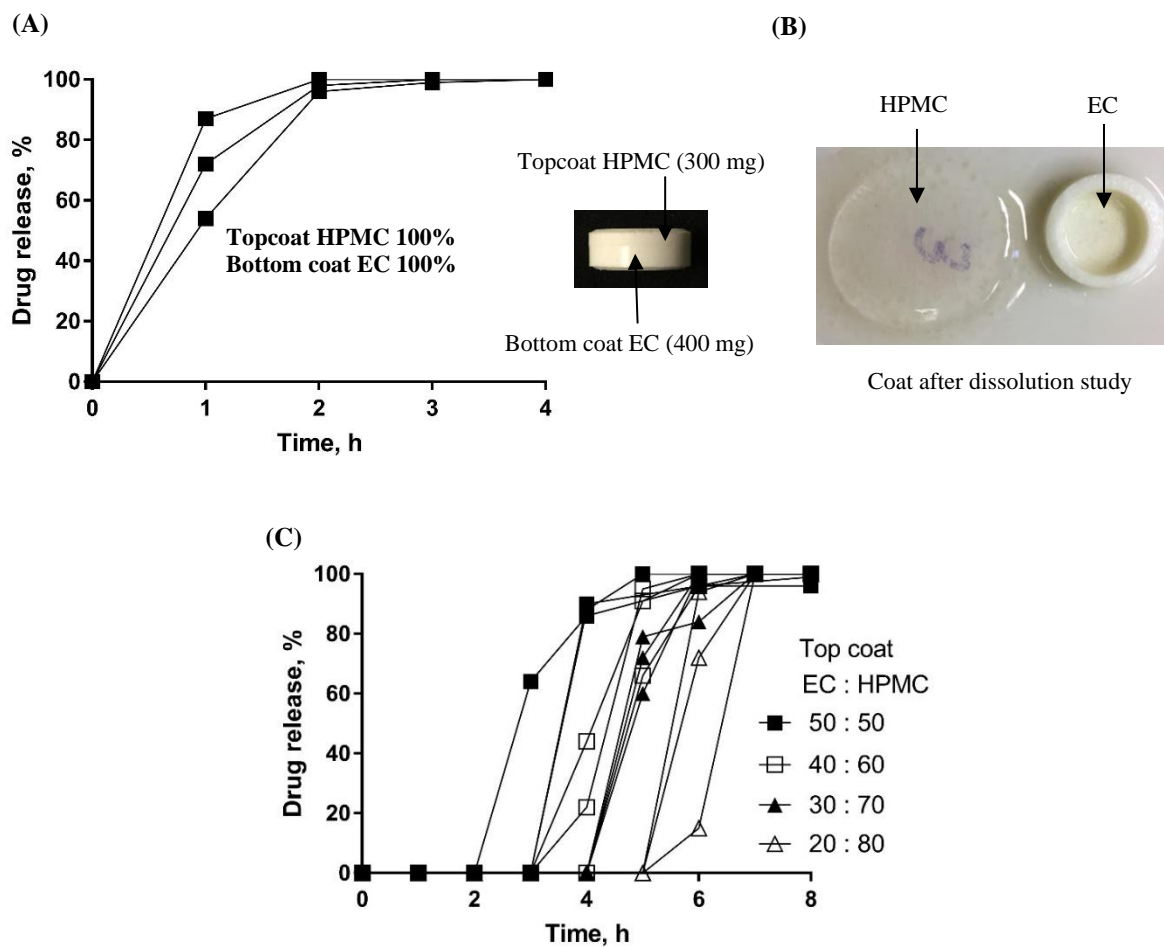
Fig. 56 Effect of ethylcellulose and HPMC ration on drug release (A) top layer: bottom layer (HPMC : EC, (B) coat after drug release study, and (C) Top layer (EC : HPMC).

3.3.3 Conclusion

Rupturable pulsatile release compression-coated tablets were investigated. The core tablets consisted of model drugs with different solubilities (carbamazepine, propranolol HCl, and metoprolol tartrate), various fillers (lactose, dicalcium phosphate, and microcrystalline cellulose), and the superdisintegrant (croscarmellose sodium). These core tablets were then compression-coated using different coating blends comprising ethylcellulose in combination with release-modifying polymers such as Eudragit RL$^®$, Eudragit RS$^®$, and HPMC, or the pore-forming agents (lactose, dicalcium phosphate, and PVP).

Among the various polymer blends tested, the combination of ethylcellulose and Eudragit RS$^®$ showed superior properties for achieving rupturable pulsatile release. This blend demonstrated lower elongation and higher mechanical strength compared to ethylcellulose with Eudragit RL$^®$ or HPMC. The polymer blend ratio not only influenced the drug release profile but also affected the mechanical properties of the coating. As the polymer content, specifically, Eudragit RL$^®$ and HPMC, increased, water uptake also increased, leading to changes in the lag time and elongation of the coat.

The addition of lactose or dicalcium phosphate as pore former resulted in immediate drug release, while the incorporation of PVP showed a lag time followed by pulsatile release. The lag time decreased with increasing PVP content, primarily due to the enhanced permeability of the coating.

The solubility of the drug had a significant impact on the lag time observed from the ethylcellulose and Eudragit RS$^®$ coated tablets. Notably, no release was observed from the metoprolol tartrate-containing tablets due to high solubility. However, by increasing the particle size of ethylcellulose, pulsatile release with metoprolol tartrate could be achieved.

Additionally, the choice of core filler played a role in determining the lag time. Tablets containing highly soluble fillers exhibited longer lag times compared to those with less soluble fillers. This can be attributed to the competition for available water within the core, resulting in decreased swelling and delayed coat rupture.

4 Summary

4.1 Effect of coating formulation parameters on pulsatile release based on lipid-based compression-coated tablets

The development of pH-independent lag times in rupturable pulsatile compression-coated tablets can be achieved by incorporating lactose as a pore-former in a lipid-based coating layer. This pore-former effectively influenced the pulsatile release profile by controlling the water permeability and mechanical properties of the coat. Furthermore, the inclusion of a binder, such as 5-10% PVP, in the coating layer plays a crucial role in determining the lag time of the tablets. Notably, with the presence of the binder, a distinct lag phase is observed in the dissolution profile, followed by rapid drug release after the lag time has elapsed. Additionally, the pulsatile release profile can be further modulated by adjusting factors such as the amount and particle size of the pore-former, the thickness of the coating layer, and the compression force. These parameters directly impact the water permeability and mechanical strength of the coating, thereby influencing the lag time and subsequent drug release behavior. A minimum coating thickness of 2 mm was required to achieve pulsatile release characteristics. This ensured the formation of a crack at the middle of the tablet and facilitates the rapid release of the drug upon swelling while maintaining the structural integrity of the coat. Tablet size, agitation rate (0 rpm to 150 rpm) and log time storage (25°C / 60% RH) did not affect drug release. The mechanical properties of the coating decreased with increasing storage humidity (0% RH to 84% RH) and storage time (0 d to 60 d), as indicated by increasing moisture uptake. Despite the changes in mechanical properties, the elongation of the coating remained unchanged.

4.2 Effect of core formulation parameters on pulsatile release based on lipid-based compression-coated tablets

Pulsatile release compression-coated tablets were developed using core tablets containing model drugs with different solubilities (carbamazepine, propranolol HCl, and metoprolol tartrate), various fillers (lactose, dicalcium phosphate, and microcrystalline cellulose), and different superdisintegrants (croscarmellose sodium, sodium starch glycolate, and crospovidone). These core formulations were compression-coated with a fixed coating blend consisting of lipid, pore-

former, and binder materials to explore the impact of core formulation parameters on pulsatile drug release. The inclusion of a superdisintegrant was essential for achieving pulsatile release.

The rupture of the coating and subsequent lag time was strongly influenced by the drug solubility and loading, which affected the swelling properties of the core. Higher solubility of the drug led to increased lag time due to reduced swelling of the core (metoprolol > propranolol > carbamazepine). Furthermore, a small amount of water was needed to reach the critical pressure for carbamazepine and propranolol HCl. In contrast, metoprolol tartrate required a larger quantity of water due to its higher solubility. Macroscopic observation confirmed the localized swelling at the weak point, resulting in coat rupture.

Among the superdisintegrants, AcDiSol exhibited a high degree of swelling, resulting in a decreased lag time with increasing concentration. The ratio of water uptake to energy remained constant, indicating that water uptake was the driving force behind the generation of swelling force.

The addition of a highly soluble filler in the core increased the lag time by enhancing the solubility and decreasing the overall swelling behavior (lactose > dicalcium phosphate > microcrystalline cellulose). Core hardness had no effect on lag time.

4.3 Preparation and characterize of polymer-based compression-coated tablets with pulsatile drug release

Rupturable pulsatile release compression-coated tablets were investigated. The core tablets consisted of model drugs with different solubilities (carbamazepine, propranolol HCl, and metoprolol tartrate), various fillers (lactose, dicalcium phosphate, and microcrystalline cellulose), and the superdisintegrant (croscarmellose sodium). These core tablets were then compression-coated using different coating blends comprising ethylcellulose in combination with release-modifying polymers such as Eudragit RL®, Eudragit RS®, and HPMC, or the pore-forming agents (lactose, dicalcium phosphate, and PVP).

Among the various polymer blends tested, the combination of ethylcellulose and Eudragit RS® showed superior properties for achieving rupturable pulsatile release. This blend demonstrated lower elongation and higher mechanical strength compared to ethylcellulose with Eudragit RL® or HPMC. The polymer blend ratio not only influenced the drug release profile but also affected the

mechanical properties of the coating. As the polymer content, specifically, Eudragit RL® and HPMC, increased, water uptake also increased, leading to changes in the lag time and elongation of the coat.

The addition of lactose or dicalcium phosphate as pore former resulted in immediate drug release, while the incorporation of PVP showed a lag time followed by pulsatile release. The lag time decreased with increasing PVP content, primarily due to the enhanced permeability of the coating.

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Additionally, the choice of core filler played a role in determining the lag time. Tablets containing highly soluble fillers exhibited longer lag times compared to those with less soluble fillers. This can be attributed to the competition for available water within the core, resulting in decreased swelling and delayed coat rupture.

5 Zusammenfassung

5.1 Einfluss der Formulierungsparameter des Überzugs auf die pulsatile Freisetzung von lipidbasierten Manteltabletten

Die Entwicklung einer pH-unabhängigen Wirkstofffreisetzung in pulsatilen, mit Press-coatings beschichteten Tabletten kann durch den Einbau von Laktose als Porenbildner in einen lipidbasierten Überzug erreicht werden. Dieser Porenbildner beeinflusst effektiv das pulsatile Freisetzungsprofil, indem er die Wasserdurchlässigkeit und die mechanischen Eigenschaften des Überzugs kontrolliert. Darüber hinaus spielt die Zugabe eines Bindemittels, z. B. 5-10 % PVP, in den Überzug eine entscheidende Rolle bei der Bestimmung der Verzögerungszeit der Tabletten. Bei Vorhandensein des Bindemittels wird im Freisetzungprofil eine deutliche Verzögerungsphase beobachtet, gefolgt von einer schnellen Wirkstofffreisetzung. Darüber hinaus kann das pulsatile Freisetzungsprofil weiter moduliert werden, indem Faktoren wie die Menge und Partikelgröße des Porenbildners, die Dicke des Überzugs und die Presskraft angepasst werden. Diese Parameter wirken sich direkt auf die Wasserdurchlässigkeit und die mechanische Festigkeit der Beschichtung aus und beeinflussen so die Verzögerungszeit und das anschließende Freisetzungsverhalten des Wirkstoffs. Um pulsatile Freisetzungseigenschaften zu erreichen, war eine Mindestschichtdicke von 2 mm erforderlich. Dies gewährleistet die Bildung eines Risses in der Mitte der Tablette und erleichtert die schnelle Freisetzung des Wirkstoffs nach dem Platzen des Überzugs, wobei vorher die strukturelle Integrität des Überzugs erhalten bleibt. Die Tablettengröße, die Rührgeschwindigkeit (0 U/min bis 150 U/min) und die Lagerung über einen längeren Zeitraum (25 °C / 60 % relative Luftfeuchtigkeit) hatten keinen Einfluss auf die Wirkstofffreisetzung. Die mechanischen Eigenschaften des Überzugs nahmen mit zunehmender Lagerungsfeuchtigkeit (0% RH bis 84% RH) und Lagerungsdauer (0 d bis 60 d) ab, was auf eine zunehmende Feuchtigkeitsaufnahme hindeutet. Trotz der Veränderungen der mechanischen Eigenschaften blieb die Ausdehnung der Beschichtung unverändert.

5.2 Auswirkung von Formulierungsparametern des Tablettenkerns auf die pulsatile Freisetzung von lipidbasierten Manteltabletten

Für die Entwicklung von Tabletten mit pulsatiler Freisetzung wurden Tablettenkerne verwendet, die Arzneistoffe mit unterschiedlichen Löslichkeiten (Carbamazepin, Propranolol HCl und Metoprololtartrat), verschiedene Füllstoffe (Laktose, Dicalciumphosphat und mikrokristalline Cellulose) und unterschiedliche Superzerfallsmittel (Croscarmellose-Natrium, Natriumstärkeglycolat und Crospovidon) enthielten. Diese Formulierungen wurden mit einer festen Beschichtungsmischung aus Lipid, Porenbildner und Bindemittel kompressionsbeschichtet, um die Auswirkungen von Formulierungsparameter der Kerne auf die pulsatile Wirkstofffreisetzung zu untersuchen. Die Zugabe eines Superzerfallsmittels ist für die pulsatile Freisetzung von wesentlicher Bedeutung.

Der Bruch des Überzugs und die anschließende Verzögerungszeit wurden stark von der Löslichkeit des Wirkstoffs und der Beladung beeinflusst, die sich auf die Quelleigenschaften des Kerns auswirkten. Eine höhere Löslichkeit des Wirkstoffs führte zu einer längeren Verzögerungszeit aufgrund einer geringeren Quellung des Kerns (Metoprolol > Propranolol > Carbamazepin). Außerdem war für Carbamazepin und Propranolol HCl eine geringe Menge Wasser erforderlich, um den kritischen Druck zu erreichen. Im Gegensatz dazu war für Metoprolol aufgrund seiner höheren Löslichkeit eine größere Wassermenge erforderlich. Makroskopische Beobachtungen bestätigten die lokale Quellung an der Schwachstelle, die zum Platzen des Überzugs führte.

Unter den Super-Zerfallsmittel zeigte AcDiSol einen hohen Quellungsgrad, was zu einer Verkürzung der Verzögerungszeit führte, wenn seine Konzentration erhöht wurde. Das Verhältnis von Wasseraufnahme zu Energie blieb konstant, was darauf hindeutet, dass die Wasseraufnahme die treibende Kraft hinter der Erzeugung der Quellkraft war.

Interessanterweise erhöhte die Zugabe eines gut löslichen Füllstoffs im Kern die Verzögerungszeit, indem sie die Löslichkeit erhöhte und das gesamte Quellverhalten verringerte (Laktose > Dicalciumphosphat > mikrokristalline Cellulose). Die Härte des Kerns hatte keinen Einfluss auf die Verzögerungszeit.

5.3 Herstellung und Charakterisierung von überzogenen Tabletten auf Polymerbasis mit pulsatiler Wirkstofffreisetzung

Ziel dieser Studie war die Entwicklung polymerbasierter, Manteltabletten für die pulsatile Freisetzung auf der Grundlage der Kompressionsbeschichtung einer Pulvermischung aus Ethylcellulose in Kombination mit freisetzungsmodifizierenden Polymeren wie Eudragit RL®, Eudragit RS® und HPMC oder porenbildenden Mitteln wie Laktose, Dicalciumphosphat und PVP. Die Tablettenkerne enthielten Arzneistoffe mit unterschiedlichen Löslichkeiten (Carbamazepin, Propranolol HCl und Metoprololtartrat), verschiedenen Füllstoffen (Laktose, Dicalciumphosphat und mikrokristalline Cellulose) und dem Superzerfallsmittel (Croscarmellose-Natrium).

Unter den verschiedenen Polymermischungen zeigte die Kombination aus Ethylcellulose und Eudragit RS® die besten Eigenschaften für die Erzielung einer aufbrechbaren, pulsatilen Freisetzung. Diese Mischung wies im Vergleich zu Eudragit RL® oder HPMC eine geringere Ausdehnung und höhere mechanische Festigkeit auf. Das Mischungsverhältnis der Polymere beeinflusste nicht nur das Wirkstofffreisetzungsprofil, sondern auch die mechanischen Eigenschaften des Überzugs. Eine Erhöhung des Polymeranteils (insbesondere Eudragit RL® und HPMC) erhöhte die Wasseraufnahme, was zu Veränderungen der Verzögerungszeit und der Ausdehnung des Überzugs führte.

Der Zusatz von Laktose oder Dicalciumphosphat als Porenbildner führte zu einer sofortigen Wirkstofffreisetzung, während die Einarbeitung von PVP eine Verzögerungszeit mit anschließender pulsatiler Freisetzung ergab. Die Verzögerungszeit verringerte sich mit zunehmendem PVP-Gehalt, was in erster Linie auf die verbesserte Permeabilität des zurückzuführen ist.

Die Löslichkeit des Arzneimittels hatte einen erheblichen Einfluss auf die Verzögerungszeit. Insbesondere wurde aufgrund der hohen Löslichkeit von Metoprololtartrat keine Freisetzung beobachtet. Durch Erhöhung der Partikelgröße von Ethylcellulose konnte jedoch eine pulsatile Freisetzung von Metoprololtartrat erreicht werden.

Außerdem spielte die Wahl des Füllstoffs der Kerne eine Rolle bei der Bestimmung der Verzögerungszeit. Tabletten mit hochlöslichen Füllstoffen wiesen im Vergleich zu weniger löslichen Füllstoffen eine längere Verzögerungszeit auf. Dies kann auf den Wettbewerb um das

verfügbare Wasser im Kern zurückgeführt werden, was zu einer geringeren Quellung und einem verzögerten Aufbrechen des Überzugs führt.

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7 Publications and Poster Presentations

7.1 Publications

1. Alam, M. N., Ali, R, Dashevskiy, A. Bodmeier, R. 2023. Effect of coating formulation parameters on pulsatile release based on compression-coated tablets (Manuscript in preparation).

2. Alam, M. N., Dashevskiy, A., Bodmeier, R., 2023, Effect of core formulation parameters on pulsatile release based on compression-coated tablets (Manuscript in preparation).

3. Alam, M. N., Dashevskiy, A., Bodmeier, R., 2023, Pulsatile release from polymer-based compression-coated tablets (Manuscript in preparation).

7.2 Poster Presentation

1. Alam, M. N., Dashevskiy, A., Bodmeier, R., 2022. Pulsatile drug release from compression-coated tablets. 12th DPhG Scientific Symposium in Berlin 2022, Poster. #01

2. Alam, M. N., Ali, R, Bodmeier, R. 2020. Pulsatile release from high dose lipid press-coated tablet. 12th PBP World Meeting in Vienna 2020, Poster. #193

8   Curriculum Vitae

For reasons of data protection,

the curriculum vitae is not included in the online version.