Universidade de Lisboa

Faculdade de Farmácia

Preparation and characterization of time-dependent drug delivery system by tablet press-coating

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Mestrado Integrado em Ciências Farmacêuticas

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Abstract

Time-dependent delivery systems are designed to offer a fast or prolonged release of the drug after a programmed time, called lag time. These systems have many applications, either as chronotherapeutical formulations or to obtain drug delivery into the colon. The goal of this study was to obtain press-coated time-dependent tablets containing prednisone in the core. Two main formulations were prepared, both comprised of rupturable materials, one with ethyl cellulose and another containing a mixture of glyceryl behenate, a hydrophobic lipid, and dicalcium phosphate. The results indicated that drug release from the optimized press-coated formulations was characterized by a distinct lag time followed by burst drug release. The presence of a superdisintegrant in the core was crucial to develop the adequate pressure to rupture the coat, especially with the glyceryl behenate/dicalcium phosphate formulation. Dicalcium phosphate revealed to be helpful in decreasing the size of the tablets, without changing their mass, therefore offering the possibility of increased intake, and, consequently, increased compliance. Dicalcium phosphate exhibited an impact on the variability of lag times between different media, causing lower lag times in acidic pH. However, if the percentage of dicalcium phosphate was kept at 20%, formulations pH independent were obtain. Glyceryl behenate had a negative impact on lag time, while a soluble excipient, PVP K30, had a positive impact. The lag time could be controlled by varying the ratio glyceryl behenate:PVP K30. With the optimized formulation of glyceryl behenate, water uptake was high, especially in HCl (35.93 ± 1.92%). With the ethyl cellulose formulations, not only did the presence of a soluble excipient have a positive impact on lag time, but also the presence of a swellable excipient in the coat. It was also proven that the presence of a good binder was crucial when using EC of a bigger diameter, to prevent immediate release. The water uptake of this formulation remained relatively low, 4.82 ± 0.20% in HCl and 4.05 ± 0.07 % in phosphate buffer. Further, different diameter tablets were prepared, keeping the same coat:core mass ratio, to understand if the formulations were capable of undergoing higher drug loading. Lag time remain similar for both formulations.

Keywords: Time-dependent delivery systems; Press-coating; Rupturable coat; Lag time.

Resumo

Os sistemas de libertação tempo-dependente são desenhados para oferecer uma rápida libertação ou uma libertação prolongada do fármaco após um tempo programado, denominado de *lag time*. Estes sistemas apresentam diversas aplicações, por exemplo, como formulações cronoterapêuticas ou para obtenção de libertação de um fármaco no cólon. Este trabalho teve como objetivo o desenvolvimento de comprimidos revestidos por compressão com libertação dependente do tempo, contendo prednisona no núcleo. Foram preparadas duas formulações, ambas contendo materiais que libertam o fármaco após rutura do revestimento. Uma das formulações era constituida por etil celulose enquanto que a outra era constituida por uma mistura de behenato de glicerilo e fosfato dicálcico. Ambas as formulações otimizadas exibiram um perfil de libertação caracterizado por um distinto *lag time*, seguido de libertação imediata do fármaco. A presença de um superdisintegrante no núcleo mostrou-se ser essencial para o desenvolvimento da pressão necessária para romper o revestimento, sobretudo com a formulação de behenato de glicerilo/fosfato dicálcico. A presença de fosfato dicálcico permitiu a redução da espessura dos comprimidos, sendo possível obter comprimidos menores sem redução da sua massa. O fosfato dicálcio demonstrou ter um impacto na variabilidade de *lag times* obtidos em diferentes pH, provocando *lag times* mais curtos em pH acídico. No entanto, quando a percentagem foi mantida nos 20%, foi possivel obter formulações com um comportamento independente do pH. O behenato de glicerilo teve um impacto negativo no *lag time*, enquanto que um excipiente solúvel, PVP K30, teve um impacto positivo. Assim, o *lag time* pode ser controlado variando o *ratio* behenato de glicerilo:PVP K30. A absorção de água foi elevada com esta formulação, sendo mais significativa com o pH ácido (35.93 ± 1.92%). Com a formulação de etil celulose, a presença de um excipiente solúvel no revestimento teve também um impacto positivo no lag time. Para além disso, a presença de um excipiente com alguma capacidade de intumescimento no revestimento levou a *lag times* mais curtos. Foi também provado que a presença de um bom aglutinante no revestimento é essencial, de forma a prevenir libertação imediata do fármaco. A absorção de água foi relativamente baixa com esta formulação, 4.82 ± 0.20% em HCl e 4.05 ± 0.07 % em tampão fosfato. Adicionalmetne, comprimidos com vários diâmetros foram preparados. Respeitado o ratio de massa núcleo:revestimento, o lag time manteve-se semelhante. Assim, é possível a preparação de comprimidos maiores, de forma a aumentar a capacidade de *loading* de fármaco.

Palavras-chave: Sistemas de libertação tempo-dependente; revestimento por compressão; libertação por rutura; *lag time*.

Abbreviations

Ac-Di-Sol – Croscarmellose sodium

DCP – Dicalcium phosphate

DR – Delayed release

EC – Ethyl cellulose

ER – Extended release

GB – Glyceryl behenate

GI – Gastrointestinal

HEC – Hydroxyethyl cellulose

HPC – Hydroxypropyl cellulose

HPMC – Hydroxypropyl methyl cellulose

HPMCAS – Hypromellose acetate succinate

IBD – Inflammatory bowel disease

IR – Immediate release

OSDRC – One-step dry-coated

PEO – Polyethylene oxide

RA – Rheumatoid arthritis

SDL – Spray-dried lactose

SD – Standard deviation

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1. Introduction

1.1. Modified Release Dosage forms

Conventional immediate release (IR) dosage forms, typically provide an immediate or rapid drug release, without any rate control. IR results in relatively rapid drug absorption and onset of pharmacodynamic effects. Despite being widely used, these formulations offer some disadvantages, particularly in situations where multiple administration is required or when used in the treatment of numerous diseases where the symptoms mainly occur during the night or early morning (1).

Modified release (MR) offers the possibility of continuous or constant-rate drug delivery, alteration of the time of drug release and or/ alteration of the site of drug release. Possible benefits of MR dosage forms include, improved efficacy and reduced side effects, through minimizing the drugs "peak and valley" levels in the blood, increased convenience and patient compliance, optimal clinical performance, greater selectivity of activity, or new indications. They also offer an enhancement of activity duration, for short half-life drugs (1–3). At a commercial level, they lead to product differentiation and/or line extension, maximized drug potential, and increased cost effectiveness (2).

The objective of MR dosage forms is to modulate the rate of drug's dissolution or absorption in the gastrointestinal (GI) tract to achieve a predefined plasma profile (3). MR dosage forms includes extended release (ER) and delayed release (DR), with the latter being either site or time specific (Figure 1). An ER dosage forms is intended to release the drug over an extended period after ingestion, allowing at least two-fold reduction in dosing frequency or significant increase in patient compliance or increased therapeutic performance as compared to an IR dosage form. A DR dosage form releases the drug at a time other than immediately after administration and it can be either time or site specific, as mentioned before (2–4)**.**

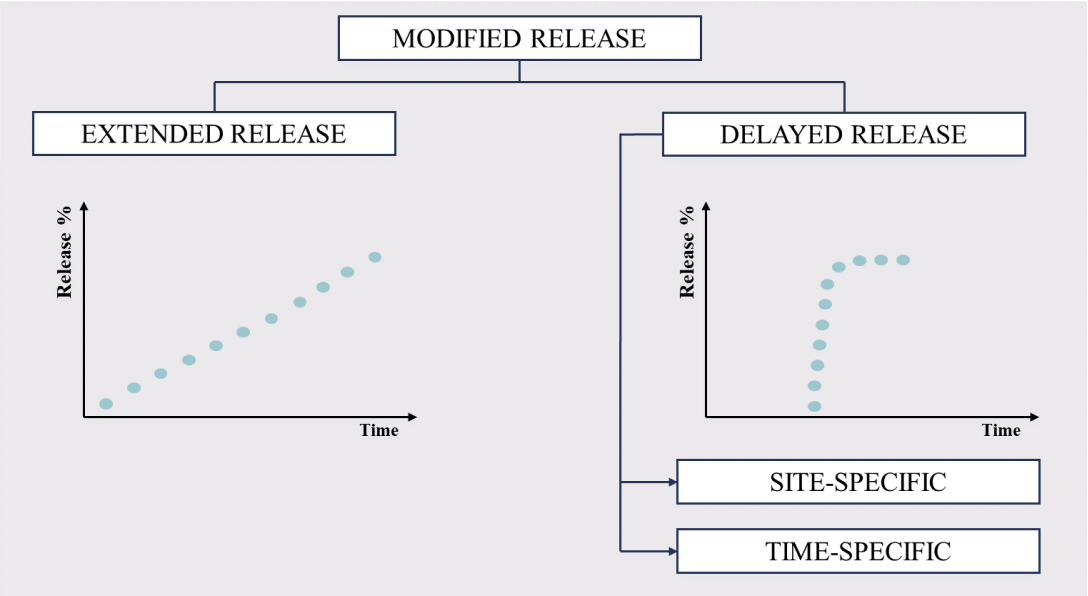

Figure 1 – Modified release dosage forms.

1.1.1. Time-dependent delivery systems

Time-dependent delivery systems (TDDS) are DR dosage forms designed to offer a fast and complete or extended release of drug after a programmed time, called lag phase or lag time (5–7). The release process may be triggered by external signals (e.g. chemical, thermal, electric and magnetic stimuli) or, it can be regulated by inherent mechanisms, that are expected to perform consistently, independent of major physiological variables, such as, pH, ionic strength or temperature (5,6).

TDDS reduces dosing frequency and, unlike sustained release delivery systems, provide a timely pharmacological effect, enabling a reduction in side effects associated with a prolonged, and at times unnecessary, exposure to a drug (8). The great potential of such formulations is their suitability for providing the patient with the correct dosage, at the correct time, thus allowing a reduction in dosing, cost and frequency. This time-dependent approach is particularly important in pathologies with predominant night or early morning symptoms (bronchial asthma, rheumatoid arthritis, etc.). In this case, TDDS could provide a therapeutic effect, without having to interrupt the normal sleep pattern of patients, which could lead to reduced compliance (5).

Another interesting application of TDDS is the delivery into the large bowel, with a time dependent approach that relies on the small intestinal transit time, practically

independent of the characteristics of the dosage form, as well as of the fasted and fed state of the subject (5,6).

Despite moderate drug absorption properties, the colon represents an interesting site of absorption for drugs that may cause irritation or be degraded in the upper GI tract, as well as for nonabsorbable molecules that are supposed to act in the gut lumen (9,10). The latter fact could be particularly interesting for colon delivery in the treatment of inflammatory bowel disease (IBD) and chemoprevention of colorectal adenocarcinoma (5,6). Currently, the dosage forms most commonly used in the treatment of IBD rely on the different pHs of the GI tract. However, the pH of the GI tract is highly variably in these patients and most of the drug is released in the upper small intestine after gastric emptying (11).

For time dependent colon delivery, an entering coating is usually employed in order to overcome the highly variable stomach emptying time (5,6). Moreover, peptide and protein drugs, which are known to be more prone to enzymatic degradation in the small bowel, may have their oral bioavailability increased (12).

Besides, time-dependent dosage forms, can prevent the occurrence of detrimental drug-drug interactions, without the need of changing the administration schedule of combined medication, which could lead, once more, to increased compliance (5,14).

Time controlled systems can consist or single-unit or multiple unit systems. Single unit systems consist mainly of capsule-shaped and advanced osmotic devices (9). Multiple unit systems decrease the unit-to-unit variability, when compared to single unit. On the other hand, however, low drug loading, incomplete drug release, proportionally higher need for excipients, lack of manufacturing reproducibility and efficacy, a large number of process variables, multiple formulation steps, higher cost of production, and need of advanced technology are some of the disadvantages (9,10).

It is widely known that the oral route presents itself as the preferred one, mostly because of the cost-effectiveness and usually high compliance of patients (5). Therefore, oral time-dependent release dosage forms have been developed and according to the coating agents employed, the release mechanism may involve erosion, rupture or diffusion (the coat becomes more permeable, allowing the drug to diffuse outwards) (Figure 2) (5,7,14).

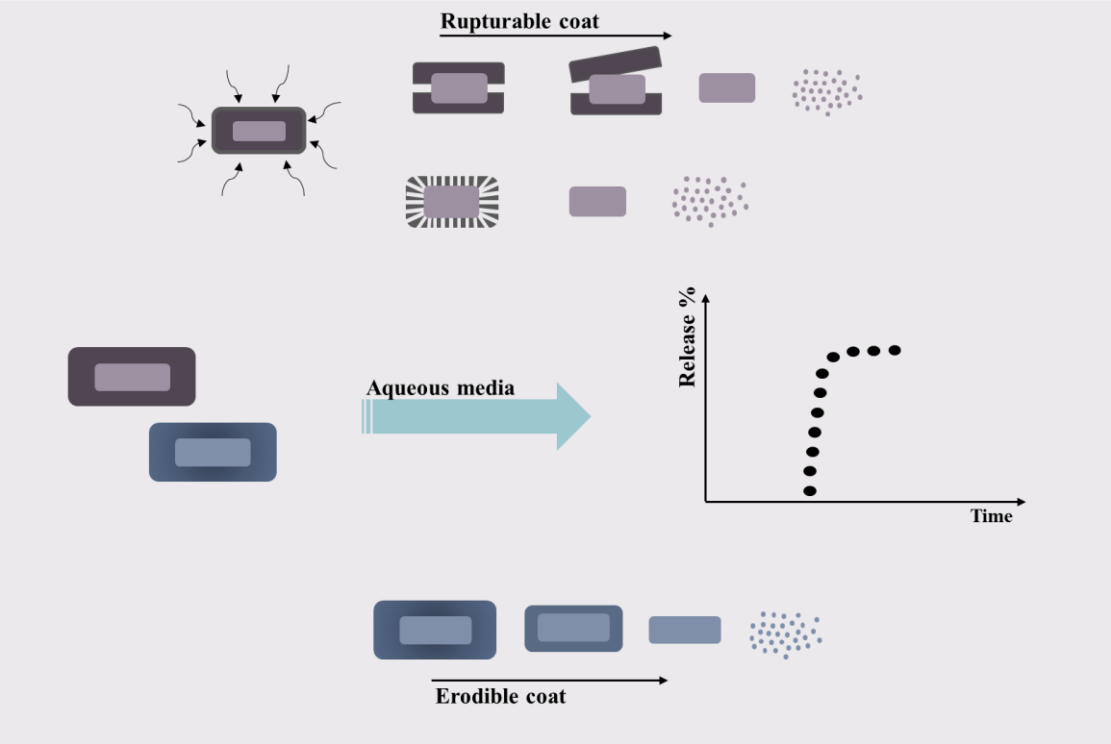

Figure 2 – Outline of the performance of coated delivery systems for oral time-dependent release on exposure to aqueous fluids. Adapted from (14).

1.1.1.1. Delivery systems with rupturable coating layers

Rupturable systems usually consist of an inner core that contains the drug and an outer coat, water-insoluble but moderately water permeable, often in addition to pore-formers/plasticizers, to improve its inherent flexibility and permeability characteristics (5,6).

When these systems come in contact with water, water penetrates the outer coat and the inner core expands, developing an increasing outward pressure that ultimately leads to the rupture of the coating (partial or complete). Afterwards, the drug is rapidly released (5,15). The necessary pressure to rupture the coat can be achieved by using excipients that react, causing effervescence, swelling agents or osmotic pressure. The release is mainly controlled by the thickness and composition of the rupturable coat (5).

The main excipient used in these types of TDDS is ethyl cellulose (EC) (14–17).

1.1.1.2. Delivery systems with swellable/erodible coating layers

Erodible release systems are mostly based on hydrophilic polymers that form the coating. These, in turn, may swell, erode and/or dissolve when in contact with aqueous fluids, due to the glassy-rubbery polymer transition, which results in an appropriate lag time before drug release occurs (14). Lag time is mostly dependent on the appropriate polymer particularly, molecular mass of the polymer, and coating level (10).

Hydrophilic cellulose ethers, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) and hydroxypropyl methyl cellulose (HPMC) are employed as the main components of the coating as they have shown to have an adequate swelling behaviour, an established safety profile, ease of handling, availability in different grades and reasonable costs as well as pH independence, due to the non-ionic nature of their polymers (5,6,14,18).

1.2. Coating technology

Pharmaceutical coating is used for various reasons, such as achieving superior organoleptic and aesthetic characteristics, providing physical and chemical protection (protection from moisture, light and/or air; protection from gastric acid or gastric enzymes; enhanced mechanical strength) or to attain modified drug release profile, either by altering the site, the time of release and/or the release rate (19,20).

Sugar coating was the first modern pharmaceutical coating and was mainly used in order to improve the palatability of bitter medicines. However, this technique had long processing times (up to 5 days), 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 (18).

Film coating, carried out by a fluid bed or rotating pan equipment, involves spraying the coating onto the substrate cores that can be powder, granules, pellets, tablets and capsules. The coating materials are solubilized or suspended in an organic and/or aqueous vehicle (19).

Film coating offers many advantages, for instance, good reproducibility of the process, ability of being applied to different dosage forms, process automation, increased process control and improved batch-to-batch uniformity of the product (18,19).

However, organic solvents, despite offering 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 (18).

The use of water as a solvent eliminates many of the disadvantages of using organic solvents in solvent-based coating techniques. Despite, heat is necessary for evaporating the water present in the coating and, because of the relatively high latent heat of vaporization of water, slow drying rate of the coating becomes an issue, causing longer processing times. In addition, drugs can be sensitive to residual moisture in the film and this can cause long-term stability problems and may ultimately change the permeability of the core to the drug and alter the performance of the coating layer. Another problem stemming from using water as the solvent is that the control of microbial presence becomes an problem, especially when cellulose polymers are used as the coating material (18).

Thus, the limitations of film coating include mostly problems related with the use of solvents and their removal. Consequently, the elimination of solvents from the coating process can present a significant advancement (18).

Solventless coating techniques allow for a reduction in costs, by eliminating the slow and expensive processes of solvent treatment. Furthermore, it can significantly reduce processing time as it eliminates the slow drying and evaporation steps. Also, techniques where there is no heating source can provide an alternative method to coat heat-sensitive drugs. Solvent free techniques may offer an alternative for preparation of microcapsules containing antigens or proteins, which can be of much importance due to the current trend towards biopharmaceutical molecules (18,21).

Techniques that would be classified into solvent free can be further divided according to the physical state of the coat-forming agents when applied onto the surface (Figure 3). In liquid-based techniques, melts or liquid precursors applied onto the surface are consolidated either by cooling (hot-melt coating) or by UV-initiated polymerization (coating by photocuring), to attain a continuous layer. In solid-based techniques, the coating may be directly applied by compression (press-coating), or it can be layered and simultaneously consolidated by heating (powder coating). Furthermore, in powder coating, the process can

be optimized, especially as regards to the initial deposition phases, by spraying liquid aids and/or through particle charging (19).

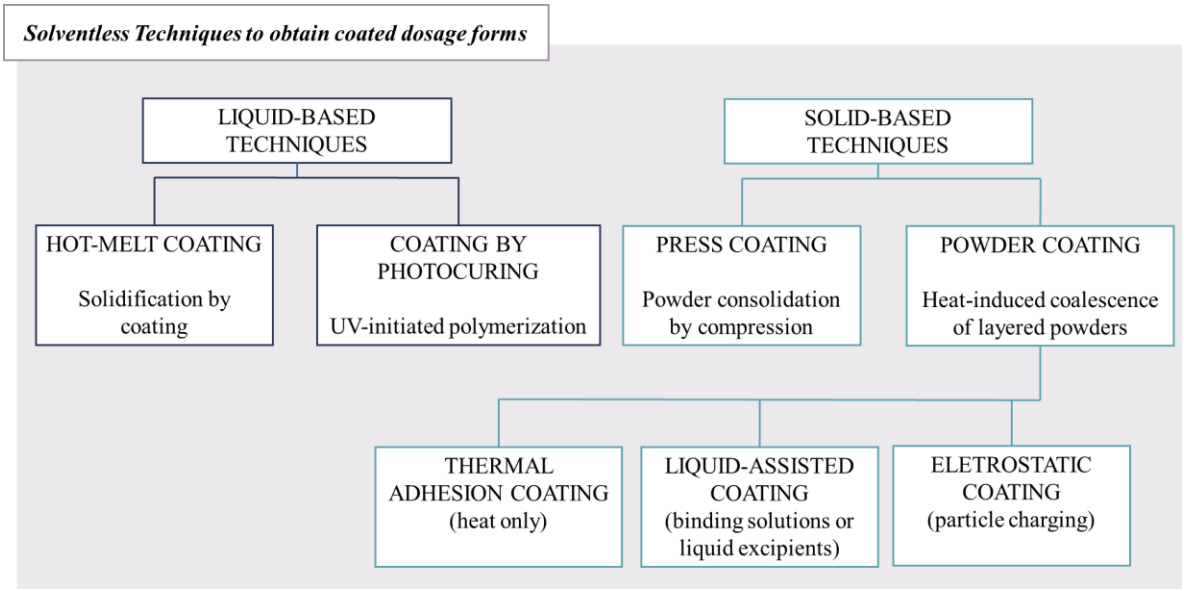

Figure 3 – Classification of solventless techniques to obtain coated dosage forms. Adapted from (19).

1.2.1. Press-coating

Press-coating, also known as compression coating or dry coating or double compression was one of the first solvent-free coating techniques (18,19). Generally, it consists of an inner core surrounded by an outer coat. Conventionally, the inner core is compressed first. Then, a tableting machine is pre-filled with a certain amount of coating material, the inner core is placed on the centre of the powder bed and the remaining coating mixture is added on top. Finally, all of the contents are compressed in order to obtain an outer layer of defined thickness (Figure 4) (1,19).

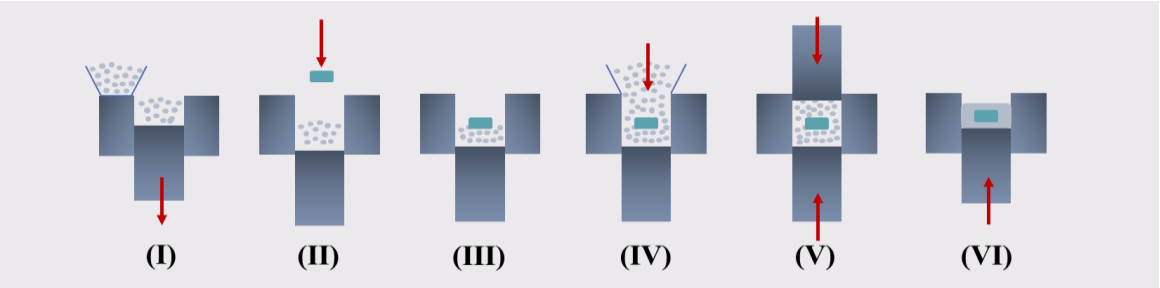

Figure 4 – Manufacturing process of press-coating. (I) – Prefilling the die with about half of the coating materials; (II) – Placing the tablet on top of the powder bed; (III) – Centring of the tablet; (IV) – Filling the die with the rest of the coating material; (V) – Compression; (VI) – Ejection of the tablet. Adapted from (1).

It offers several advantages, like the possibility of separation incompatible drugs in the core and the coat within the same dosage form. Additionally, it is possible to formulate a dosage form that releases two active substance in different parts of the GI tract. Moreover, it offers protection to hygroscopic, light sensitive, oxygen labile and acid-labile drugs (18,21).

The manufacturing of dry coated tablets using this method is high cost because of the requirement of preparing the core tablets beforehand. The process is relatively slow when compared to other solventless techniques, the coatings are thick and may not be suited for immediate release (26). Also, the requirement for core tablet supply system leads to problems such as double-core, non-core, off-centre and inlay (22).

One of the major problems associated with this technique is the centring of the inner core. When the core is not centred correctly, there may be variation in the release profile of the inner core (1,18,19). To solve this problem Ozeki et al. developed the one-step dry-coated tablet manufacturing method (OSDRC system). This system does not require the preparation of the core tablet beforehand, as the whole system is prepared in a single process (22). The manufacturing method was executed by using upper and lower punches, which had a double structure, a centre punch and an outer punch surrounding the centre punch. The three-step process involves the formation of the first outer layer (lower), the core and the upper outer coat layer, followed by a compression in every step (18,22).

The OSDRC system eliminates the necessity of a supply system and therefore eliminates the problems that stem from such. Also, this system provides thinner coatings compared to conventional dry coating (22).

1.2.1.1. Factors affecting performance and drug release of press-coated delivery systems

Press-coated tablets consist of two layers, an inner core and an outer coating. The coating may have different rate-controlling materials in order to achieve time or site-specific drug delivery and/or attain extended release. The drug release behaviour is controlled by different variables that may be present in the inner core and outer coat. These factor include, the solubility of the drug, the ratio core:coat, the composition of both inner core and coat, the compression force and also the location of the inner core (21).

The solubility and permeability are important variables to think of when formulating as they affect the absorption of the drug. Therefore, the solubility of the drug present in the inner core is an important factor to monitor (21). It has been shown that higher solubility drugs offer shorter lag times (23). Rujivipat and Bodmeier prepared HPMC compression-coated tablets containing different solubilities drugs in the inner core (24). It was shown that depending on their solubility the drugs were released either by diffusion and/or erosion of the gelled HPMC coat. Carbamazepine, the least water-soluble drug was released completely after a lag time, after erosion of the HPMC coat. The release of the other drugs, more water-soluble, happened by diffusion through the gel prior to erosion, showcasing a sigmoidal release profile.

Other components of the inner core can also affect the lag time. Lin et al showed that diluents with different solubilities affect the lag time (23). More soluble diluents, such as spray-dried lactose, facilitate the dissolution, shortening both disintegration and lag times. Also, it was shown that the presence of an osmotic agent, sodium chloride, for instance, generates a higher internal osmotic pressure and distinctly decreases the lag time. Additionally, the presence of a superdisintegrant results in the bursting effect of the tablets, caused by the swelling, and enhances the drug release from press-coated tablets (25).

The ratio core:coat has also been shown to influence lag time. Due to faster erosion/rupture of the press coat, a higher core:coat ratio leads to a shorter lag time (26).

Likewise, the constitution of the coat effects the release profile. The coating material is of extreme importance as it affects variables such as mechanical strength, release profile and stability (18). For instance, the presence of water insoluble/rupturable (EC), erodible

(low molecular weight HPMC, HPC, PEO), gellable or swellable (high molecular weight HPMC, gums), pH-dependent soluble (HPMCAS, Eudragit copolymers) polymers or a mixture of these can modulate the drug release (1). The compressibility is also highly dependent of the coating material, making its selection a central step (18).

The choice between a rupturable or swellable/erodible material also affects the release of the drug from the inner core. An erodible coating does not modify the release profile of the drug present in the core; a swelling coat, however, may delay the release of the drug and alter the release performance of the inner core (27). Because of this, when an extended release is required after lag time, often a swellable coat is employed. When a burst effect is required, an erodible or rupturable coat seems to be the best choice.

Several studies have demonstrated the effect of hydrophilic excipients present in the inner core on the lag time (28,29). Lin et al. studied the effect of several direct-compressible excipients, spray-dried lactose (SDL) and a polymer with hydrophilic properties (HPMC) (28). It was shown that the lag time was dependent on type of excipient present in the coat, with SDL providing a shorter lag time. The different physico-chemical properties of HPMC and SDL can explain the different lag time. The quick dissolution of SDL provides a more porous structure for medium penetration, while a more viscous gel layer of HPMC swollen on the whole tablet might delay the penetration of the medium and cause prolongation of the lag time. A different study used as hydrophilic excipients HPMC (E5), HPC (EF and SSL), povidone (K30), copovidone, polyethylene glycol (4000), lactose and mannitol. With increasing concentration of the excipients, there was a reduction in the lag phase before release, with the freely water soluble diluents having a bigger influence (lactose and mannitol) (29).

The size of the polymer particle can also influence lag time. Various lag times were obtained by using different EC particle sizes, with smaller particles providing longer lag times. The finner the article, the less residual porosity remains, providing a more torturous path for medium penetration. Therefore, by choosing the size of the particle, one can modulate the lag time (30).

1.3. Chronopharmaceuticals

Chronopharmaceuticals comprises the fundamentals of chronobiology and pharmaceutics, with chronobiology being the study of biological rhythm and its mechanism (1,9). Chronobiology assumes that all organisms, when it comes to bioprocesses and functions, exhibit predictable variability over time (21). The biological rhythm is controlled by a number of factors, internal or external, such as food intake, metabolism, appetite, digestion, hormonal changes, etc (31).

It has been shown that many diseases follow the circadian rhythm. In these, medications pharmacodynamics and pharmacokinetics are influenced by the chronopharmacological phenomena (9,29,31). For instance, some disorders provoke either night-time or early morning symptoms. The traditional way of treating these, is to deliver a higher dose of drug in the form of either an IR or ER drug formulation before going to bed, in order to maintain therapeutic concentrations until the next morning. This, however, leads to increased side effects and also subjects the body to a metabolic load even when not necessary (29).

Therefore, it makes sense for a drug to be administrated at the correct time, in order to achieve concentration peaks at times where the symptoms are present or exacerbated. Hence, chronopharmaceuticals may improve efficacy and minimize side-effects, by releasing a drug at a rhythm that matches the biological needs. Many studies have showed exactly that the timing of administration can increase the efficacy and diminish toxicity of many drugs (31). For instance, a study of 26 patients with rheumatoid arthritis showed that the administration of low dose prednisolone at 2 a.m., instead of 7.30 a.m., resulted in an improvement of morning symptoms (32). However, a long-term therapeutic regimen based on waking up patients is not only impractical but could also affect the circadian rhythm itself.

Chronotherapeuticals, involves not only new medicines but the improved application of established ones in a different and more biologically manner (33). The new chronotropic technology may be developed by synchronizing the drug concentrations to rhythms in disease activity. With chronopharmaceutical dosage forms, the drug is released at a desired time to match the biological needs, which results in improved efficacy and patient-compliance (1,31). By not exposing the patient to unnecessary doses of drug, a reduction of side-effects can be achieved too (9).

Not only it can be achieved by using TDDS to match the peaks in the disease activity but also, in certain instances, it can be achieved by unequal morning and evening dosing

schedules of sustained release 12h medication systems, or application of a special tablet and capsule formulations dosed at designed times to proportion medications over the 24h in synchrony with the biological rhythm (33).

For the development of chronotropic drug delivery system, an extensive knowledge of the pathology is required, therefore, these system may be used in diseases having enough scientific background in order to justify their need as compared to a conventional drug delivery systems (1). These include asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases, diabetes, hypercholesterolemia, neurological disorders etc. which have a well stablished circadian rhythm (

Table 1) (34).

A drawback, however, is that, although drug release can be controlled, drug absorption cannot. Therefore, drugs with variable absorption in the GI tract, are not good candidates for chronopharmaceutical drug delivery systems (31).

1.3.1. Chronopharmaceutical dosage forms on the market

A few technologies have been developed as chronopharmaceutical dosage forms to fulfil unmet medical needs in the treatment of various diseases. OROS technology, Geoclock® Technology, TimerX® technology, Pulsicap™, DIFFUCAPS®, CEFORM® technology and CODAS® technology are example of marketed technologies that have the chronopharmaceutical concept as a basis for their development (Table 2).

Table 1 – Diseases that require time dependent delivery systems. Adapted from (10).

Disease	Chronological behaviour	Drugs used
Bronchial asthma	Precipitation of attacks during night or at early morning	B2 agonist, antihistamines
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Cancer	Blood flow to tumours is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase	Vinca alkaloids, Taxanes
Duodenal ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are slower at night	Proton pump inhibitors
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during daytime	HMG CoA reductase inhibitors
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Arthritis	Pain and stiffness in the morning and increased level of pain at night	NSAIDs, Glucocorticoids
Cardiovascular diseases	Blood pressure is at its lowest during the sleep and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blockers, ACE inhibitors
Attention deficit syndrome	Increased in DOPA level in afternoon	Methylphenidate

Table 2 – Marketed technologies of Chronopharmaceutical dosage forms.

Drug (registered trademark®)	Technology	Drug release mechanism	References
Verapamil HCl (Covera-HS) Nifedipine (Procardia XL) Doxazosin mesylate (Cardura XL) Oxybutynin HCl (Ditropan XL) Glipzide (Glucotrol XL) Paliperidone (Invega)	OROS® technology	**Osmotic Regulation.** Comprised of a bilayer or trilayer tablet core, one push layer and one or more drug layers. The push layer contains an osmotic agent and swellable polymers. A semipermeable membrane surrounds the core (drilled with a delivery orifice). The active pharmaceutical is pushed away through the channel due to pump effect of the osmotic agent. Usually designed for extended release.	(1,10,34)
Prednisone (Lodotra)	Geoclock® technology	**Time-dependent delivery** Consists of an active drug core inside an outer layer consisting of a hydrophobic material. The drug is released after rupturing of the outer core.	(10,35)
Oxybutynin HCl (cystine CR) Oxymorphone (Opana ER)	TIMERx®	**Swelling, diffusion, erosion.**	(34)

		This technology combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix. This technology can provide from zero order to chronotherapeutic release.	
		Time-dependent delivery	
Dofetilide	Pulsincap™	It consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug that is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When this capsule comes in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug.	(9,10)
		Controlled release/delayed release	
Propranolol HCl (InnoPran XL)	DIFFUCAPS®	Capsule based system containing one or more drug containing particles. Each bead shows pre-programmed rapid or sustained release profile with or without lag time.	(9)
Diltiazem HCl (Cardizem LA)	CEFORM®	**Diffusion/erosion**	(34)

		Microspheres that may be coated for controlled release with an enteric coating or may be combined into a fast/slow release combination.	
		Multiparticulate pH dependent system/a delayed onset of drug release.	
Verapamil HCl (Verelan)	CODAS®	A non-entering coating is applied in order to delay the release of the drug up to 5 h. Release controlling coat consists of a mixture of both water-soluble and water insoluble polymers. After water soluble polymers get dissolved, pores are formed, and the drug diffuses through the pores.	(1,34)

Geoclock® technology, developed by SkyePharma, consists of a new oral drug delivery system in the form of a press-coated tablet. Geoclock® tablets are provided with an active drug core, surrounded by an outer layer entailing of a mixture of hydrophobic wax and brittle material in order to obtain a lag time pH independent. This technology allows for the delivery of immediate and slow release active cores. It not only offers application in controlled release but also improved release of colonic drug delivery as well as for multiple pulse drug delivery (10).

Lodotra, developed by this same company, makes use of this technology. This dosage form consists of an inner core containing the drug, prednisone, and an inert, non-soluble and non-swellable coating. The coat consists of a mixture of a hydrophobic lipid, glyceryl behenate, a mostly non soluble diluent, dicalcium phosphate dihydrated, and a pore former, povidone K 29/32. The core is mainly comprised of lactose as a diluent and it also has a superdisintegrant, croscarmellose sodium (36).

The coating prevents release of the drug over an extended period of time, so that no absorption occurs for around 4 h. After this lag time, the drug is rapidly released and after 2 h more than 80% of the drug should be released. This tablet is produced using a press-coating technology where a previously compressed core tablet is compressed using a multilayer tablet press-coat to form a press-coated tablet (10,36).

This dosage form has been designed to achieve maximum plasma levels 6 h after administration (Figure 5). This enables the patient to swallow the tablet at around 22.00h, with the dose of prednisone not being released until after 4 h, which is regarded as the optimal timing to relieve the early morning symptoms of stiffness and pain (10,37).

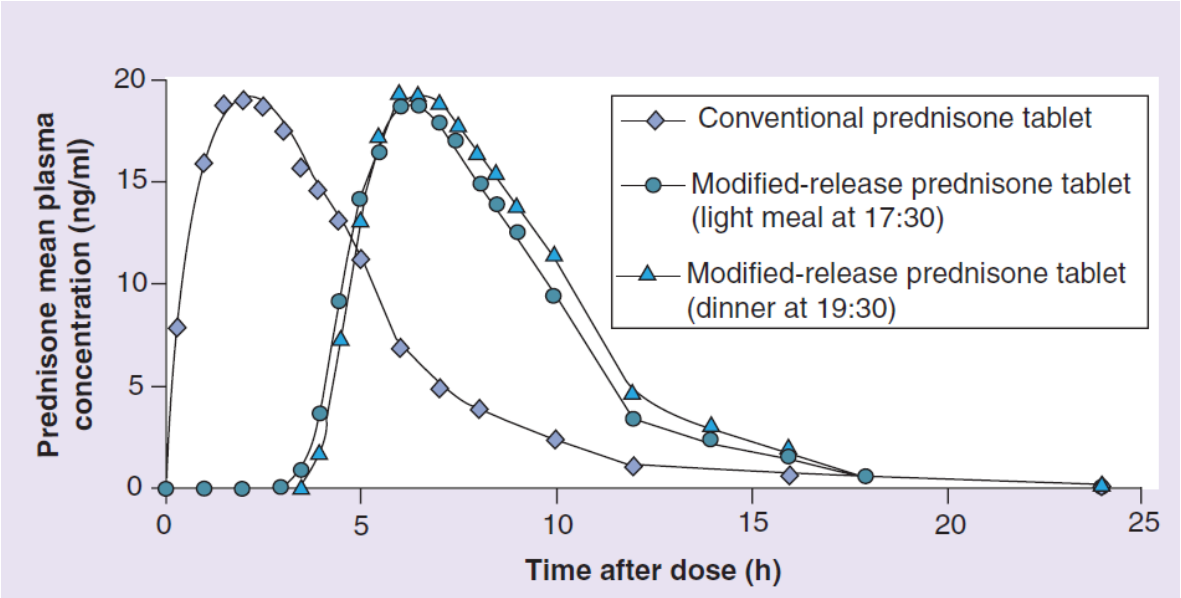

Figure 5 - Pharmacokinetics of modified-release prednisone and conventional prednisone (38).

This mechanism is distinct from other prednisone formulations that are enteric-coated, which are dependent on pH and location within the GI tract and do not address the need for programmed release of glucocorticoids at an appropriate time in order to reach maximum efficacy (35).

This tablet offers application in rheumatoid arthritis (RA), where pain is usually more present during the night and early morning. This is due to increase of IL-6 during the night, reaching its peak at around 7:00h. RA patients exhibit a 10-fold increase of serum concentrations of this inflammatory cytokine, when compared to healthy subjects (39–41). At the same time, cortisol, and anti-inflammatory hormone, also shows a circadian rhythm, with a nadir at midnight and a maximum at around 8.00h (41). Despite this, it seems that in patients with RA, endogenous cortisol production is not enough to counteract the inflammatory effects of the high serum levels of cytokines, leading to the need of exogenous glucocorticoid therapy (38). Also, this tablet may also be beneficial in the treatment of asthma and other inflammatory pathologies (35).

2. Aim of the project

The aim of this project was to develop a time-dependent drug delivery system and study the effect of formulation variables on lag time. Tablets were prepared by press-coating, with a rupturable coat, in order to modulate the release profile. The desired release profile was characterized by a lag time, followed by immediate and complete release of the drug.

Two main formulations were prepared, one with ethyl cellulose and another with a mixture of glyceryl behenate and dicalcium phosphate, as the water-insoluble excipients of the coat. The core tablet was formulated using prednisone, a borderline BCS Class I compound, used in the management of diseases such as rheumatoid arthritis or bronchial asthma.

Physical characterization was performed for each formulation, more particularly, the mass, height and thickness of the tablets was assessed.

The ratio of excipients of the coat was altered in order to study their effect on lag time. Specifically, the effect of the ratio soluble/insoluble excipient was studied, for both formulations. Also, the influence of the presence of an excipient with solubility dependent on pH, on lag time, was evaluated. To determine the lag time and release profile, release studies were performed for each formulation; to determine if the formulation had a behaviour pH independent, these studies were performed in different pH.

One of the main concerns of press-coated tablets is low drug loading; with larger tablets, a higher drug loading could be achieved. Thus, tablets with different diameter were prepared using the optimized formulations, in order to establish if by keeping the same core:coat mass ratio the release profiles stayed similar.

Since water uptake is one the most important steps that influence drug release from tablets with a rupturable coat, the model formulations were compared with a commercially available formulation, with a similar release profile, in terms of water uptake and dry mass loss.

3. Materials and methods

3.1. Materials

The materials used were: Prednisone (Prednisone, micronized), HPMC K4M (Methocel™ K4M DC2 Premium), Ethyl cellulose 10 cP (Ethocel™ Std 10 cP Premium), Microcrystalline cellulose (Avicel® PH105), Direct compressible lactose (Flowlac® 100), Polyvinylpyrrolidone K 30 (Kollidon® 30), Glyceryl dibehenate (Compritol® 888 ATO), Dicalcium phosphate anhydrous (DI-CAFOS® A 60), Colloidal silicon dioxide (Aerosil® 200), Magnesium stearate (Ligamed® MF-2-V), Croscarmellose sodium (Ac-Di-Sol ®).

3.2. Methods

3.2.1. Preparation of core tablets of prednisone

Lactose, prednisone, croscarmellose sodium and PVP K30 were sifted through a 355 µm mesh, while colloidal silicon dioxide and magnesium stearate were sifted through a 250 µm mesh.

According to the formulations in Table 3, the prednisone, lactose, croscarmellose sodium and PVP K30 were blended for 10 min using a Turbula® mixer. Magnesium stearate (1% w/w) and colloidal silicon dioxide (1% w/w) were added afterwards and blended for a further min. Additionally, colorant (0.5% w/w) was added in order to allow the visibility of the drug release from the coat, during the dissolution tests.

The core tablet was prepared using a single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany) by direct compression. Two different punches were used, a flat 5 mm punch (Core 1-Core 6) and a bevelled edge 8 mm punch (Core 6, Core 7).

Table 3 – Composition of core tablets (%)

	Drug	Lactose	Ac-Di-Sol	PVP K30	MgSt	Aerosil
Core 1	10	89	-	-	1	-
Core 2	10	83	5	-	1	1
Core 3	10	80.5	7.5	-	1	1
Core 4	10	78	10	-	1	1
Core 5	10	78	5	5	1	1

Core 6	10	73	10	5	1	1
Core 7	4.5	78.5	10	5	1	1

3.2.2. Preparation of press-coated tablets

	EC	MCC	Povidone	HPMC
TDDS 1	80	10	5	10
TDDS 2	85	10	-	5
TDDS 19	80	10	-	10
TDDS 20	45	45	-	10
TDDS 21	80	10	10	-
TDDS 22	70	-	20	-
TDDS 26	90	-	-	-

Two formulations were prepared, one with ethyl cellulose as the main release-controlling excipient (TDDS EC), while the other had a combination of glyceryl behenate (GB) and dicalcium phosphate anhydrous (DCP) (TDDS GB).

Ethyl cellulose was sifted through a 500 µm mesh; Glyceryl behenate, PVP K30, lactose, dicalcium phosphate and microcrystalline cellulose were sifted through a 355 µm while magnesium stearate was sifted through a 250 µm mesh.

The press-coat excipients (Table 4 and

Table 5) were blended for 10 min using a Turbula® mixer. Subsequently, magnesium stearate (1% w/w) was added and mixed for a further min.

The press-coating of tablets was performed using a single station compression tableting machine (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany). First, ~60% of the coating mixture was filled into the die, the powder was then compressed in order to obtain a flat surface. Next, the core tablet was placed on the centre of the powder bed and compressed into the powder. The remaining powder was filled into the die and the contents were compressed using either a flat 9 mm punch or a bevelled edge 11 mm punch.

Table 4 – Composition of the coat of press-coated tablets formulated with glyceryl behenate (%)

	Glyceryl Behenate	Dicalcium Phosphate	Povidone
TDDS 10	40	50	10
TDDS 11	30	60	10
TDDS 12	50	40	10
TDDS 13	30	50	20

Table 5 –

	EC	MCC	Povidone	HPMC
TDDS 14	80	10	5	10
TDDS 15	85	10	-	5
TDDS 16	80	10	-	10
TDDS 17	45	45	-	10
TDDS 18	80	10	10	0
TDDS 19	70	-	20	10
TDDS 20	90	-	-	10

Composition of the coat of press-coated tablets formulated with ethyl cellulose (%)

	Glyceryl Behenate	Dicalcium Phosphate	Povidone
TDDS 21	30	50	20
TDDS 22	40	40	20
TDDS 23	30	60	10
TDDS 24	50	40	10
TDDS 25	20	20	60

3.2.3. *In vitro* release studies

Dissolution studies were carried out using EP apparatus I (paddle, rotating at 50 rpm) in 500 mL of 0.1 N HCl and pH 6.8 phosphate buffer (37.0 ± 0.5°C) as the dissolution media (Vankel VK 300, Vankel Industries, Edison, NJ, USA). Dissolution samples were withdrawn at predetermined time intervals and the drug assayed by UV-Vis spectrophotometry at a wavelength of 244 nm. Tablets were crushed before the end of the test in order to establish the cumulative drug release %. The lag time was taken as the time of >10% drug release

3.2.4. Water uptake and dry mass loss measurement

Tablets were placed separately into a container filled with 40 mL 0.1 N HCl and phosphate buffer pH 6.8 (n=2). Afterwards, the containers were placed in a horizontal shaker (37ºC, 80 rpm; Gesellschaft fuer Labortechnik, Burgwedel, Germany). Samples were withdrawn at 1h, 2h and 3h and accurately massed (wet mass (t)). Subsequently they were dried to constant mass at 60ºC (dry mass (t)). The water content and dry mass loss at the time *t* was calculated using the following equations:

$$Water\ content\ (\%)\ (t) = \frac{wet\ mass\ (t) - dry\ mass\ (t)}{wet\ mass\ (t)} \times 100 \quad (1)$$

$$Dry\ mass\ loss\ (\%)\ (t) = \frac{dry\ mass\ (0) - dry\ mass\ (t)}{dry\ mass\ (0)} \times 100 \quad (2)$$

4. Results and discussion

4.1. Physical characterization of the tablets

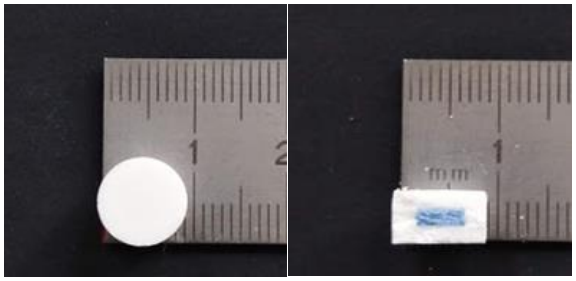

Figure 6 – Time Dependent Delivery System (TDDS).

Tablets were composed of an inner core, in blue, surrounded by a coat, white (Figure 6). The inner core contained the drug, while the coat had no active substance. Both formulations were composed of an inner core with a diameter of 5 mm, surrounded by a coat that had a thickness of 2 mm. The total diameter was 9 mm for both formulations. The height was 6 mm for the formulation with EC and 5 mm for the GB formulation. The mass of the inner core was 50 ± 3 mg, and the total mass was 400 ± 21 mg for both formulations (Table 6).

Table 6 – Physical characteristic of 9 mm press-coated tablets.

	Core			**Coat**			**Total**		
	Mass (mg)	**Height (mm)**	**Diameter (mm)**	**Mass (mg)**	**Height (mm)**	**Thickness (mm)**	**Mass (mg)**	**Height (mm)**	**Diameter (mm)**
TDDS EC	50 ± 3	2	5	350 ± 17,5	2	2	400 ± 20.5	6	9
TDDS GB	50 ± 3	2	5	350 ± 17,5	1,5	2	400 ± 20.5	5	9

When comparing both formulations, the main difference resided in the height of the tablet, with TDDS GB having a smaller height in the coat, therefore affecting the tablet's total height. This can be explained because of the presence of DCP in the TDDS GB formulation. This powder has a high density, which allows for a significant reduction of tablet size, without changing its mass (42). This reduction is particularly visible when DI-CAFOS

A60 is used, due to its smaller and more spherical particles, when compared to DI-CAFOS A150, as previously shown (43).

Table 7 – Physical characteristics of 11 mm press-coated tablets

	Core			Coat			Total		
	Mass (mg)	**Height (mm)**	**Diameter (mm)**	**Mass (mg)**	**Height (mm)**	**Thickness (mm)**	**Mass (mg)**	**Height (mm)**	**Diameter (mm)**
TDDS EC	110 ± 5.5	2	8	660 ± 33	3.5	1.5	770 ± 38.5	9	11
TDDS GB	110 ± 5.5	2	8	660 ± 33	3	1.5	770 ± 38.5	8	11

The same findings were established with the 11 mm press-coated tablets (Table 7). In these, TDDS EC's tablets had a height of 9 mm, whereas TDDS GB's had a height of 8 mm. The mass of tablets was 770 ± 38.5 mg for both formulations. The mass ratio inner core:coat remained the same. The thickness of the coat was slightly smaller, 1.5 mm, when compared to the 5 mm tablets.

4.2. *In vitro* release studies from GB coated tablets

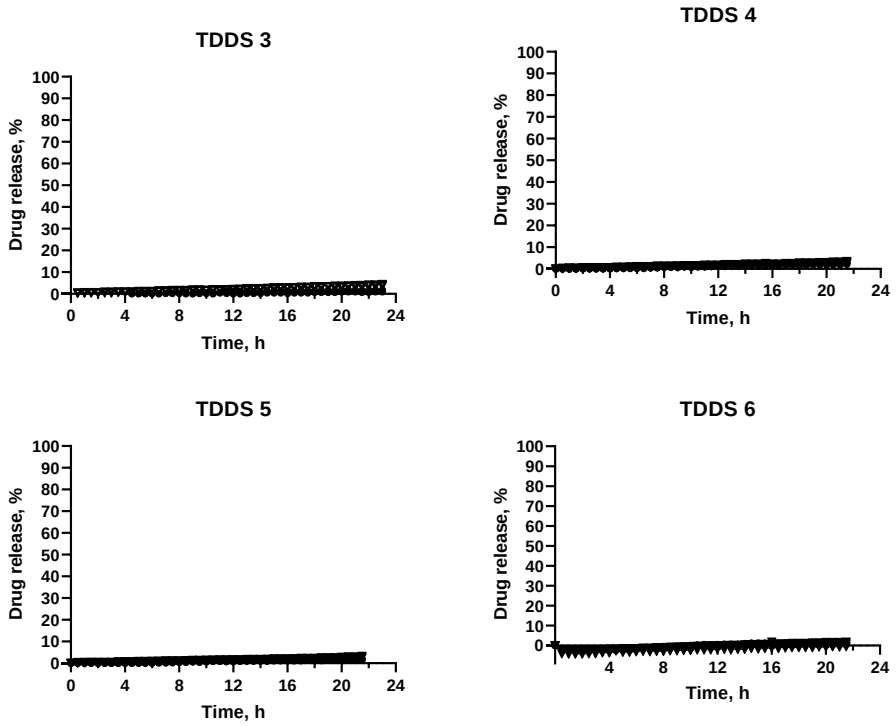

Figure 7 – Release profiles of TDDS 3-TDDS 6, containing inner core 1.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 3: *GB 50%; DCP 50%.* ***TDDS 4:*** *GB 50%; Lactose 50%.* ***TDDS 5:*** *GB 50%; Lactose 25%; DCP 25%.* ***TDDS 6:*** *GB 50%; DCP 30%; PVP K30 20%*

TDDS 3 to TDDS 6 all contained the inner core 1, consisting of only drug and lactose. TDDS 3, TDDS 4, TDDS 5 and TDDS 6 displayed no release above 5% and so, the desired release profile was not obtained (Figure 7).

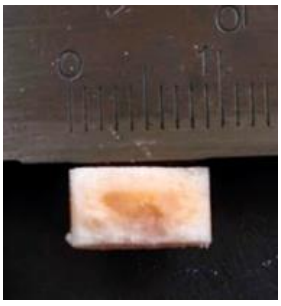

Figure 8 – TDDS 4 after release study

Two different soluble excipients were used in TDDS 3 to TDDS 6. Lactose, due to its water soluble and hydrophilic nature, rapidly dissolves and therefore decreases the tortuosity and/ or increases the porosity of the coat. It has previously been used to perform as an hydrophilic excipient and has led to a quick rupture of the press-coated tablet (28). Because of this, initially, with TDDS 4 and TDDS 5, lactose was used in the coat to act as a channelling agent. However, there was diffusion of the colorant through the coat (Figure 8) also suggesting the diffusion of the drug. Subsequently, PVP K30 was chosen to be the pore former excipient. For this, a small molecular mass was selected, with a higher dissolution rate (44).

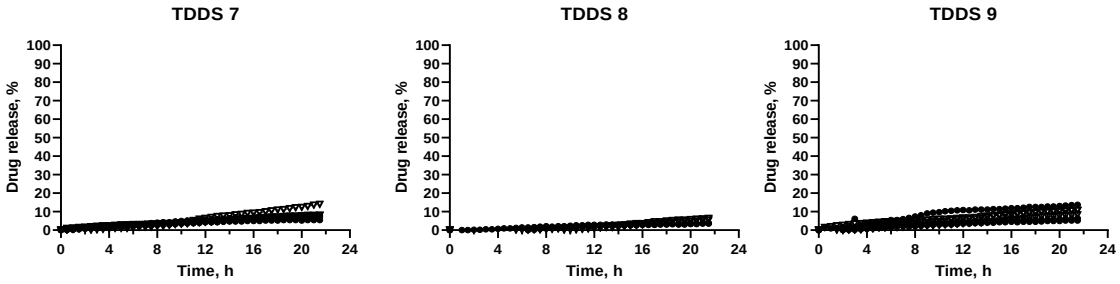

Figure 9 – Release profiles of TDDS 7, TDDS 8, TDDS 9, containing inner core 1.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 7: *GB 35%; DCP 35%; PVP K30 30%.* ***TDDS 8****: GB 30%; DCP 50%; PVP K30 20%.*
TDDS 9: *GB 30%; DCP 30%; PVP K30 40%*

With PVP K30 as the hydrophilic excipient, diffusion of the colorant was not visible. There was still no sudden release of the drug after a lag time, but as the concentration of the pore former increased, there was more release of the drug through diffusion with TDDS 7 (~8.38% drug release), TDDS 8 (~4.80% drug release) and TDDS 9 (~9.17% drug release)

(

Figure 9 – Release profiles of TDDS 7, TDDS 8, TDDS 9, containing inner core 1.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 7: *GB 35%; DCP 35%; PVP K30 30%.* ***TDDS 8****: GB 30%; DCP 50%; PVP K30 20%.*
TDDS 9: *GB 30%; DCP 30%; PVP K30 40%*

). The highest drug release (almost 10%) was obtained with TDDS 9, the formulation with the highest fraction of PVP K30. With increasing ratios of soluble excipient, the porosity of the coat increased, causing more water intake, which prompted dissolution of the drug. After dissolution, the drug was able to diffuse through the coat. However, even though water penetrated the core, there was still no rupture of the coat due to lack of adequate outward pressure.

None of the previous formulations exhibited the desired release profile and all tablets remained intact until the end of the release study. Since the inner core had no swelling agent, there was not enough outward pressure to rupture the coat and it remained intact until the end of the release study. Croscarmelose sodium (Ac-Di-Sol) has a higher swelling energy and therefore is preferable for this purpose (45). Thus, a superdisintegrant, Ac-Di-Sol, was added in the core, as it had been shown to enhance drug release from press-coated tablets (25).

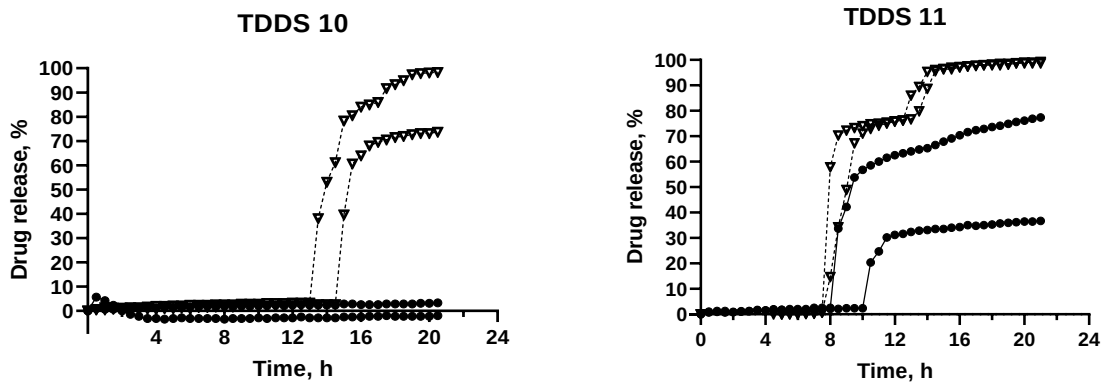

Figure 10 – Release profile of TDDS 10, TDDS 11, TDDS 12, containing inner core 2.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 10: *GB 40%; DCP; 50%; PVP K30 10%.* ***TDDS 11:*** *GB 30%; DCP 60%; PVP K30 10%*

With formulations TDDS 10, TDDS 11, Ac-Di-Sol was added in the core, allowing the drug to be released (Figure 10).

TDDS 10, only showed release in HCl 0.1 N, and complete drug release was only obtained with one of the tablets. Tablets in phosphate buffer remained intact.

With TDDS 11 all tablets ruptured but there was only full release in the acidic media. The lag time was 8.00 ± 0.00 h in HCl and 10.00 ± 1.50 h in phosphate buffer. Even though full release was obtained, in HCl 0.1 N, the release had two pulses, one at ~8h and another at ~14h. This was because, even though the tablet ruptured, it did not split into two halves until later, hindering drug release. In basic media, there was not complete release as the tablet never fully separated, and the lag time had a higher variability.

Also, when comparing TDDS 10 and TDDS 11 lag times, TDDS 10, with 40% GB had the highest lag time. Thus, the increase of GB concentration led to an increase in the lag time.

The rupture of the tablets happened on the sides of the tablets. This occurs because the compression force is applied to the bottom and upper sides of the tablets, making the sides less compressed and more prone to rupture.

With TDDS 12 (GB 50%; DCP 40%; PVP K30 10%), there was only one tablet that had drug release, in HCl 0.1N, with the lag time of 21.5 h (results not shown).

The sudden splitting of the outer coat of press-coated tablets after the lag time is a key factor for achieving time-controlled drug release (28). Since the tablets did not open completely right away, it was possible that there was still not enough swelling power in the inner core. Therefore, the core was optimized, more Ac-Di-Sol was added, and PVP K30 was added in order to facilitate the disintegration of the inner core (core 6).

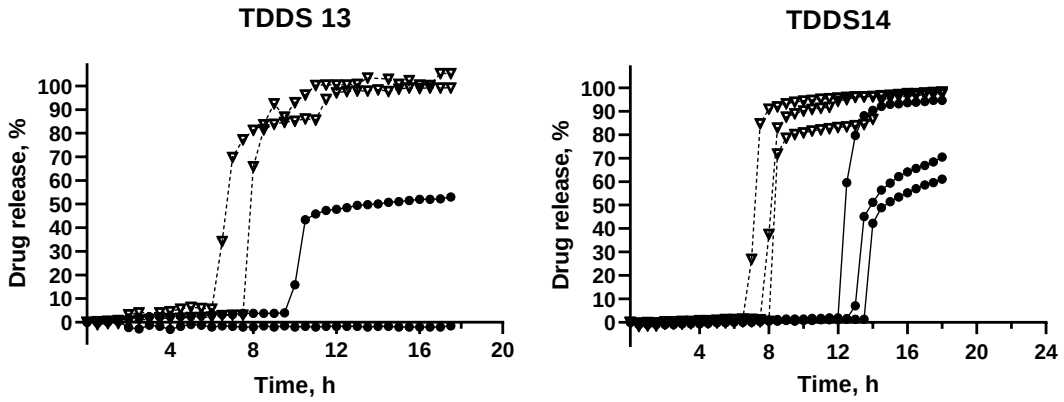

Figure 11 – Release profile of TDDS 13 and TDDS 14, containing inner core 6.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 13: *GB 30%; DCP 50%; PVP K30 20%.* ***TDDS 14:*** *GB 30%; DCP 60%; PVP K30 10%*

TDDS 13 allowed the complete release of the drug in HCl, but in phosphate buffer there was only one tablet that ruptured (Figure 11).

With TDDS 14 there was full release of the drug in HCl 0.1 N, with a lag time of 7.83 ± 0.62 h. In phosphate buffer, all tablets had immediate drug release but there was only ~100% release with one of the tablets. The SD was higher in phosphate buffer with a lag time of 13.17 ± 3.00 h. (Figure 11).

When comparing the lag time in HCl with the lag time in phosphate buffer, the lag time in phosphate buffer was higher. Generally, calcium salts are insoluble in aqueous media at neutral or alkaline pH. However, they are soluble in diluted acids, such as HCl 0.1 N (46). Therefore, in acidic media, DCP dissolved and formed more pores, causing more water to go into the core while weakening the coat and the rupture happened more quickly.

In order to reduce the lag time variability between different media, the ratio GB:DCP was increased in order to reduce the influence of dicalcium phosphate and achieve a pH independent formulation.

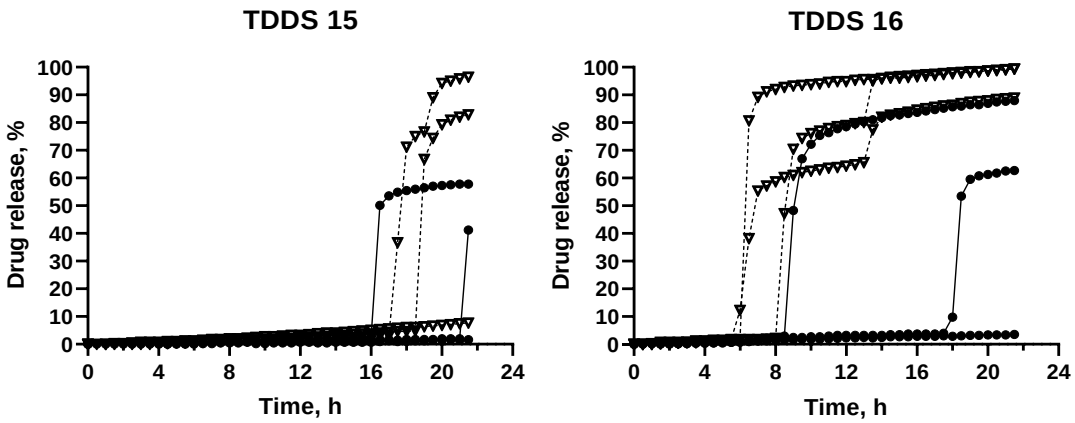

Figure 12 – Release profile of TDDS 15 and TDDS 16, containing inner core 6.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 15: *GB 50%; DCP 40%; PVP K30 10%.* ***TDDS 16:*** *GB 50%, DCP 30%, PVP K30 20%*

TDDS 15 did not show to be a good formulation, as the lag time was very high and there was high variability between different media as well as within the same media (Figure 12).

TDDS 16 also showed variability, within the same pH, as well as between different media Figure 12. The lag time was 7.00 ± 1.08 h, in HCl 0.1 N. The lag time in phosphate buffer was higher and showed more variability.

The formulations with a higher percentage of GB, saw the lag time increase, particularly TDDS 15 that had less PVP K30, thus, less soluble excipient in the coat. The presence of a high percentage of GB, an insoluble hydrophobic lipid, made for a less porous coat and prevented the penetration of media, with a negative influence on lag time, such as shown previously (47). The next action was to increase the ratio PVP K30:GB in order to increase the soluble excipient and decrease the insoluble lipid, to achieve a shorter and less variable lag time.

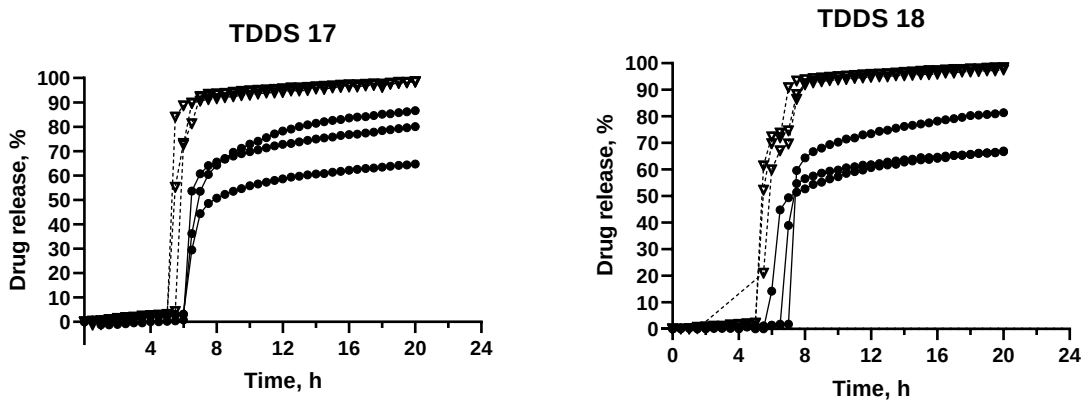

Figure 13 – Release profile of TDDS 17 and TDDS 18, containing inner core 6.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 17: *GB 30%; DCP 30%; PVP K30 40%.* ***TDDS 18:*** *GB 30%; DCP 40%; PVP K30 30%*

Comparing TDDS 17 and TDDS 18 with the previous formulation, TDDS 16, the lag times were shorter and less variable. Reducing the percentage of GB and increasing the percentage of PVP K30, led to shorter lag times caused by a higher porosity, leading to more water uptake.

TDDS 17 had similar lag times in different media, 5.67 ± 0.24 h in HCl and 6.50 ± 0.41 h in phosphate buffer (Figure 13). The release in HCl was complete, after 1h the drug release was >80% in all vessels. However, in phosphate buffer, the release was not complete, after 20h the release was ~80%. This happened because even though the tablets ruptured, they did not separate into two halves.

TDDS 18 had, again, similar lag times in different media, 5.50 ± 0.00 h in HCl and 6.83 ± 0.62 h in phosphate buffer (Figure 13). With this formulation, it took 2h to reach a >80% release in HCl. Still, in phosphate buffer the tablets did not separate into two halves.

Comparing both formulations, it was possible to understand that by increasing the percentage of PVP K30, the pore former, the lag time decreased; TDDS 17 had a lag time of 6.08 ± 0.45 h, while TDDS 18 had a lag time of 6.67 ± 0.85 h (Figure 13). Again, the higher

percentage of PVP, led to a higher porosity of the coat and consequently, to a weaker coat, more easily ruptured. Also, the porosity of the coat increased the water uptake.

Moreover, by comparing the lag times in different pH, it was possible to conclude that by decreasing the quantity of dicalcium phosphate, the influence of pH on lag time is diminished. TDDS 17, with less DCP, had more similar lag times for different pH.

Subsequently, to attain full release in phosphate buffer, the percentage of dicalcium phosphate was further reduced, in order to have less insoluble excipients in phosphate buffer and thus, more porosity. The percentage of dicalcium phosphate remained at 20%, while the ratio GB:PVP K30 was varied.

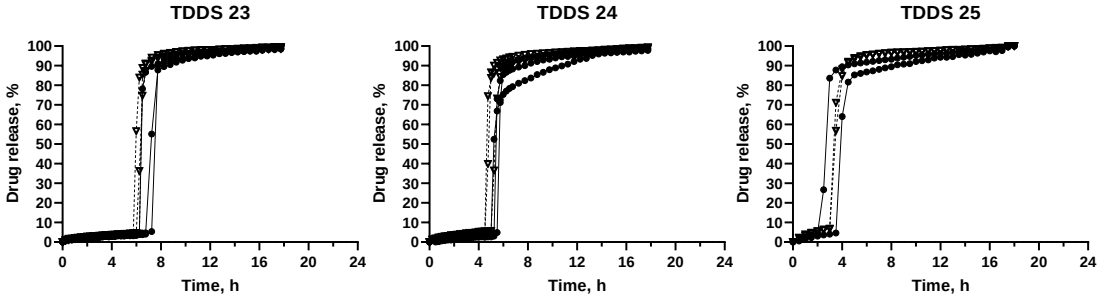

Figure 14 – Release profiles of TDDS 23, TDDS 24 and TDDS 25, containing inner core 6.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 23: *GB 40%, DCP 20%, PVP K30 40%.* ***TDDS 24:*** *GB 30%, DCP 20%, PVP K30 50%* ***TDDS 25:*** *GB 20%, DCP 20%, PVP K30 60%*

All three formulations showed full release and similar lag times in both pH, showcasing again that by decreasing the percentage of DCP it was feasible to get a formulation that was pH independent (Figure 14). Comparing the three formulations, it was possible to determine that by increasing the ratio GB:PVP K30 the lag time correspondingly increased.

With TDDS 25, the formulation with more PVP K30 in the coat, there was some diffusion of the drug through the coat before it reached the lag time, even though it remained below 10% (Figure 14). This could become a concern if a more soluble drug is used in the

core. In this instance, there might happen a higher release of the drug before the rupturing of the tablet, due to a higher dissolution rate of the drug.

All formulation had >80% drug release, 2h after lag time was over in both pH. Therefore, the desired release profile was obtained.

The release mechanism of TDDS 24 can be found in Figure 15. When the coated tablet was exposed to aqueous medium, water diffused through the coat due to the gradient of water, hydrating the core. The dissolution of the osmotic agent, in this case lactose, created a constant osmotic pressure difference between the core contents and the external environment. The hydration caused swelling of the disintegrant, resulting in rupture of the coat. After the lag phase, the tablet ruptured into two halves and allowed burst release of the drug in both pH. After the drug was delivered, the tablet shells remained intact.

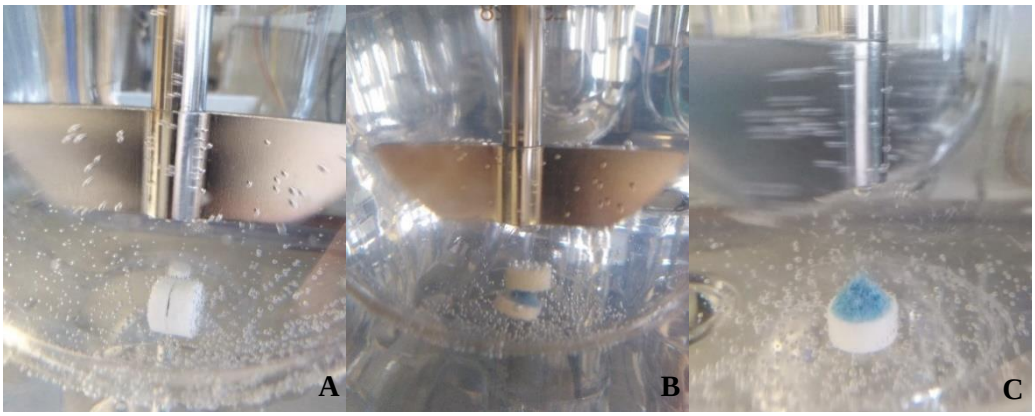

Figure 15 – Release mechanism of TDDS 24.

***A:** Rupture of the coat; **B:** Swelling of the inner core; **C:** Complete rupturing of the tablet.*

4.2.1. Study of different sized tablets, containing the same core:coat ratio

One of the disadvantages of press-coated tablets is their low drug loading capacity. In this work, the inner core had only 50 mg, therefore very limited drug loading. Consequently, in order to increase the drug loading capacity, bigger tablets were prepared. The same core:coat mass ratio was maintained, in order to establish if the formulations would preserve the same lag times and release profiles. Also, different percentages of drug were used in the core in order to determine if the release was independent of drug loading. TDDS 24 was chosen as the model formulation.

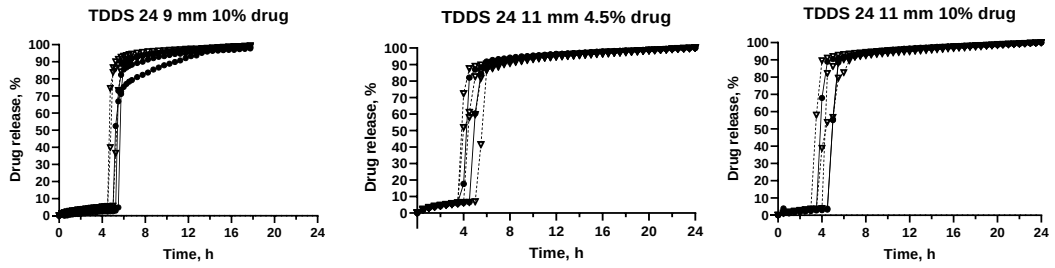

Figure 16 – Comparison of the release profile of TDDS 24, with different diameters and drug loading.

HCl 0.1 N; Phosphate buffer pH 6.8

With the increase of diameter, the lag time did not suffer many changes (Figure 16). The behaviour was identical, they all had a release profile characterized by a distinct lag time and released >80% of the drug after 2h, maximum. TDDS 24's lag time was 5.12 ± 0.37 h; TDDS 24 11 mm, 4.5% drug was 4.5 ± 0.58 h and TDDS 24, 11 mm, 10% drug was 4.33 ± 0.55 h. The lag time decreased to some extent with the 11 mm tablets. The thickness of the coat is one of the parameters that most affect the lag time. The 11 mm tablets were less thick, the thickness was only 1.5 mm, whereas the 9 mm tablets had a thickness of 2 mm. Thus, the decrease of thickness may explain the decrease of the lag time as it led to a quicker medium penetration into the core (10,17). The variability between pH remained low with both formulations. Drug loading had no effect on lag time.

4.3. *In vitro* release studies of EC coated tablets

TDDS 1, formulated with EC, had a profile characterized by a lag time of 16.17 ± 0.62 h, followed by immediate release of the drug (Figure 17). The release was pH independent, as it was evident by comparing lag times between different media (16.33 ± 0.47 h in HCl and 16.00 ± 0.71 h in pH 6.8).

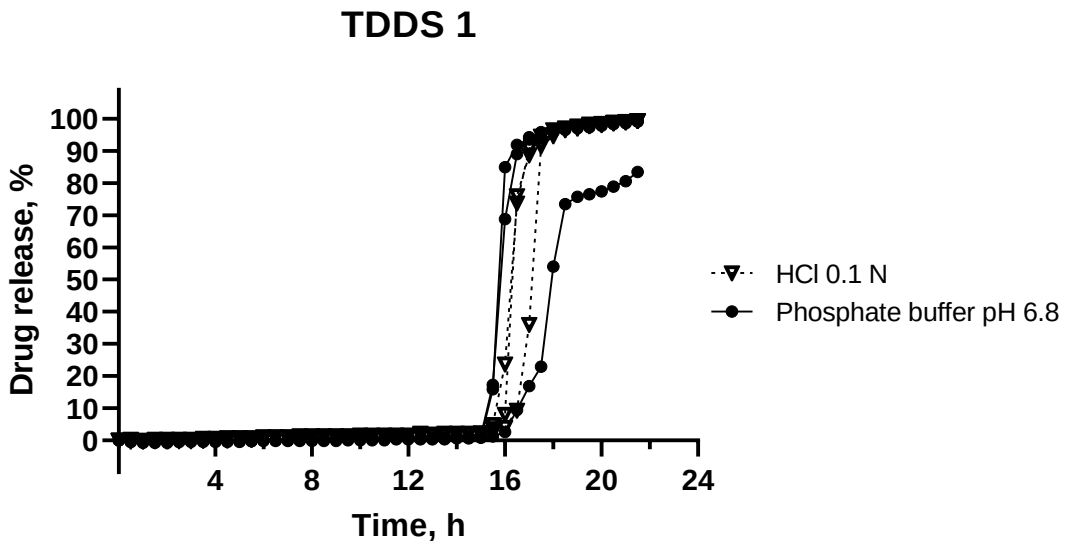

Figure 17 – Release profile of TDDS 1, containing inner core 1.

TDDS 1: *EC 80%, MCC 10%, HPMC 10%.*

After optimization of the core, two coat formulation were prepared, TDDS 19 and TDDS 20. Both had in their composition MCC, EC and HPMC with different ratios.

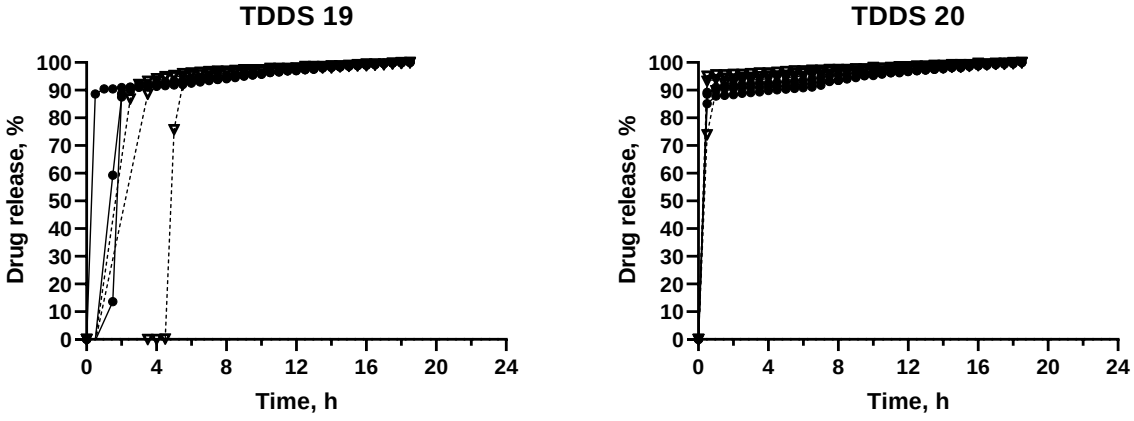

Figure 18 – Release profile of TDDS 19 and TDDS 20, containing inner core 6.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 19: *EC 80%; MCC 10%; HPMC 10%.* ***TDDS 20****: EC 45%; MCC 45%; HPMC 10%*

Both formulations allowed the complete release of the drug (Figure 18). It is well known that the porosity of the coat plays an important role in the rate at which media goes into the core. The size of EC powder and the porosity in compact are major factors that influence the medium uptake (28). In this work, Ethocel^{TM} Std 10 cP Premium was used. This polymer has a larger particle distribution and is of lower viscosity. The particle size distribution as well as the viscosity (molecular mass) of the polymer impacts the release profile. A lower molecular mass coat forms less entanglements, resulting in a coat with more defects and increased free volume, causing water transport to increase through the polymer layer. A larger particle size distribution also leads to a more porous structure (48,49). So, in this instance, MCC and HPMC were not good enough as binders to prevent immediate entry of media. Thus, PVP K30 was used to substitute HPMC as it is a better binder and had proven before to be a good pore former.

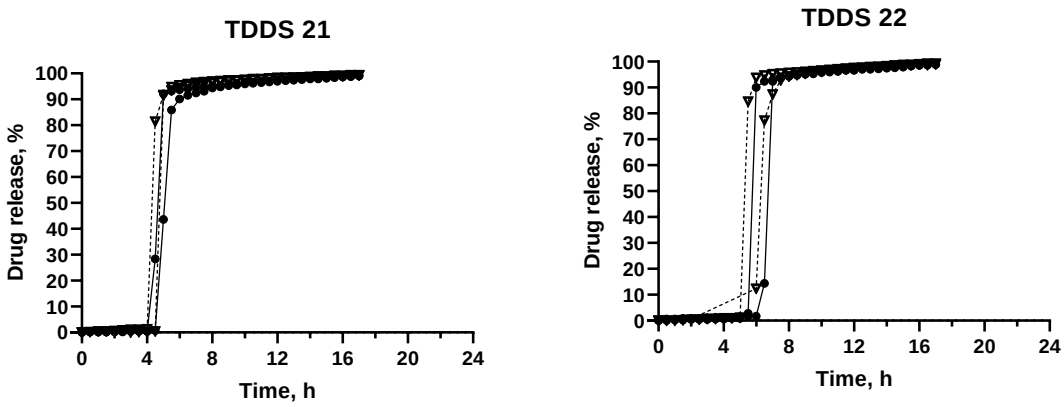

Figure 19 – Release profile of TDDS 21 and TDDS 22, containing inner core 6.

HCl 0.1 N; Phosphate buffer pH 6.8

***TDDS 21**: EC 80%; MCC 10%; PVP K30 10%. **TDDS 22:** EC 80%; PVP K30 20%*

TDDS 21 had a delayed release profile and, after 1h >80% of the drug was released (Figure 19). The overall lag time was 4.75 ± 0.25 h and the lag time was very similar in different pH. TDDS 22 behaved in a similar fashion (Figure 19). The overall lag time was 6.0 ± 0.35 h and there was only a half h difference between different pH. Also, 1h after the lag time, >80% of the drug was released from the core.

Comparing both formulations, TDDS 21 had a shorter lag time. This was unexpected, as TDDS 22 had more pore former than TDDS 21. However, although being water insoluble, MCC has some swelling capacity and this might help the tablet to rupture faster. Particularly, it has been shown that when MCC with a higher porosity (bigger diameter), as in the case of AVICEL® PH-102, is used in the manufacturing of tablets, these tend to swell more. Also, MCC is a disintegrant and it enhances liquid transport into the core, accelerating both diffusion and capillary action (50). Therefore, the presence of MCC in the coat led to a shorter lag time.

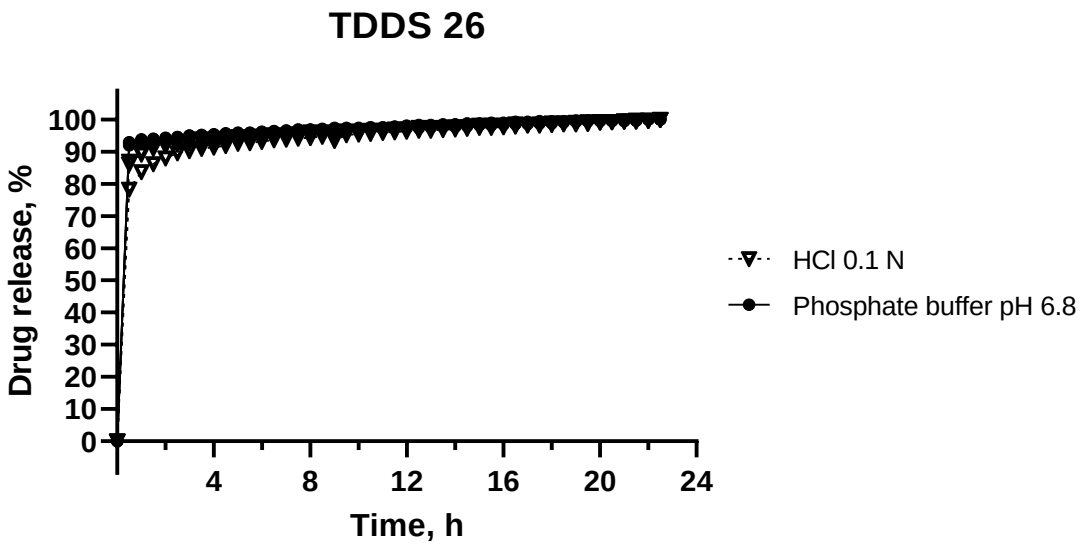

Figure 20 – Release profile of TDDS 26, containing inner core 6.

TDDS 26: *EC 90%; 10%*

TDDS 26 showed immediate release (Figure 20). Without the presence of PVP, there was not enough binder to fill in the porous created by the EC coat. Therefore, the coat was too porous, and media went into the core immediately. This result shows again the importance of having a good binder when using EC of a larger particle size distribution.

4.3.1. Study of different sized tablets, containing the same core:coat ratio

To confirm the scale up ability of a formulation, tables with 8 mm inner core and 11 mm total diameter were prepared, keeping the core:coat mass ratio. Tablets with different

ratios of drug were prepared to determine if the drug loading influenced the release profile. TDDS 21 was chosen as the model formulation.

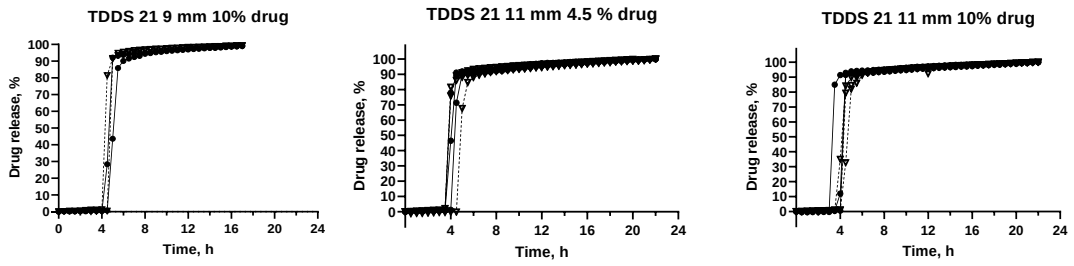

Figure 21 – Comparison of the release profile of TDDS 21, with different diameters and drug loading.

HCl 0.1 N; Phosphate buffer pH 6.8

TDDS 21, 9 mm, had a lag time of 4.75 ± 0.25 h and in 1h after lag time, >80% of the drug was released (Figure 21). Similarly, the formulations with the bigger diameter, had 80% of drug release, 1h after lag time was over. They had slightly different lag time when compared with TDDS 21 5 mm; TDDS 21 11 mm, 4.5% drug, had a lag time of 4.25 ± 0.38 h and TDDS 21 11 mm, 10% drug, had a lag time of 4.25 ± 0.25 h. All tablets had a pH independent behaviour. Similarly to the TDDS 24 formulation (Figure 16), the decrease of lag time might have been due to the reduced thickness of the coat in the sides. The thickness is one of the parameters that most affect lag time in rupturable systems as it controls medium permeability (10,17). With reduced thickness, medium penetrated the core more easily and the ruptures happened faster. Again, the concentration of the drug had no effect on lag time.

4.4. Characterization of a commercially available formulation (Lodotra)

4.4.1. Physical characterization

Lodotra is a commercially available formulation that is designed to release the drug, present in the core, after a lag time of approximately 4h. The mechanism is meant to rely on time, and be independent of other variables, such as pH.

Table 8 – Excipients in the formulation of Lodotra

Inner Core	Coat
Colloidal anhydrous sílica	Colloidal anhydrous silica
Croscarmellose sodium	Dicalcium phosphate dihydrated
Lactose, monohydrated	Glyceryl behenate
Povidone K 29/32	Povidone K 29/32
Magnesium stearate	Magnesium stearate
Red iron oxide	Yellow iron oxide

Lodotra is mainly comprised of a combination of a hydrophobic wax, glyceryl behenate, a non-fatty hydrophobic filler, dibasic calcium phosphate and a binder, PVP K 29/32. The core is constituted by the drug, lactose, croscarmellose sodium and PVP K2 9/32 (Table 8).

Table 9 – Physical characterization of Lodotra (5 mg)

	Core			Coat			Total		
	Mass (mg)	**Height (mm)**	**Diameter (mm)**	**Mass (mg)**	**Height (mm)**	**Thickness (mm)**	**Mass (mg)**	**Height (mm)**	**Diameter (mm)**
Lodotra	60	2	5	350	1,5	2	410	5	9

Lodotra had a total mass of ~410 mg, 60 mg of core and 350 mg of coat (Table 9). The inner core diameter was 5 mm, while the total diameter was 9 mm, making a coat with 2 mm of thickness. The height of the tablet was 5 mm. Thus, it had similar features to the tablets developed in this research, particularly the 5mm/9mm tablets, and so made a comparison possible.

4.4.2. Release profile of the drug

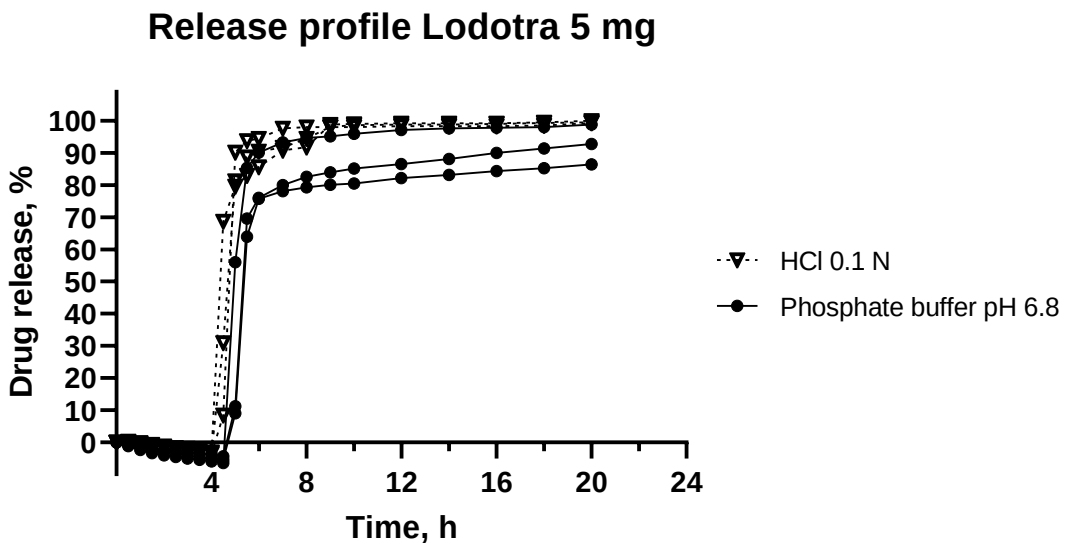

Figure 22 – Release profile of a commercially available formulation, Lodotra.

Lodotra, 5 mg, had a lag time of 4.75 ± 0.25 h, followed by immediate release of the drug. The lag time was independent on pH. In HCl, after 30 min, >80% of the drug was release; in phosphate buffer, it took 2h to reach the same drug release (Figure 22).

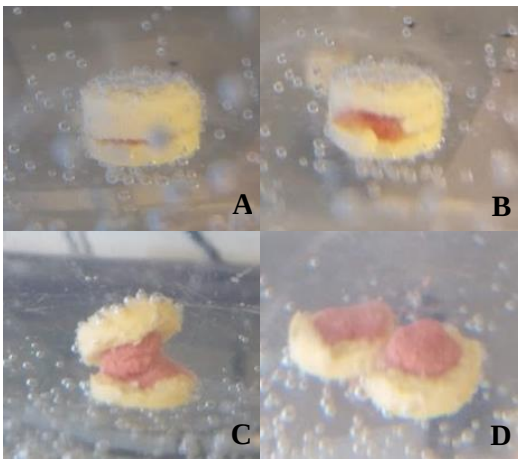

Figure 23 – Release mechanism of Lodotra.

***A:** Rupturing of the coat; **B:** Media goes into the core; **C:** Swelling of the inner core; **D:** Complete opening of the tablet.*

The release mechanism relies on a rupturable coat (Figure 23 The tablet does not release any drug until the lag time is over. When lag time is over, the tablets ruptures due to the

increase of pressure in the core. Afterwards, more water goes into the core, making the inner core swell even more. Finally, the tablet opens completely, and the drug is fully released. Hence, the mechanism is similar to the formulations developed in this work.

4.5. Comparison of different formulations

4.5.1. Water uptake and dry mass loss

Generally, the process of drug release takes place in three steps, water goes into the core, the core swells and the coat ruptures, making water uptake an important parameter to determine. Thus, gravimetric studies on hydration and dry mass loss were performed in order to determine the rate and the extent of water uptake in three formulations, TDDS 21, TDDS 24 and Lodotra (Figure 24).

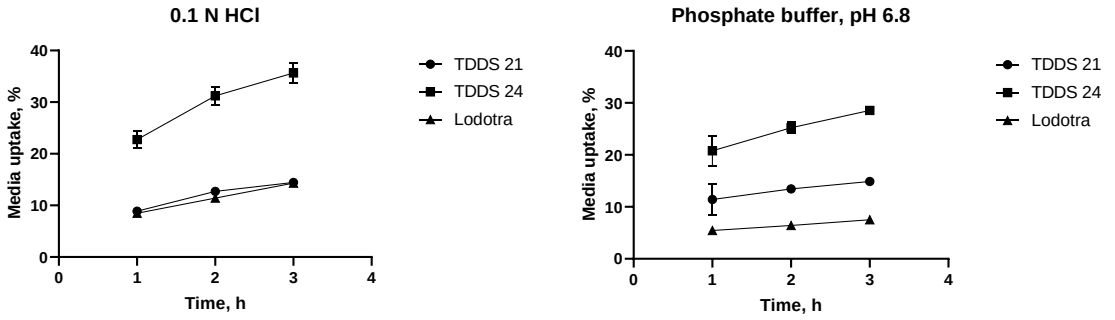

Figure 24 – Water uptake in 0.1 N HCl and phosphate buffer, pH 6.8.

TDDS 21: *EC 80%; MCC 10%; PVP K30 10%.* ***TDDS 24:*** *GB 30%; DCP 20%; PVP K30 50%.*

Lodotra had a water uptake of 17.25 ± 0.27% in HCl, after 3 h. In phosphate buffer, the water uptake was lower, 3.41 ± 0.10%, after the same time. This can be explained by the presence of DCP in the coat. As explained before, DCP is generally insoluble but it is soluble in diluted acids. Consequently, in HCl, when in contact with the medium, it formed more micro-cavities and triggered the osmotic effect which promoted the swelling and consequently, rupture of the coat.

Similarly, TDDS 24 showed different water uptake in different media, also because of DCP. TDDS 24, after 3 h, had 35.93 ± 1.92% water uptake in HCl and 24.50 ± 0.19% in

phosphate buffer. Even though the high water uptake was not a problem with the current formulations as there was no drug release >10% before the lag time, the high water uptake might be of concern if a more soluble drug is used in the core; in that case, there might be a higher diffusion of the drug, prior to the rupture of the coat. Even in phosphate buffer, where DCP is insoluble, the water uptake was high due to the high percentage of soluble excipient, PVP, in the coat.

On the other hand, TDDS 21 had comparable water uptake in different media. After 3 h, it remained low, 4.82 ± 0.20% in HCl and 4.05 ± 0.07 % in phosphate buffer. The water uptake only increased ~2% between 1 h and 3 h.

Comparing formulations, TDDS 24, due to its higher content of DCP, had a higher uptake than Lodotra. TDDS 21, had a similar behaviour to Lodotra.

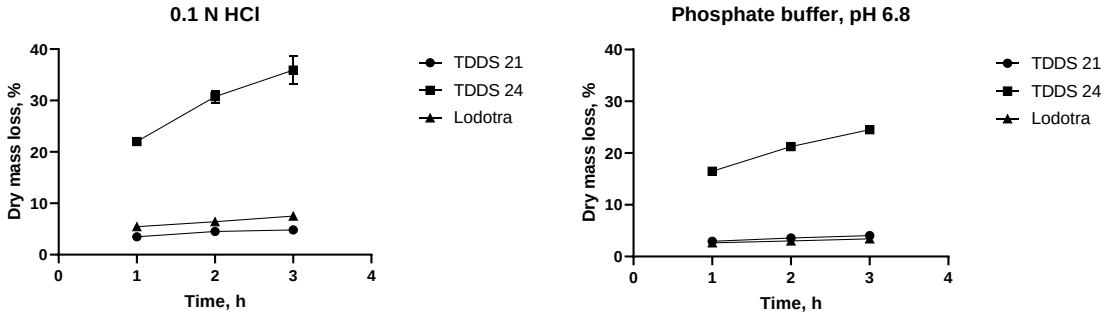

Figure 25 – Dry mass loss in 0.1 N HCl and phosphate buffer, pH 6.8.

TDDS 21: *EC 80%; MCC 10%; PVP K30 10%.* ***TDDS 24:*** *GB 30%; DCP 20%; PVP K30 50%.*

Dry mass results showed resemblance with water uptake. TDDS 21 and Lodotra showed very little dry mass loss. TDDS 24 was the formulation that showed the highest dry mass loss, since DCP and PVP K30 were present in a high fraction and so, dissolved themselves in the media. The dry mass loss was higher in HCl due to the presence of DCP, again. Due to its solubility in HCl, it is more easily dissolved and released from the coat.

5. Conclusion

Press-coating was used to develop the delivery systems in this work. It allowed to obtain tablets containing an inner core, surrounded by a rupturable coat, which was able to modulate the release of the drug from the core by modifying the excipients in the coat.

All optimized formulations (TDDS 21, TDDS 22, TDDS 23, TDDS 24, TDDS 25) exhibited the desired release profile, a lag time followed by a sudden and complete release of the drug.

Looking at the release profiles obtain with the GB formulations many assumptions can be taken. Firstly, the ratio of DCP played an important role in obtaining a formulation pH independent, owing to its higher solubility in diluted acids. It was shown that by decreasing the percentage of DCP, the lag time between different pH became less variable. Therefore, to achieve a pH independent system, DCP should not be present in a high fraction. Also, by varying the ratio GB:PVP K30, the lag time could be modified; the higher the ratio, the higher the lag time.

An issue with the GB formulations was the possibility of drug diffusion prior to rupturing of the tablet. As the percentage of soluble excipient, PVP K30, increased, so did the diffusion of the drug prior to rupturing. Additionally, water uptake was very high, stressing again this issue. In this case, the release never reached levels above 5%. But, if a more soluble drug was used in the core, there might be more diffusion and the desired profile might not be reached.

The EC formulations showed pH independence from the beginning. With these formulations, as the EC powder had a large size distribution, the presence of a good binder was pivotal. Without a binder, media went into the core to fast and immediate release was obtained. As for excipients, not only was the lag time influenced by the ratio EC:soluble excipient, but it was also influenced by the presence of swellable materials in the coat, which supported the rupture of the coat.

Both developed formulations showed that it was possible to increase the size of the tablet, and maintain the same release profile, as long as the same core:coat mass ratio was respected. This is crucial as one of the disadvantages of press-coated tablets is low drug loading. By increasing the size of the whole system, and hence the size of the inner core, a higher drug loading is possible. Also, drug concentration showed no effect on lag time.

One of the differences between the EC and GB formulations was the height of the tablet. The presence of DCP in the GB tablet, a high-density powder, led to a smaller tablet. This finding is important because dosage forms of a smaller size increase the comfort of intake and thereby enhance the compliance, particularly in paediatric and geriatric populations.

The presence of a swellable agent in the core is of extreme importance to promote the rupture of the coat, as was shown with formulations TDDS 3-TDDS 9.

One of the factors that most affect the variability of the lag time is the centring of the tablet. Since, in this case, the centring was done manually, this was a source of errors. Therefore, the high variability within batches was probably due to the lack of experience of the operator.

6. Future work

Considering the obtained results and other described in the literature, it is important to perform further studies.

Firstly, it is important to evaluate the influence the core:coat mass ratio, on lag time. Moreover, the study of other manufacturing variables should be performed, particularly, the effect of the hardness and compression force, of both the core and coat, on lag time.

As mentioned before, diffusion of the drug prior to lag time, is one of the concerns of these delivery systems. Therefore, the influence of drug solubility on the release profile, should be assessed. Specifically, release studies with a more soluble drug along with a less soluble drug ought to be executed.

One of the applications of TDDS is delivery into the large bowel. To achieve this, an enteric coating could be applied onto the press-coated tablet, to overcome the variable stomach emptying time. This approach should be tested and release studies with a continuous pH should be performed. Furthermore, it would be important to evaluate the stability of peptides and proteins, under compression, as these have application in the treatment of such diseases.

The process of manufacturing the tablets was very time-consuming and showed large variability. Therefore, if a fully automatic press-coating machine was used, coupled with the

OSDRC system, the time of manufacturing can be reduced, as well as the variability decreased. This method of manufacturing should be tested to consider its impact on lag time.

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ANNEX I

Results Release Profile with Standard Deviation

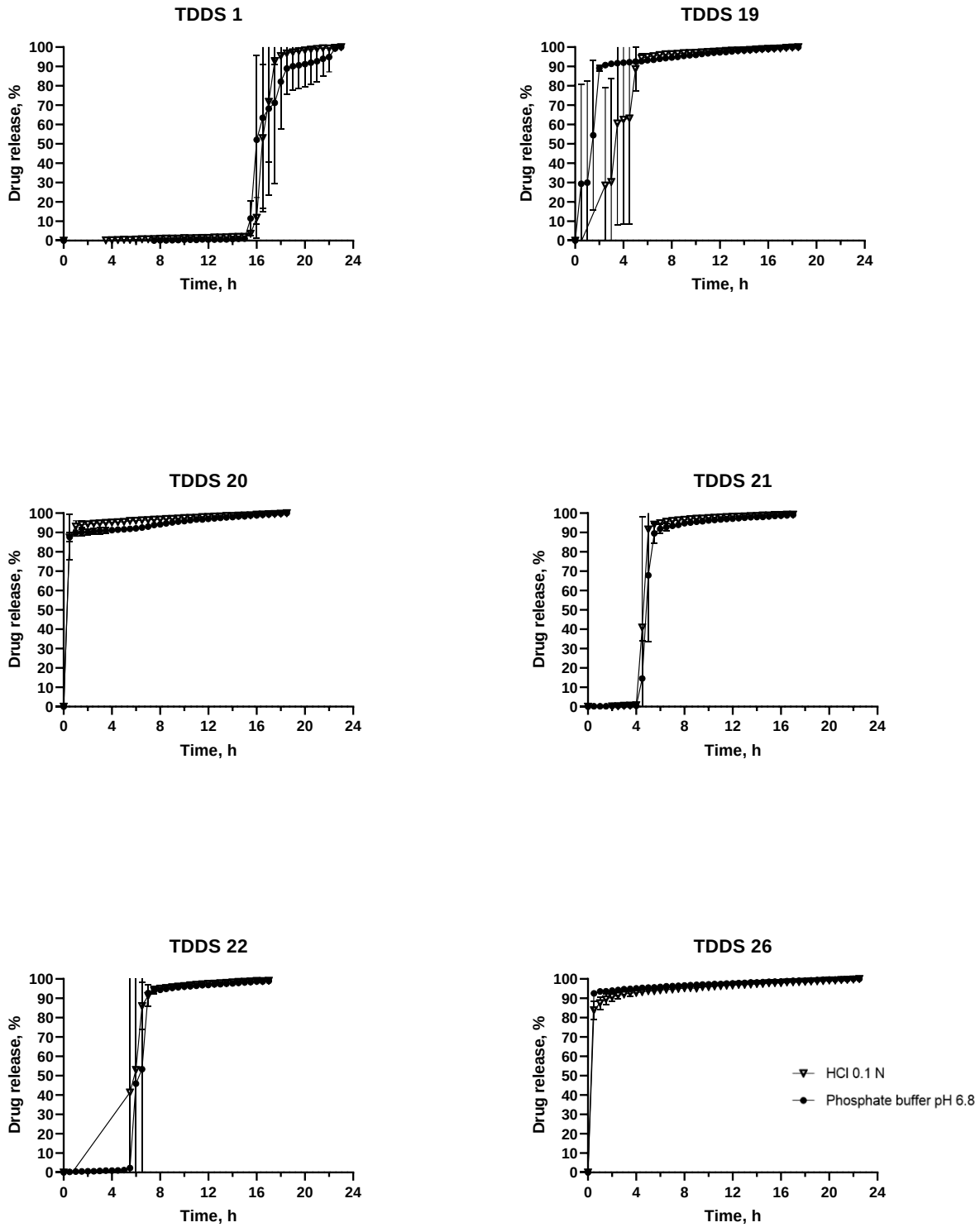

Figure 1 – Release profile of EC formulation, with SD.

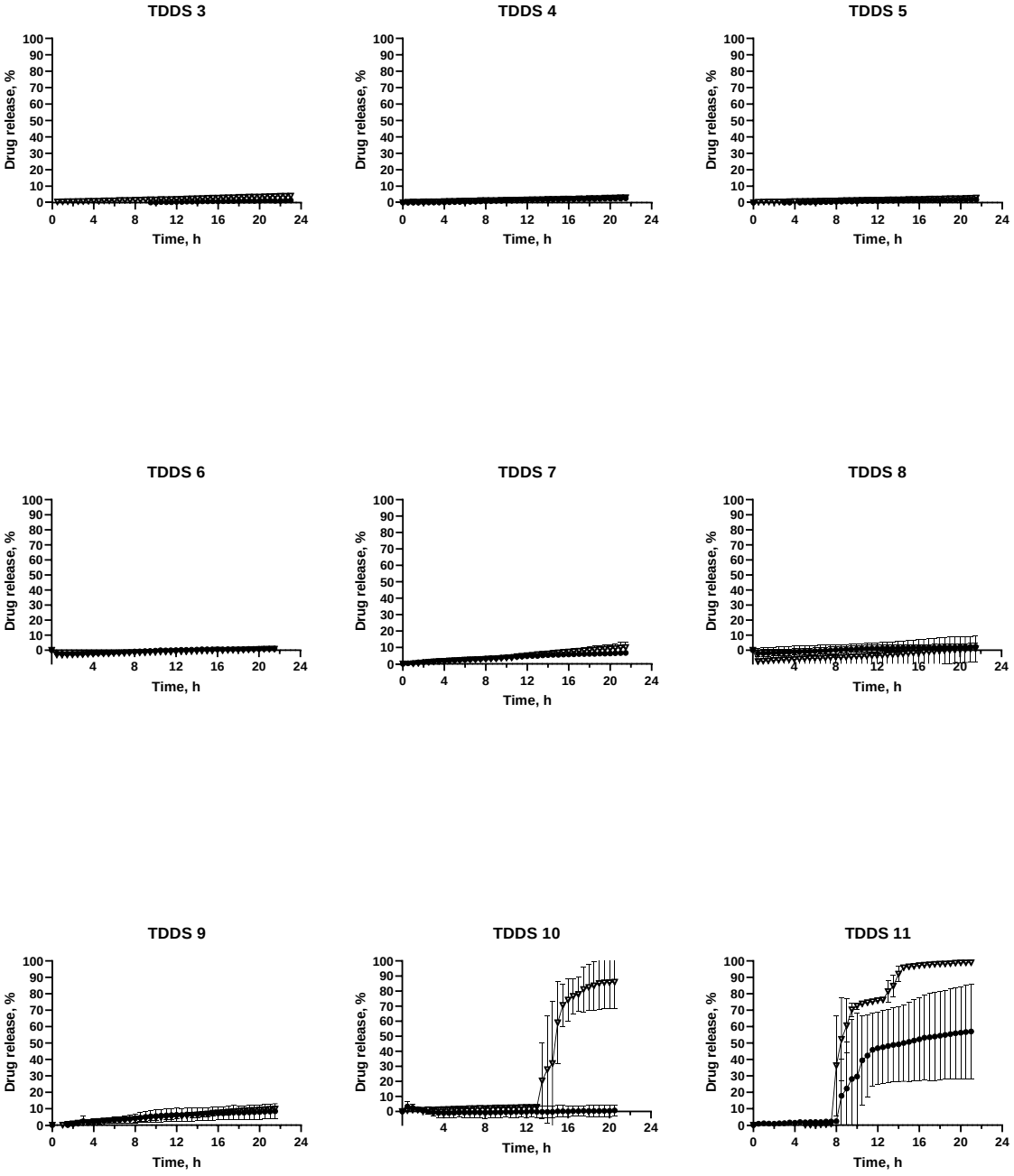

Figure 2 – Release profiles of glyceryl behenate formulations, TDDS 3 – TDDS 11, with SD.

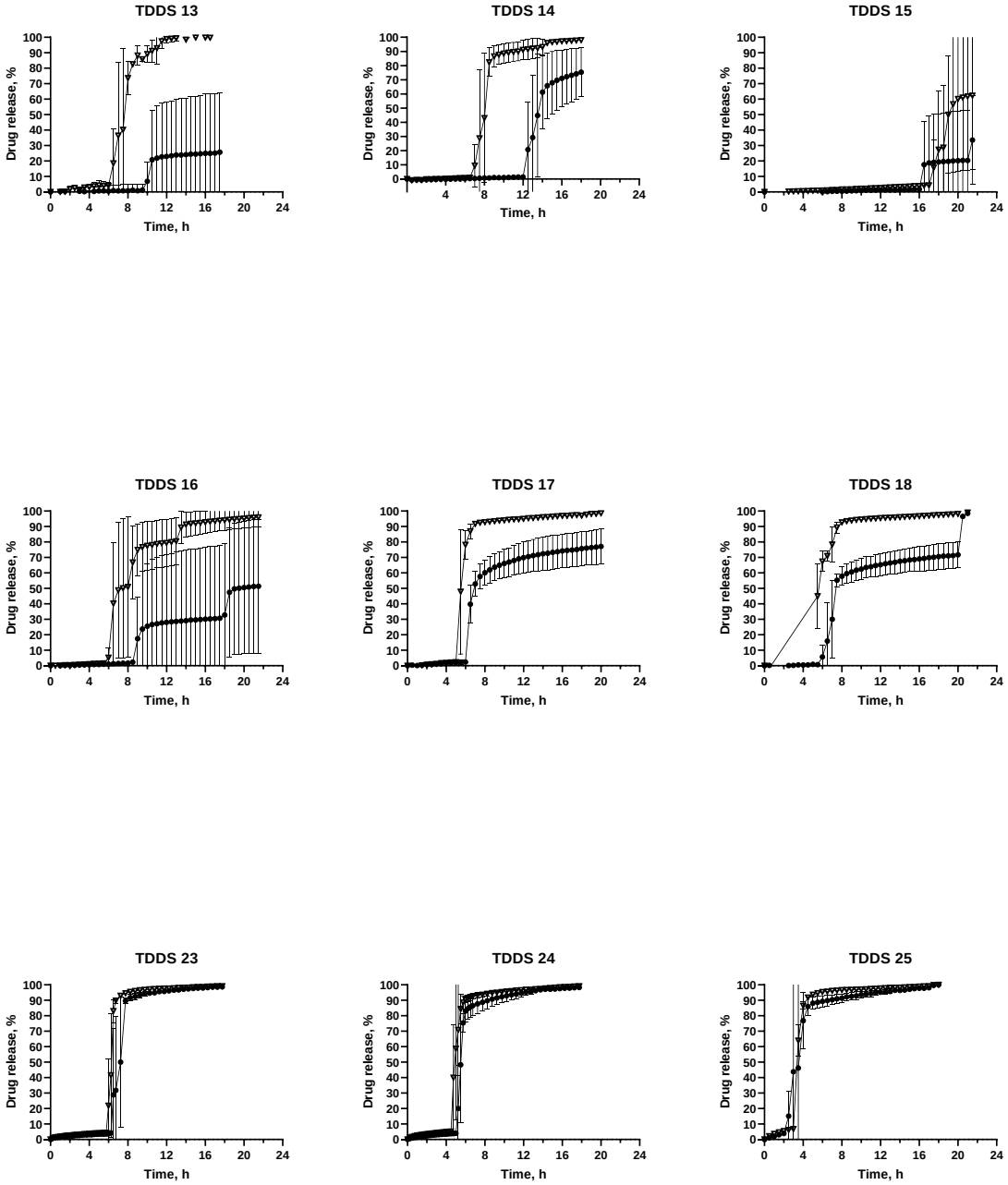

Figure 3 – Release profiles of glyceryl behenate formulations, TDDS 13 – TDDS 18 and TDDS 23 – TDDS 25, with SD.