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MASTER'S DISSERTATION IN PHARMACEUTICAL TECHNOLOGY

MODIFIED RELEASE TABLETS

CONTAINING CARNAUBA WAX

Hala Jooriah

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Hala Jooriah

Modified release tablets containing carnauba wax

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Work carried out under the orientation of:

Professor Doutor Paulo Jorge Cardoso da Costa

and co-orientation of:

Professor Doutor Rui Alexandre Santos Lapa

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Resumo

A cera de carnaúba é um sólido amarelo pálido, duro e frágil obtido das folhas da palmeira tropical brasileira *Copernicia prunifera*. Ela é normalmente usada na granulação por fusão para libertação prolongada.

O objetivo deste estudo foi examinar a possibilidade do uso de cera de carnaúba para formulação de comprimidos matriciais como sistema de liberação prolongada de fármacos por compressão direta. Comprimidos matriciais contendo paracetamol, lactose mono-hidratada, dióxido de silício coloidal e diferentes proporções de cera de carnaúba (50%, 60% e 70%), foram preparados em uma prensa hidráulica.

Os comprimidos foram avaliados quanto às suas propriedades físicas. A fórmula contendo 60% de cera de carnaúba foi escolhida para ser produzida por uma máquina de comprimir excêntrica para estudar o processo de compressão.

A libertação de paracetamol também foi estudada usando testes de dissolução. O estudo do comportamento do fluxo do pó também foi uma parte crucial deste trabalho, devido ao grande impacto do escoamento do pó no processo de compressão. Primeiramente a cera de carnaúba foi dividida por tamisação em três frações de acordo com o tamanho das suas partículas. Em seguida, as matérias-primas puras, as três frações diferentes de cera de carnaúba e a formulação a granel foram testadas quanto às suas propriedades de fluxo de duas maneiras: convencional (por exemplo, ângulo de repouso, índice de Carr, razão de Hausner) e utilizando uma célula de escoamento (índices de fluxo).

A cera de carnaúba apresentou um comportamento de fluxo muito bom e provou ser um bom material para comprimidos de liberação modificada com capacidade de prolongar a libertação por mais de 12 horas.

Palavras-chave: Cera de Carnaúba; Escoamento de Pós, Comprimidos Matriciais; Libertação Prolongada.

Abstract

Carnauba wax is a pale yellow, hard and brittle solid obtained from the leaves of the Brazilian tropical palm tree *Copernicia prunifera*, and it is normally used in melt granulation for sustained release.

This study aims to formulate matrix tablets of paracetamol by direct compression and to evaluate the effect of different concentration of carnauba wax on the release profile of paracetamol from matrix tablets. Direct compression of the matrix tablets was achieved by mixing the drug powder with the wax powder and other excipients using the Turbula, then compressed into tablets using a hydraulic press machine. Three batches were prepared using 50%, 60% and 70% of carnauba wax, then the tablets were evaluated for their weight uniformity, hardness, friability, and drug release.

After dividing carnauba wax to by sieving into three fractions according to their particle size, the pure powders the different fractions of carnauba, and the bulk formulation were evaluated for their flow properties by angle of repose, Hausner ratio, Carr's index and by using the shear cell method. The formula containing 60% of carnauba wax was chosen to be produced by an eccentric press machine, to study the compaction process of the bulk solid and to compare the drug release from tablets of the same formula produced by two different press machines.

Carnauba wax powder showed a very good flow behavior, and it proved to be a good lipid excipient in drug delivery systems since it showed its capability to slow down the release rate in modified release tablets with a capacity to prolong the drug release for more than 12 hours.

Keywords: Carnauba Wax; Paracetamol; Powder Flowability; Matrix Tablets; Prolonged Release.

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List of abbreviations and symbols

CFF – Consolidation Flow Function

CI – Carr Index

CR – Controlled Release

CSD - Colloidal Silicon Dioxide

CW – Carnauba wax

Da – Dalton (the molecular mass unit)

DCM – Direct Compression Method

DDS - Drug delivery systems

E_S - The total energy supplied by the upper punch

E_{EXP}.-. Expansion energy

E_{LA}.-. Apparent net energy

FDA - Food and Drug Administration

F_I - The applied force on the lower punch

F_S - The applied force on the upper punch

R.-. The lubrication capacity

ff_c - Flow Factor

FP – Portuguese Pharmacopeia

GI – Gastrointestinal

HR – Hausner Ratio

IVIVC - In vitro in vivo correlation

k – Release constant

MEC - Minimum Effective Concentration

MR - Modified release

MTC - Minimum Toxic Concentration

n - Release exponent

Ph. Eur. - European Pharmacopeia

PI - Plasticity Index.

pK_a – Acid-ionization constant.

PR - Prolonged release

Q - Amount of drug released

Q_0 - Initial amount of drug released

R^2 - Determination coefficient

TI - Therapeutic Index.

USP - United States Pharmacopeia

1. Introduction

For many decades, the treatment of most diseases was carried out using so-called conventional pharmaceutical dosage forms, or commonly known as immediate release dosage forms, which are characterized by a rapid release of the drug. According to Portuguese Pharmacopeia (FP), immediate release happens when the “release of the active substance(s) has not been the subject of a deliberate modification resulting from a specific formulation process and/or a special manufacturing method” (1). In the case of solid pharmaceutical dosage forms, the dissolution profile of the active substance depends essentially on its intrinsic properties. In addition to immediate release (IR) dosage forms, drug delivery systems (DDS) can also be classified in modified release (MR) dosage forms.

As stated by European Pharmacopeia (Ph. Eur), modified release dosage forms is the widest term that includes prolonged release; delayed release; and pulsatile release dosage forms (2) (Figure 1).

Modified release dosage form is a preparation where the rate and/ or place of release of the active substance(s) are different from that of the conventional-release dosage form administered by the same route. This modification is achieved by a special formulation design and/ or manufacturing method.

Prolonged release dosage form is a modified-release dosage form showing a slower release of the active substances(s) than that of a conventional-release dosage form administered by the same route. Equivalent term: ***Extended release dosage form***.

Pulsatile release dosage form is a modified-release dosage form showing a sequential release of the active substance(s).

According to United State Pharmacopeia (USP), dosage forms may be formulated in such a way that the drug release is modified (Modified Release dosage form) (3). There are two types of modified-release products: Delayed-Release, and Extended-Release.

Delayed-Release *products are deliberately modified to delay the release of the drug substance for some period after initial administration.*

Extended-release *products are formulated in such a manner as to make the drug substance available over an extended period following administration.*

1.1 Terminologies in modified release dosage forms

The main goal of this type of DDS is mainly to provide a prolonged period of action and better patient compliance (4). This work is about oral drug delivery systems, particularly tablets. Generally, the terms of this field are used to describe the different types of modified release dosage forms, nevertheless they are diverse and sometimes overlapping the concepts associated with the drug release that some of the terms can be used interchangeably

Modified release: they are coated or uncoated tablets that contain special excipients or are prepared by special procedures, or both. This system is designed to modify the rate, the place, or the time at which active substance(s) are released (2).

Controlled release*:* it is a time-controlled delivery system that suggests the control of the drug release rates, where the drug is released continuously in a planned and slower way than in the conventional dosage form providing a plasma concentrations that remain invariant over time (5-8).

Extended release: its purpose is to take the dosage units less often and keep a stable drug plasma concentration, allowing a twofold or greater reduction in the frequency of administration of a drug in comparison with the frequency required by a conventional dosage form (8, 9). This type of release is used to achieve the maintenance dose (10).

Prolonged release / Sustained released: both mean prolonged blood drug concentration and they can be used interchangeably (6). However, according to some authors, these two terms are not exactly identical, for instance, sustained release provides a slow constant release after releasing an initial dose soon after administration (loading dose) (11, 12), while in the prolonged release the effect might need some more time to appear (12).

Delayed release: these tablets are intended to release a discrete portion of the drug after a lag time which is commonly achieved by resisting gastric fluid and disintegrating in intestinal fluid (enteric-coated tablets) (11).

Repeated action: this dosage form includes two parts; the first one releases the drug immediately after the administration, like the conventional drug, followed by a second dose release after a predetermined time (13).

Site-specific and receptor release: the receptor release targets a certain drug receptor in an organ or a tissue, while in the case of site-specific release, the target is a specific tissue or organ (7, 10).

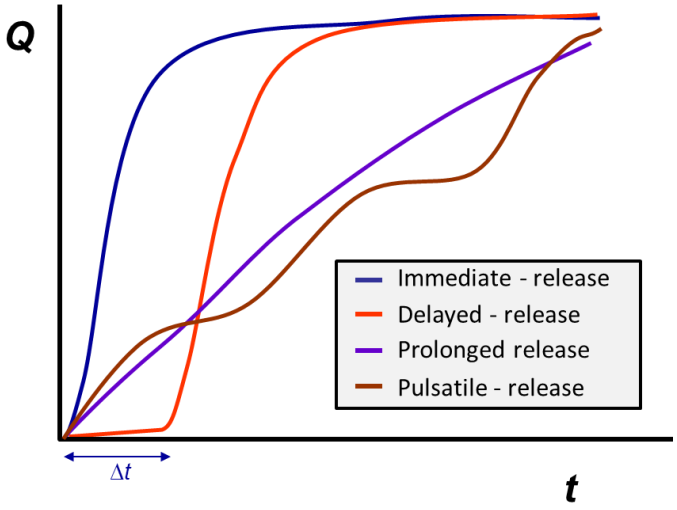


Figure 1. Types of modified release drug dosage forms according to Ph. Eur.

The prolonged release (PR) system was chosen for this work, it can be defined as a dosage form in which the drug is released slowly, at a predictable rate, and over a predetermined time, achieving a constant drug blood level (6, 14). It is important for this type of dosage form that the drug steady-state is higher than the Minimum Effective Concentration (MEC), which is the minimum required concentration for drug effect, and lower than the Minimum Toxic Concentration (MTC), the minimum concentration in which the drug toxicity occurs (Figure 2). Another goal in designing a controlled delivery system is the spatial placement of the drug, by placing the drug on the site of action (14, 15).

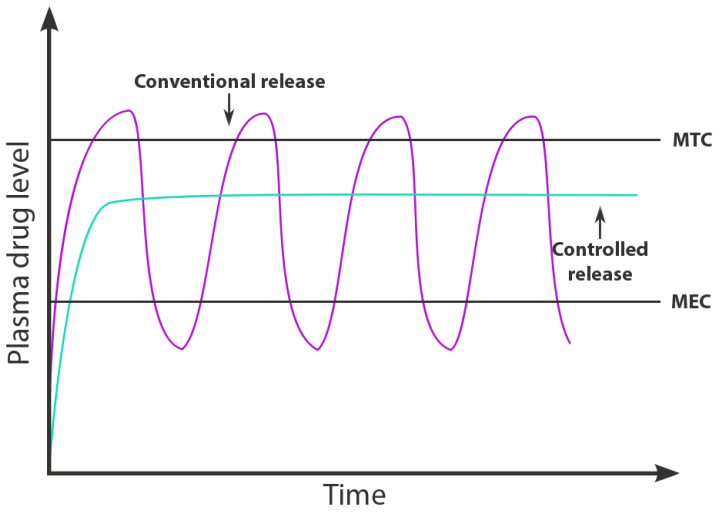


Figure 2. Plasma drug level in controlled release and conventional release.

This system is designed to improve drug safety and effectiveness, increase patient compliance by reducing the frequency of administration/dosing frequency, minimize the

adverse effects, protraction the duration of action in addition to reducing the costs of developing new drugs, since the controlled release technology is a fundamental way to improve the current drug's effectiveness (4, 14-16).

The oral route is the preferred and the most used route of administration for both immediate and modified release products (4, 5, 14) and about 90% of drug products are orally administered (15). However, in conventional dosage forms, there are some limitations that lead to problems in maintaining the desired drug level in plasma over a short period (4, 6) such as:

- Drug levels fluctuations,
- Poor compliance due to high frequency of administration,
- An overdose that appears after the dissolution of the drug may cause increased side effects, leading to iatrogenic damage.

By using PR systems, we can overcome these limitations, obtaining the following advantages (8, 17):

- Reduce dosing frequency, which leads to reduction of adverse side effects.
- Minimize gastric irritation.
- Avoid bedtime dosing.
- Increase bioavailability.
- Reduce fluctuation in the plasma drug level by maintaining a constant therapeutic level for a long period.
- Blood drug levels are kept constant within a narrow window, with no sharp summits.
- The total treatment cost using a PR product may be lower than using a conventional product, which could cause a reduction in the overall disease management expense.

When using PR systems, we can also have some disadvantages (8, 17):

- In case of giving a toxic dose, it will last for a long time because the immediate termination of the treatment is not always possible.

- Dose dumping, when a big amount of drug is rapidly released, will greatly increase the drug concentration in the body and could lead to death in case of drugs with a narrow therapeutic index (TI).
- In case of tablets, they are undividable, which can be considered as lower flexibility in the dose adjustment.
- The time required to absorb the released dose may vary between the patients.

1.2 A brief history of drug delivery technologies

Historically, the first attempt to modify the release rate and the period of action was by using the coating process for pills, tablets, and even capsules. In 1878, Charles Carter obtained a patent in Coated Compressed Medicaments, "*My invention consists in partially enveloping the medicaments in coverings of a saccharine nature in the form of powder, and then applying a top or finishing covering of powder, and compressing the whole, so that the powder covering holds by cohesion, thus producing a seamless coated compressed medicament, substantially as described*" (18). Another early invention was by Esco F. Elizey in 1927, whose invention "*relates to an improved composite pellet for the oral administration of such medicaments, as are sensitive to the contents of the stomach*". Elizy incorporated a small capsule with the drug in a larger one (disclosing a double capsule system, with one capsule within the other), for administering medicaments in which the inner hard gel capsule contained the drug, whilst the outer hard gel capsule contained an innocuous alkaline material (19, 20).

In Allan Hoffman's review about "the origins and evolution of controlled release", he considers 1962 as a starting point when a silicon rubber implanted capsule was developed by Judah Folkman as a *constant rate* drug delivery device (21).

Over the last 60 years, the modified drug delivery technology has experienced a large technological advance. During those years, several generations of this type of systems were developed (Table I).

The first generation (1st G) that lasted from 1950 to 1980, was fixated on developing oral and transdermal controlled release system and setting up mechanisms to control the release of the drugs. In the 1st G, the scientists had to deal with physicochemical problems (ex; poor water solubility, large molecular weight) which was considered controllable, so this generation was very productive (22).

For the majority of 1st G DDS (oral and transdermal), understanding the *in vitro* drug release kinetics and other physicochemical properties was enough to develop clinically

beneficial formulas. The only biological barrier that has been identified for these formulations was the gastrointestinal (GI) barrier and its related absorption properties according to the different sections of the GI tract for oral formulations.

In the second generation (2nd G), that occurred from 1980 to 2010, the efforts were allocated to develop self-regulated DDS, zero-order release systems, and nanotechnology-based DDS. After a decade of intense efforts, it was noticed that having zero-order delivery was not truly required to develop sustained DDS. That fact can be explained by knowing that zero-order release does not maintain constant drug concentration in the blood, which is not necessary for most drugs because the drug efficacy stays the same as long as its concentration is between the minimum effective level and the maximum safe concentration. Understanding those facts gave flexibility to the future design of DDS (22, 23).

In the 1990s, smart polymers and hydrogels were used in the 2nd G and notable advances were achieved. They used to design DDS that was activated by the changes in the surrounding factors, such as temperature and pH. However, their clinical applications had not yet been fulfilled. In 1989 Zoladex® Depot was introduced as the first solid implant used to deliver peptides (goserelin acetate) for 1 month or 3 months. The last ten years of the second generation were dedicated to developing nanotechnology-based DDS or targeted DDS, which has been the most popular matter in this field until today, depending on the capability of nanoparticles to reach the intended targets (23). The 2nd G conflicted with biological barriers which could not be easily controlled, so this generation was not very successful clinically (22).

The third generation (3rd G) appeared in 2010, needed to overcome both physicochemical problems and biological barriers (22). In this generation, the delivery of drugs with poor-water solubility was the main area of study. There were attempts to increase the drug solubility by adding appropriate excipients that might help in achieving this goal like surfactants, cosolvents, and polymer micelles. Genexol® is an example of an injectable formulation where PEG-PLA polymer micelle was used with paclitaxel (a poorly soluble drug). Another way was to control the pH of the weak basic or acidic drugs. Drugs with very short half-life were also a focus of attention. Depot formulation like Lupron Depot® (leuprolide acetate) was developed as a controlled drug release system with a high drug loading for a period of up to one year. Self-regulated insulin delivery was considered a very important and interesting technology that is under slow progress development with a main purpose to replace the daily insulin injections with one injection that lasts for months (6, 22, 24). Targeted delivery of anti-cancer agents using nanoparticles was also a new type of DDS to be developed during this generation (22, 24).

Table I. Modified drug delivery systems evolution (22, 23).

1950	1980	2010	2040

First generation	Second generation	Third generation
Basic of controlled release Successful control of the physicochemical properties of the delivery system	Smart delivery system Inability to overcome the biological barriers	Modulated delivery system Need to overcome both biological and physicochemical barriers
Oral delivery Once-a-day, Twice-a-day	Zero-order release Zero-order vs first order-release	Poorly soluble drug delivery Nontoxic excipients
Transdermal delivery Once-a-day, once-a-week	Smart polymer and hydrogels Environment-sensitive Self-regulated release	Peptide and protein delivery Delivery for more than 6 months Control of release kinetics Non-invasive delivery
Drug release mechanisms Dissolution, Diffusion Osmosis, Ion-exchange	Peptide and protein delivery Long-term depot using biodegradable polymers Pulmonary delivery	Smart polymer and hydrogels Single specificity and sensitivity Fast response kinetics (working in vivo)
	Nanoparticles Tumor-targeted delivery Gene delivery	Targeted drug delivery Non-toxic to non-target cells Overcoming blood-brain barrier (BBB)

The Biopharmaceutics Classification System (BCS) is a system that categorizes the drugs into four classes according to their intestinal permeability and water solubility (Table II), which can help in the prediction of the drug pharmacokinetics in the body *(in vivo)* from solubility and permeability measurements that have been done *in vitro,* and then it can be used as a basis to establish IVIVC (25). *In vitro in vivo* correlation (IVIVC) *is a predictive mathematical model describing the relationship between an in vitro property of a dosage form and a relevant in vivo response. Generally, the in vitro property is the rate or extent of drug dissolution or release while the in vivo response is the plasma drug concentration or amount of drug absorbed* (26). After the establishment of a good correlation between an *in vitro* property of a dosage form (drug release using the dissolution test) and relevant bioavailability parameters *in vivo (drug plasma concentration or drug absorption)*, *in vitro* dissolution test can serve as a surrogate marker for *in vivo* behavior (11), and it is also used to predict the *in vivo* performance (plasma concentration or absorbed amount) of the drug according to its *in vitro* release profile (rate of drug release or dissolution) (27).

Table II. Biopharmaceutics Classification System (BCS) categorize drug substances into four groups based on aqueous solubility and intestinal membrane permeability.

Class I	high permeability, high solubility
Class II	high permeability, low solubility
Class III	Low permeability, high solubility
Class IV	Low permeability, low solubility

In general, the crucial elements in developing a PR system are the drug, the formulation, and the administration route. However, only the drug and the formulation could be technologically manipulated. The variability between patients in physiology and gastrointestinal transit is an important issue in these systems (6).

1.3 Drug selection for oral modified release drug delivery system

Pharmacological and physicochemical properties, physiological factors of the gastrointestinal tract (the active substance should stay unchanged until getting to the targeted point), hazards, and therapeutic indications should be evaluated for drugs considered to be used in a modified release dosage form. Hence, it is important to measure the therapeutic index (TI) to determine the safety margin of a drug, knowing that a higher TI value means safer drugs:

$$TI = TD50 / ED50 \qquad \textit{Equation 1}$$

where TD50 is the median toxic dose and ED50 is the median effective dose.

Therefore, drugs with small TI value are not good candidates for a PR formulation due to technological limitations in controlling the drug release rate precisely (8).

1.3.1 Physicochemical properties

The physicochemical properties of the drug can affect the drug absorption rate and drug absorption extent from the gastrointestinal lumen (Table III).

- Administered dose size: drugs with a single dose size less than 0.5 g can be good candidates for PR products (7). In the case of short half-life drugs, the dosage form will require a large quantity of the drug (8).
- Partition coefficient *K* affects how easily the drug can reach the intended target, and how long it stays active in the body (5). Because all the biological membranes are lipophilic, drugs with a high partition coefficient, easily penetrate these biological membranes, accumulate in the tissue, and have a slow elimination (7). In the case of a low partition coefficient, the drug does not permeate easily through the biological membranes but can move around the aqueous area readily (28).
- Water solubility affects the dissolution rate and the tissue penetration rate of the drug (7). Drugs with low water solubility have low oral bioavailability due to the small amount of dissolved drug (28). On the other hand, it is considered difficult for drugs with high water solubility to slow/extend their dissolution rate, because of their rapid diffusion after water penetration (29, 30). Generally, drugs having a solubility lower than 0.1 mg/mL in water solutions are likely to give low bioavailability; the drug should have a pH-independent solubility as well (5).
- Protein binding: the drug duration of action prolongs as the drug has a high degree of plasma protein binding, which changes the drug pharmacokinetics (7).
- Drug stability: the drug may be exposed to enzymatic or chemical degradation by the biological fluids in the body. Unstable drugs in gastric pH (poor acidic stability) is a good choice for a delayed release dosage form by coating it with an enteric coating, so it can pass the stomach and release the drug in the intestine. Forming prodrugs protect the drug from enzymatic degradation (28). On the contrary, drugs with higher instability in the small intestine cannot be used in oral PR DDS (7).
- pK_a and ionization: uncharged/unionized drug is absorbed easily from the body tissue, so the drugs that are mostly in the ionized form are not good candidates for PR DDS (7). The pK_a is a value that indicates the strength of an acid, the lower the pK_a, the stronger an acid, and the greater the ionization. The ideal pK_a range for the optimal absorption for acidic drugs is 3.0 - 7.5, and for basic drugs pK_a range is 7.0 - 11.0 (4, 5).
- Molecular weight: to get a quick and complete absorption, low molecular weight is necessary. Drugs could be absorbed either in a pore transport mechanism and

in this case the molecular size should be between 150-400 Dalton (Da), or in passive diffusion and the limit size here is 600 Da (4).

- Drug permeability: Class I and Class II drugs (Biopharmaceutics Classification System) are better candidates due to their high permeability through the GI epithelium (31).
- Stability: drugs should be stable in both gastric and intestinal pH (31).

Table III. Physicochemical properties for drug selection.

Parameter	Value
Dose size	< 0.5 g
Partition coefficient	1-2
Water solubility	> 0.1 mg/mL
Dissociation constant pK_a	Acidic drug > 2.5 Basic drug < 11.0
Molecular weight	< 600 Da

1.3.2 Pharmacokinetic properties

Pharmacokinetic term refers to the activity of the drug in the body over time or what the body does to a drug (absorption, distribution, metabolism, and excretion). Hence, the pharmacokinetic properties of the drug should be also considered important in a modified release study of the drug:

- Drug half-life: the half-life of a drug is the time required to reduce the drug plasma concentration by 50%. A good drug candidate should have a half-life range from 2 h to 8 h. If it is less than 2 h, the drug will be quickly removed from the body, and the prolonged release dosage form may need to carry a large quantity of drug. If the half-life is more than 8 h, there is no need to formulate a modified release dosage form (13).
- Absolute bioavailability: bioavailability is the fraction of administered drug that reaches the systemic circulation. It should be equal to or greater than 75% (4, 10).

- Absorption: drug absorption is the process of movement of unchanged drug from the site of administration to the systemic circulation. Drug absorption rate should be equal or greater than the drug release rate (4, 10). Slowly absorbed drugs are not a good candidate for a prolonged release system, and the drug must be absorbed through the entire GI tract (5).
- Therapeutic index: the therapeutic index is the ratio between the drug dose that causes the therapeutic effect and the dose that causes toxicity. Drugs with narrow TI have limitations to control the release rate so they are not a good candidate because any small deviation above the safety margin (MTC) can cause toxicity and a slight deviation under the (MEC) causes insufficient therapeutic action, while large TI ensures a safe product (5). Generally, a drug with TI higher than 10 is safe (8).

1.4 Gastrointestinal tract physiological considerations

It is important to study the properties, histology, and functions of the GI tract to develop a good PR formulation since those factors affect drug absorption. The main function of the gut is to break down the food, basically in the stomach, so it could be absorbed into the body across the epithelium of the small intestine, the reabsorption of the excess water happens in the large intestine (32).

The digestive tract extends from mouth to anus and can be divided into the upper and lower GI tract (Figure 3). The upper GI tract is the mouth, esophagus, stomach, and the first part of the small intestine (duodenum). The lower GI tract consists of the other two parts of the small intestine (jejunum and ileum) and the large intestine (cecum colon and rectum) (33).

The absorption of the drug along the GI tract is affected by (31, 33):

I. The transit profile of food through the stomach, small intestine, and colon, hence in the case of modified release systems different sites of drug release will occur.
II. Luminal pH changes along the gut.
III. Food, fluid consumption, and gastric secretions (gastric or intestinal phase).
IV. Gastric emptying and absorptive mechanism.
V. The blood flow to the site.
VI. The absorption surface area.

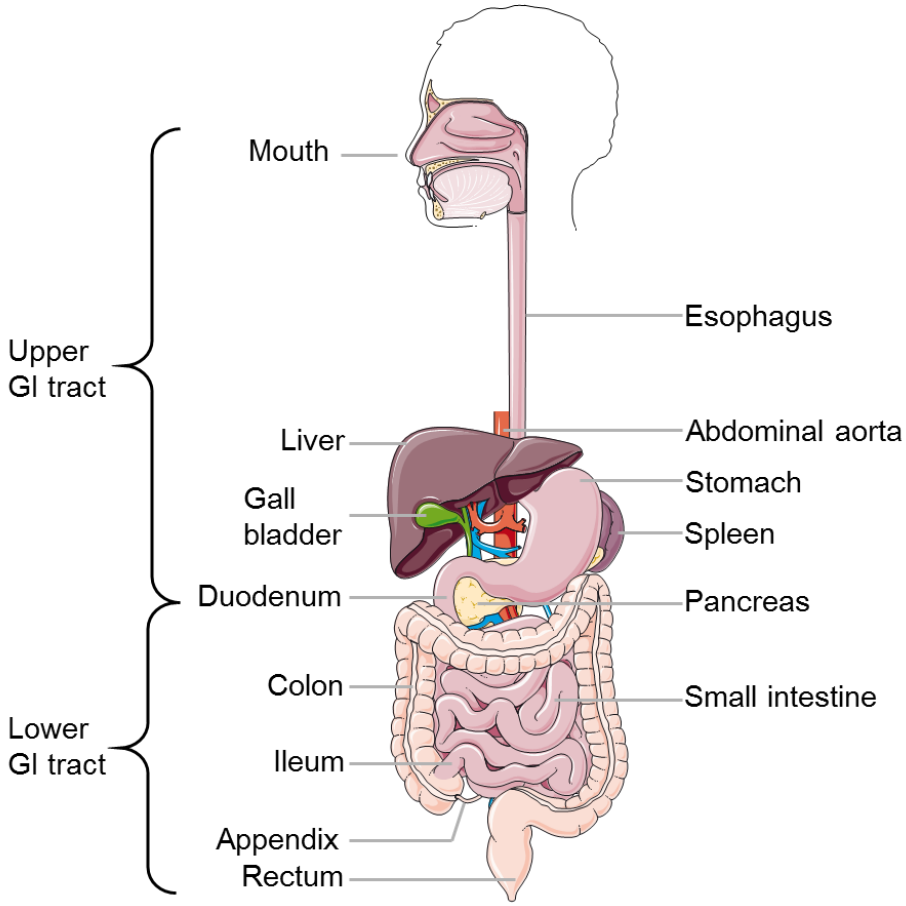


Figure 3. Upper and lower gastrointestinal (GI) tract (34).

1.5 Modified release mechanisms

It should be pointed out first that the release mechanism of a drug depends on the nature of the drug, pH, and the used polymer. Drug release from matrices usually includes water penetration into the matrix, hydration, swelling, diffusion of the dissolved drug, and/ or erosion of the gelatinous or matrix layer (35). The release rate could be modulated by (10, 36):

- Using different types or grades of polymers and different fillers (soluble or insoluble).
- Controlling the amount of drug or excipients.
- Changing the matrix porosity and the length of the pores.

In hydrophilic polymers, the drug in the outermost layer dissolves after being exposed to the solution and then diffuses out of the matrix. As a result of the hydration, the matrix swells blocking up the pores. A gel layer is formed, and the soluble drug diffuses through, a viscous solution occurs creating a positive pressure that opposes the liquid entry causing matrix

disintegration (4). The swelling process happens due to a severe change in the polymer state from glassy to rubbery when it comes in contact with water, which is explained by the decrease in the polymer transition temperature (10, 37). With time, the gel layer becomes thicker and the drug release rate lower (37). In the case of water-soluble drugs, the drug is released by diffusion out of the swelled layer or by erosion, while in the case of poorly soluble drugs, the release generally happens slowly and only by erosion (36) (Figure 4).

In waxy or inert matrices, the release mechanism is generally described by the diffusion model (38). The eluting solution dissolves the polymer from a surface-forming porous network in the core (37), then the fluid enters through the pores and cracks that are formed in the matrix (39). The amount of soluble drug that diffuses from the matrix through the porous is insignificant. In this diffusion process, the leaching of the drug by the eluting medium is involved (39). Differently, poorly soluble drugs embedded in the inert matrix are released by erosion (37).

1.5.1 Diffusion Controlled Release Systems

In this system, the release rate is controlled by the diffusion of the dissolved active substance through pores in the tablet, when these pores are filled by gastric or intestinal fluids (10, 16) (Figure 4). This process is the transport of molecules from a region of high concentration to a region of low concentration (28). The release rate depends partially on how easily the film or matrix will dissolve within the surrounding media (40), and the release unit must be intact during the release process (10). Diffusion happens through pores in the matrix when two polymers with different solubility are used, or across the coating by drug passing a hydrophobic polymer according to the drug concentration gradient between inside and outside the coating (40, 41).

There are two major types of diffusion PR systems; *reservoir devices* and *matrix or monolithic devices* that generally release the drug according to two different release models, i.e. zero-order and Higuchi model (10, 16, 28).

1.5.1.1 Reservoir devices

The reservoir devices consist of a drug core surrounded by a polymeric membrane that controls the drug diffusion (16, 40, 42). The main release mechanism is diffusion, which happens by penetration of the surrounding liquid in the dosage form and dissolve the drug creating a drug concentration gradient between the interior and exterior medium. Then the dissolved drug diffuses across the membrane to the surrounding medium (10). Some important factors to be considered in these devices are uniformity of film thickness and density

(the film should not have cracks) and its quality should be good enough so the final product stays stable and the drug remains protected (40). There are two different diffusion-controlled reservoir systems (34):

I. Nonporous reservoir systems, in which the drug should diffuse through the polymeric membrane,

II. Microporous reservoir systems, where the diffusion happens through the pores.

Polyurethane, polyethylene, silicone rubber, and ethylene-vinyl acetate copolymers are examples of polymers used in this type of system (16).

1.5.1.2 Matrix devices

In the matrix devices, the drug is trapped in hydrophobic or hydrophilic materials (16, 43, 44). One way of diffusion is by using a fluid permeable polymer, where the fluid medium leach the drug out of the matrix causing drug release; another way is by adding a soluble material to the matrix which will turn over to linked channels when the fluid dissolves it and enter the matrix (16). In hydrophilic polymers, the matrix swells and dissolves leading to drug release (42). The compression of powder drug with the matrix polymer forms a dispersed active agent system (16).

In this type of controlled DDS, the drug is released by both diffusion (after the water penetration) and dissolution mechanisms (matrix erosion) (31, 45). The drug is homogeneously dispersed in a polymeric skeleton, so the molecules are enclosed into the matrices of the polymers (46). The polymers hydrate when contacting the dissolution media and then swell up or erode depends on the type of the polymer (46). The direct compression method (DCM) of a mixture of the active substance and a polymer is one of the simplest methods to produce this system (45, 47), and it can also be produced by dissolution or melting (36). A wide variety of polymers has been used as drug slowing agents depending on the physicochemical properties of the drug, where each offers a different technique to the matrix concept (48, 49).

Several factors contribute to the widespread use of this method, which leads to it being considered the most used oral PR technology (15, 36, 50):

- First, because they are easy to manufacture due to the possibility of using conventional methods and equipment.
- Second, due to a convenient time of production and low cost.

- Third, unlike the reservoir device, there is no danger of membrane rupture causing an accidental high drug dosage release.
- Finally, this system can accommodate the low and high load of drugs and release high molecular weight compounds.

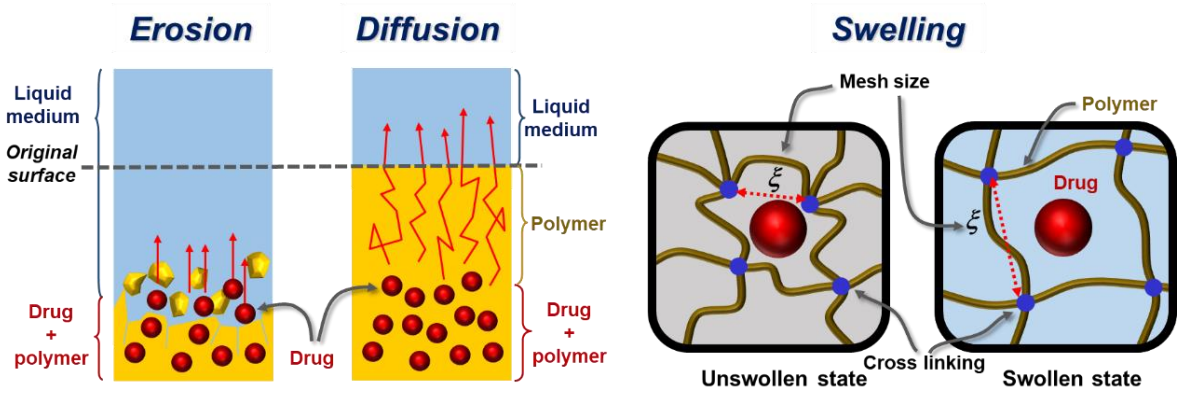


Figure 4. Erosion/diffusion/swelling-controlled release systems.

1.5.2 Dissolution controlled release systems

Generally, this system depends on reducing the dissolution rate of water-soluble drugs by covering the drug with a dissolving coat (normally a hydrophilic polymer) that dissolves slowly within the surrounding medium causing a slower drug release (10, 40, 51), or by dispersing the drug homogeneously in a polymer matrix (monolithic system). The surroundings liquid dissolves the coating then reaches the solid drug causing it to dissolve and subsequently to release the drug (10, 15, 51). A preparation of sparingly water-soluble drugs or a slow dissolution rate drug could be used in this system because it shows sustaining drug release properties. The dissolution rate of the drug, the coat, or the matrix is the rate-limiting step in this system (10, 15). The thickness of the surrounding polymer also plays an important role in the drug release rate (34).

1.5.3 Swelling-controlled release systems

It is a water penetration-controlled release system, in which the drug release is achieved by the water or body fluids penetration into the system (51). The drug is dissolved or dispersed homogenously in a dry swellable polymeric matrix. Immersing this system in the body fluids will hydrate the matrix causing it to swell and the matrix network mesh size will increase (Figure 4), leading to dissolution and diffusion of the entrapped drug into the surrounding medium through the polymeric network (16, 51).

1.6 Matrix tablets

This term refers to the tablets in which the drug is dispersed in a skeleton of a soluble or insoluble material (36). In other words, the drug is homogeneously dispersed in a hydrophobic matrix, swellable hydrophilic matrix, or a plastic matrix (36, 45, 47). It is simply formed by direct compression method (DCM) of a mixture of an active substance, retardant material (polymer), and other excipients (36, 45, 47). This method is preferred not only because of the ease of manufacturing but also because it is appropriate for moisture and heat-sensitive drugs (46). Since there is not any material that by itself has completely ideal tableting properties (especially flowability and compressibility), co-processed dry binders are important to be used (52). Co-processed dry binders are substances that are modified to enhance the required properties for direct compression (52, 53). Matrix tablets are a good choice for drugs with high or low water solubility (46). It was reported that many factors influence the drug release from matrix tablets, including (37, 47):

- Drug water solubility.
- Drug/excipient amounts.
- Particle size.
- Polymer type, proportion, particle size, and diffusivity.
- Excipients/additives.
- Processing techniques.

1.6.1. Hydrophobic matrices

In this system, the drug is mixed with a hydrophobic material and then is compressed to obtain the tablets (45). The most widely used hydrophobic materials include fatty acids, glycerides, polyethylene, ethyl cellulose, and methacrylate copolymers (15, 45, 50). To adjust drug release, it is necessary to add some soluble ingredients like lactose to the formulation (15). The drug release happens when the soluble ingredient (channeling agents) dissolves leading to a formation of a network of channels inside the compacted particles, that facilitates the dissolution and diffusion of the drug through the channels (45, 49, 54), while the insoluble ingredients maintain the physical dimension of the tablet (15). In this system, the drug diffusion is generally the prolonged release mechanism, and the liquid penetration into the matrix also plays an important role (45). Generally, hydrophobic matrix systems are suitable for drugs with high water solubility (35, 42). The particle size and the amount of hydrophobic material in the formulation are rate-determining factors (35). Hydrophobic matrix tablets stay intact and keep

their integrity for longer periods in contrast to tablets prepared with hydrophilic polymers which swell and disperse with time (55).

Lipid matrices are prepared using waxes with related materials (56) providing a hydrophobic environment and control the aqueous medium entry into the matrix. The drug release occurs through digestion and/or erosion of the lipid matrix (57), and drug diffusion through the water-filled capillaries (55, 58). Wax is chemically inert which gives its use a special advantage (59). The excipients most used in lipid matrices (55) are waxes (carnauba wax, bee wax), hydrogenated vegetable oils (hydrogenated castor oil), cetyl alcohol, and stearyl alcohol.

1.6.2. Hydrophilic matrices

This type of matrix system is widely used in oral controlled DDS because of its low manufacturing cost (42), flexibility to get the desired release profile, and wide regulatory compliance (45, 58). When the hydrophilic polymer is exposed to an aqueous medium, it goes through a hydration process and starts swelling, forming a highly viscous gelatinous surface barrier that is responsible for controlling the liquid penetration into the tablet and the drug release (48, 60). Then the drug molecules pass through the gel layer via diffusion or erosion of the polymer chains causing drug release (42). This system is also known as a swellable controlled release system (45, 54). The most widely used hydrophilic polymers can be seen in Table IV (42, 45, 50).

Table IV. Most used hydrophilic polymers.

Cellulose derivatives	Non-cellulose polymers
Hydroxypropyl methylcellulose (HPMC)	Sodium alginate
Hydroxypropyl cellulose (HPC)	Xanthan gum
Hydroxyethyl cellulose (HEC)	Chitosan
Methylcellulose	Polyethylene oxide
	Carbomers

1.6.3 Biodegradable matrices

This consist of biodegradable polymers, which are composed of monomers linked together through functional groups and have unstable bonds in the backbone chain (56). These polymers degrade because of a natural biological process by the action of enzymes, water, and microorganisms into oligomers and monomers that can be metabolized or eliminated. Proteins and polysaccharides are examples of natural polymers, and aliphatic polyesters is an example of synthetic polymers (47, 56).

1.6 Mathematical models in drug delivery

Mathematical models are used to design a drug delivery system, and to predict or describe the release behavior by analyzing the process of drug release (61). The obtained values from the dissolution test can be interpreted by using an equation that translates mathematically the dissolution curve points into parameters related to the pharmaceutical dosage form (62). There are many models to describe drug release profiles from immediate or modified dosage forms and some of the main and most used models are zero-order, Higuchi, Weibull, and Korsmeyer-Peppas (63).

1.7 Powder flowability

It is essential to investigate the physical and chemical properties of the active substance and the excipients separately and when combined. One of the most important pre-compression parameters to evaluate is the flowability of the material because it results in the pharmaceutical production process. The flow of the powder also affects the product weight and content uniformity, which influences the tablet properties (strength, weight, dosage variations between tablets) and consequently the product quality (44, 64, 65).

Flow behavior depends on several physical properties of the powder (particle shape and size, moisture content, etc.) that explains why it is a complex characteristic (66). It is also considered a multifaceted behavior, therefore, there is no unique test that could quantify powder flow [48]. Good flow properties and accurate assessment of them are essential in any pharmaceutical formulation for tablets or capsules (67). For this reason, it is necessary to improve the flowability of the powder by adding flow activators (glidants), which reduce the adhesion and cohesion properties (68).

2 Experimental part

2.6 Materials

To carry out this laboratory work, several raw materials were used and are indicated in Table V.

Table V. Raw materials used in the project.

Raw materials	Origin	Batch
Paracetamol	Acofarma	170882-P-1
Carnauba wax	Guinama	0061562
Lactose	Acofarma	171322-P-1
Aerosil® 200	Evonik	2020 405

2.6.3 Paracetamol

Paracetamol, also known as acetaminophen or N-acetyl-para-aminophenol (APAP), is an odorless white crystalline solid with a bitter taste, and it is the model drug used in the formulation of the present work. According to BCS, paracetamol is a class III compound, it is sparingly soluble in cold water, more soluble in hot water and alcohol (69). It is an analgesic and antipyretics (commonly used to relieve pain and reduce fever), that is available in many dosage forms, syrup, tablets, effervescent tablets, suppository, and injection (70).

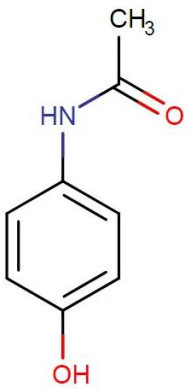


Figure 5. Paracetamol chemical structure.

2.6.4 Carnauba wax

Carnauba wax (CW) has been used as a retardant material for the preparation of the tablets. It is a pale yellow, hard and brittle solid obtained from the leaves of the Brazilian tropical palm tree *Copernicia prunifera*. It is a mixture of several chemical compounds, mainly fatty acid esters (80-85%) such as aliphatic esters, alpha-hydroxy esters, cinnamic aliphatic diesters, and also contains free acids (3-6%), free fatty alcohols (10-16%), hydrocarbons (1-3%), and resins (39, 71). CW is not soluble in water but is partially soluble in boiling ethanol. It has a melting range of 80-86° C (72).

2.6.5 Lactose

Lactose is an odorless white hard crystalline powder with a sweet taste, and it is freely soluble in water (73). It is a disaccharide consisting of one glucose and one galactose moiety, widely used as a filler or binder in the pharmaceutical industry. It is used here as a diluent to adjust the drug release kinetics.

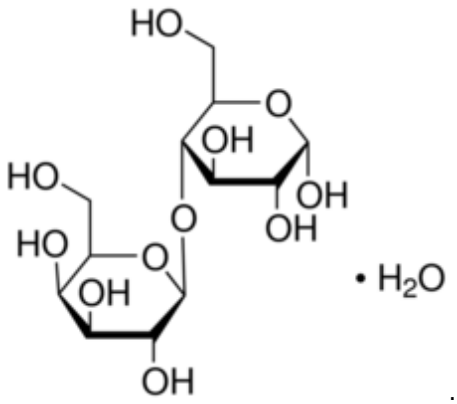


Figure 6. Alpha lactose monohydrate chemical structure.

2.6.6 Colloidal silicon dioxide

Aerosil® 200 is a high purity amorphous anhydrous colloidal silicon dioxide (CSD), which it is a light, loose, bluish-white-colored, odorless, and tasteless powder (73). It is a free flow and anticaking agent that enhances the powder flowability, in addition to improving the tablet hardness and friability (74).

2.7 Methods

2.7.3 Powder preparation

The pulverization of carnauba wax (CW) flakes was made using a mill (ERWEKA, TG2, Germany). Measuring the powder particle size distribution by sieving was performed according to Ph. Eur. (75), using the following series of test sieves (710, 500, 355, 250, 180, 125, 90, and 63 µm, Retsch, Haan, Germany) and a vibratory sieve shaker (Retsch AS 200 digit, Germany) with an amplitude of 2 mm, for 15 minutes with measuring the amounts retained in each sieve every 5 minutes. Followed by fractionating the CW to obtain several fractions to analyze their flowability characteristics.

Due to the small amounts of powder (low percentage) retained in the (63, 90, 125, 180, 250, 355, and 1000 µm) sieves, they were removed to get the CW in just three fractions and sufficient amounts to fulfill all the tests and to study the different flow properties of each fraction. The bulk powder (CW_{Total}) and the CW fractions are described in Table VI.

Table VI. Different fractions of carnauba wax.

Acronym	Definition
CW_{Total}	Bulk powder
CW < 500	Particles smaller than 500 µm
CW > 500	Particles between 500-710 µm
CW > 710	Particles higher than 710 µm

2.7.3.1 Moisture determination

The moisture content of each material, expressed as a percentage, was determined by performing a thermogravimetric analysis using an infrared drying balance (AD-4713, Japan) with a heating cycle of 60°C for CW (because of its melting point 82°C) and 80°C for the other powders. The powder was weighed in a scale plate (about 1.5 g) and it was exposed to an infrared lamp that causes desiccation.

2.7.3.2 Angle of repose

A simple method to determine the powder flowability is to get to know the angle of the free surface of a heap of particulate material poured from a container to a horizontal plane

forming a cone (68, 76) (Figure 7). This angle of repose is a characteristic of the cohesion (internal fraction) of the particles (68, 77). Knowing the value this angle is useful to choose the storage container for powders or to predict the flow behavior of those powders (65, 76) (Table VII). However, it cannot be used to predict how powders will act in a tablet press or within a bin (65). Smaller values of the angle of repose indicate smaller interparticle forces, which will cause an increase in powder flowability and this occurs in powders with large particle size. With smaller particle size comes a larger surface area and a higher degree of contact which causes larger cohesion forces, and the particles adhere to each other reducing their ability of easily flowing (66). The problem with the angle of repose is that its calculation depends on the heap formation, fall height, orifice size which means it is not necessarily constant for a same tested material (76).

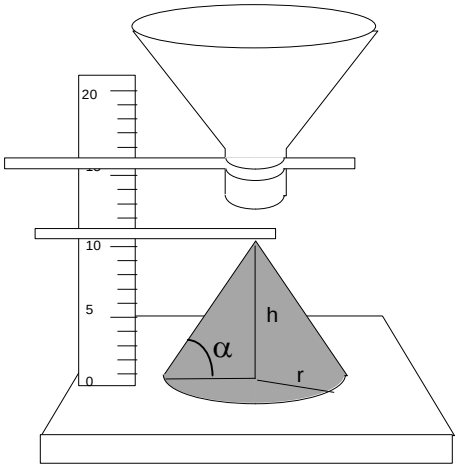


Figure 7. Measuring the angle of repose.

The angle of repose was determined by using a granulate flow tester (GT, Erweka, Germany) and will be expressed by the mean $\pm$ standard deviation. Each powder was drained through a funnel fixed at a predetermined height above a circular plate forming a cone and a laser measures the angle of this cone. The used funnel has three different nozzle diameters: 10 mm, 15 mm, and 25 mm. For this work, the 25 mm orifice was used. Each material was measured three times and the mean value was calculated, then the good or poor flowability characteristics of the powder can be assessed by determining its angle of repose (Table VII).

The angle of repose was calculated using the following equation:

$$\alpha = tan^{-1}\left(\frac{h}{r}\right) \qquad \text{Equation 2}$$

where h is the height of the cone and r is the radius of the cone.

Table VII. Powder flow properties according to the angle of repose (1).

Angle of repose (°)	Flow property
25-30	Excellent
31-35	Good
36-40	Fair (aid not needed)
41-45	Passable (aid might be needed)
46-55	Poor (agitation or vibration needed)
56-65	Very poor
> 66	Very, very poor

2.7.3.3 Bulk and tapped density

The compressibility index (CI) and Hausner ratio (HR) were considered as simple and fast methods to predict powder flow characteristics (78). The compressibility index or Carr's index can be defined as the tendency of a powder to consolidate, this method reflects the importance of the interactions between the particles, which in turn influence the flow of the powder. Their values are used to classify the flowability of powders (79, 80) (Table VIII). In a freely flowing powder, there are few inter-particulate interactions, and the values of bulk and tapped densities are close, which is the opposite in a powder with poor flow characteristics, because of some surface interactions like liquid bridging, van der Waals, and electrostatic forces (81). The HR was reported by Hausner in 1967 as "an indicator of the friction condition between powder particles" (82). HR and CI are closely related because both are determined by measuring the bulk and tapped powder volume (densities) (78, 80).

Tap density tester (Electrolab ETD-1020, India) was used to estimate the bulk and tapped density (Figure 8). For each sample, a specified quantity of powder (between 50 - 250 mL) was poured in a measuring cylinder (250 mL), then the sample mass and initial volume (V0) were determined. Next, the mechanical device repeatedly taps the cylinder in a specified number of taps causing the powder to settle. The taps count was 10, 500, and 1250 taps according to Ph. Eur. 7 (2). The settled volume is compared to the original one, then the untapped (unsettled) apparent volume and the final tapped volume are obtained and used to calculate the HR and CI. The mean value was calculated after measuring each sample in triplicate.

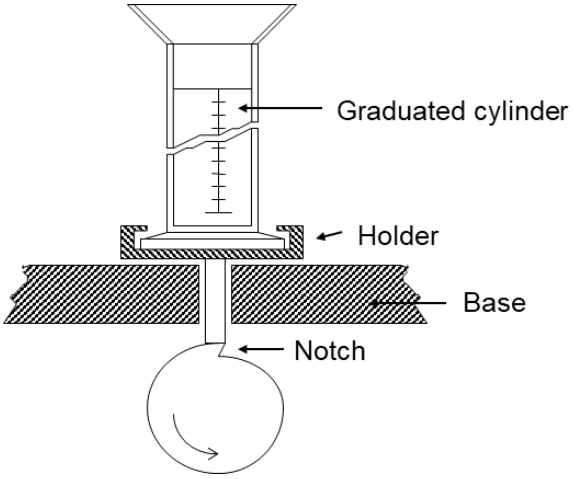


Figure 8. Apparatus for the measurement of bulk and tapped density of powders.

The compressibility index (CI) and the Hausner ratio (HR) were calculated using the following equations (68):

$$\boldsymbol{CI} = \frac{\boldsymbol{V_0 - V_f}}{\boldsymbol{V_0}} \times \mathbf{100} \qquad \textit{Equation 3}$$

$$\boldsymbol{HR} = \frac{V_0}{V_f} \qquad \textit{Equation 4}$$

where V_0 is the untapped (unsettled) apparent volume and V_f is the final tapped volume.

Table VIII. Powder flow properties according to CI and HR (68).

Compressibility index	Type of flow	Hausner ratio
1-10	Excellent	1.00 – 1.11
11-15	Good	1.12 – 1.18
16-20	Fair	1.19 – 1.25
21-25	Passable	1.26 – 1.34
26-31	Poor	1.35 – 1.45
32-37	Very poor	1.46 – 1.59
> 38	Very, very poor	> 1.60

2.7.3.4 Flow properties

Shear cell method allows more accurate and precisely defined evaluation of powder flow properties on a more fundamental basis, providing more reproducible results (78, 80). In this method, the powder flow properties are assessed by *unconfined yield strength or compressive strength* (σ_c) as a function of *consolidation stress* (σ_1) and *storage time* (t) (81, 86). The unconfined yield strength (σ_c) is the vertical stress or pressure that causes the bulk solid to fail or break leading to a point known as “point of incipient flow” which represents the moment when the consolidated bulk solid starts to fail (flow) (86). The consolidation stress (σ_1) represents the forces or stress that has acted on the bulk solid causing or increasing the adhesive forces or the bulk solid strength, also referred to it as “stress history” (86).

The unconfined yield strength is important for studying the flowability because of its relation to the force needed to fracture a consolidated solid bulk to initialize the flow. In other words, the material will flow only if the applied force is higher than its unconfined yield strength (87). A graph of the unconfined yield strength versus consolidation stress “(σ_c, vs σ_1) curves” by measuring the strength bulk solid without the influence of time consolidation (storage time t = 0) is called the flow function (Figure 9), which represents the material's response to pressure and hence it helps in flowability prediction (81, 86, 87). On the other hand, an effect called time consolidation or caking occurs when some bulk solids are stored for long time causing an increase in the strength under compressive stress. In this case, different consolidation stresses σ_1 are used, but for different defined periods (t1, t2, etc.) to get different pairs of values (σ_c vs σ_1). Finally, the σ_c vs σ_1 curves are drawn for storage periods (t > 0) called time flow functions (86) (Figure 9).

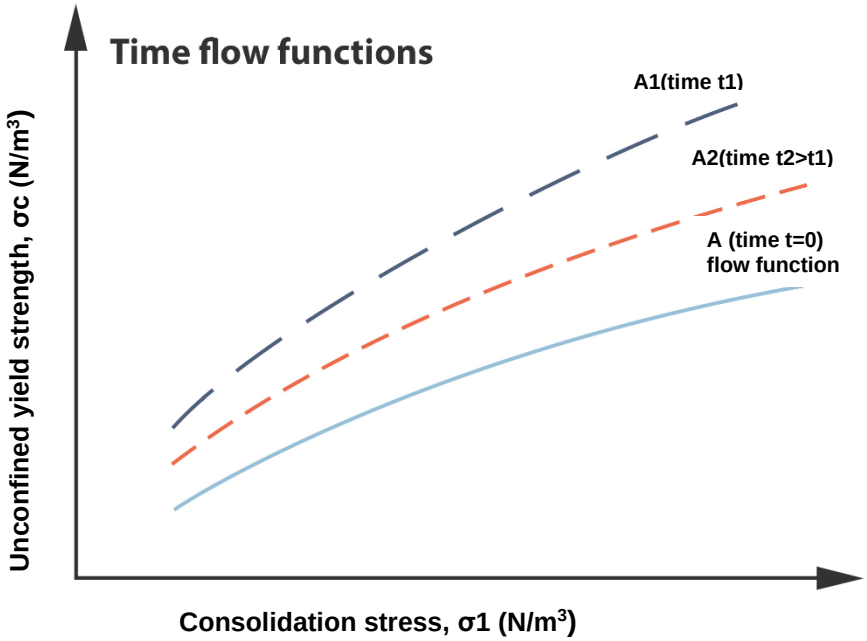


Figure 9. Flow function and time flow functions for different storage times t1 and t2.

In these shear cell tests, the powder was placed in a cylindrical cell and compacted by exerting certain normal stress, σ_1 (Figure 10 a). The mold was then removed, observing a compacted column of powder (Figure 10 b). Finally, the normal stress exerted on the formed powder column was gradually increased until rupture occurred, and the normal stress peak, σ_c, was recorded (Figure 10 c).

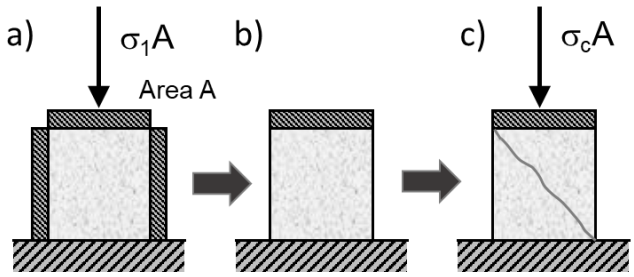


Figure 10. Uniaxial unconfined failure test.

The flow factor (ff_c), which is the numerical characterization of flowability, is calculated by dividing the consolidation stress (σ_1) by the unconfined yield strength (σ_c):

$$ff_c = \frac{\sigma_1}{\sigma_c}$$ *Equation 5*

This flow factor is used to classify the materials in different categories such as non-flowing (ff_c < 1), very cohesive (1 < ff_c < 2), cohesive (2 < ff_c < 4), easy flowing (4 < ff_c < 10) and free flowing (ff_c > 10) (Figure 11).

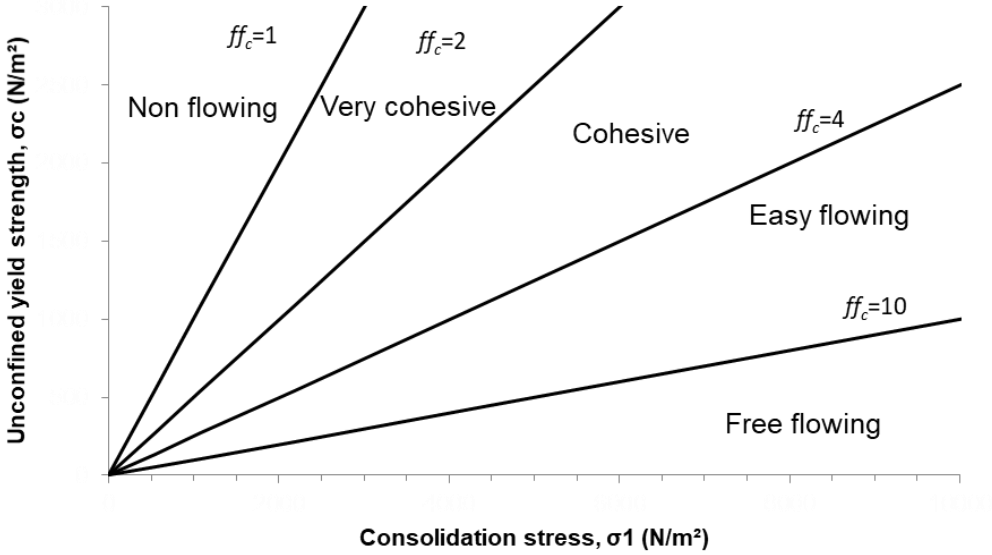


Figure 11. Graphical representation of the flow function.

This method is widely used because it provides a wide variety of parameters such as "yield loci representing the shear stress-shear strain relationship, the angle of internal friction, the unconfined yield strength, the tensile strength, and a variety of derived parameters such as the flow factor and other flowability indices" (78).

The powders flow properties were analyzed using the shear cell equipment (Brookfield Powder Flow Tester (PFT), AMETEK Brookfield, Middleboro, MA) (Figure 12). The machine was linked to a computer and Powder Flow Pro software was used (Figure 13). An annular shear cell (trough) was filled with the powder sample with a defined volume and weight, then the shear cell was fixed in its place. The apparatus drives a compression lid vertically downward into the sample. When it reaches the sample, the shear cell is rotated at a defined speed and the torque resistance of the powder is measured allowing flow characteristic to be determined using several tests. Several powder flow properties could be measured through PFT to classify flowability, such as the unconfined failure strength, time consolidation, the angle of internal friction, the angle of wall friction, and bulk density. These are the most used indicators to relate measurements to flow behavior. In this work the following tests were made:

- Standard Flow Function Test (FF) with a duration of approximately 25 minutes (n = 3), using the vane lid.
- Standard Wall Fraction Test (WF) with a duration of approximately 7 minutes (n = 3), using the wall friction lid.
- Standard Bulk Density Test (BD) with a duration of approximately 2 minutes (n = 3) using the wall friction lid.
- Regarding Time Consolidated Tests, since the standard test would take about 60 hours, it was chosen to use the Quick Time Consolidated Flow Function Test (QC), lasting approximately 12 hours (n =1), using the vane lid.

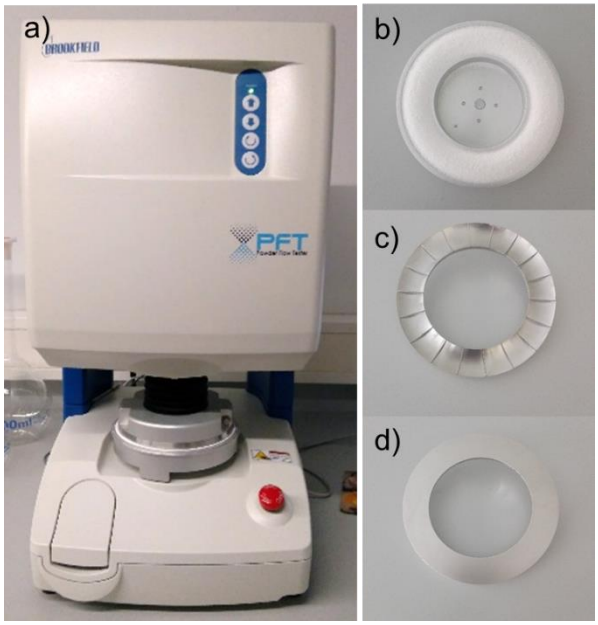


Figure 12. a) Brookfield Powder Flow Tester; b) Powder in the trough c) Vane lid; d) Wall friction lid,

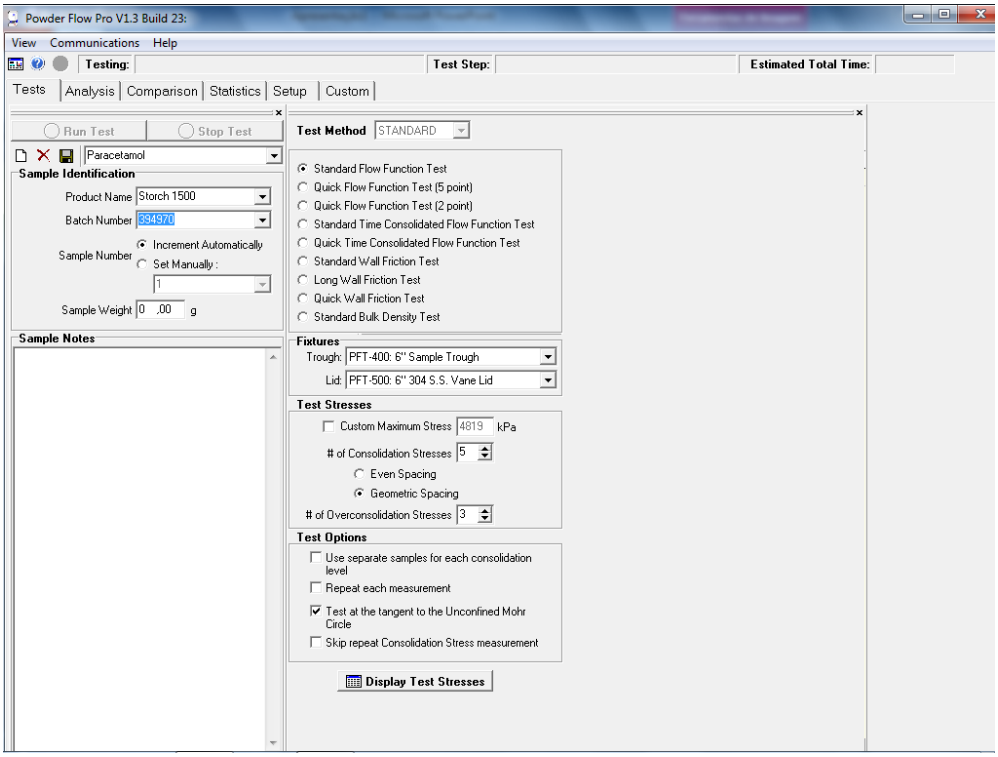


Figure 13. Powder Flow Tester software menu.

2.7.3.5 Particle size analysis

The principle of laser diffraction relies on measuring the angle of diffraction which results from the scattering of laser light by the edges of the particles. The small particles scatter the beam light at higher angles and large particles scatter it at smaller ones. Then the angle of the scattered light is measured via detectors after passing through a focusing lens (84) (Figure 14).

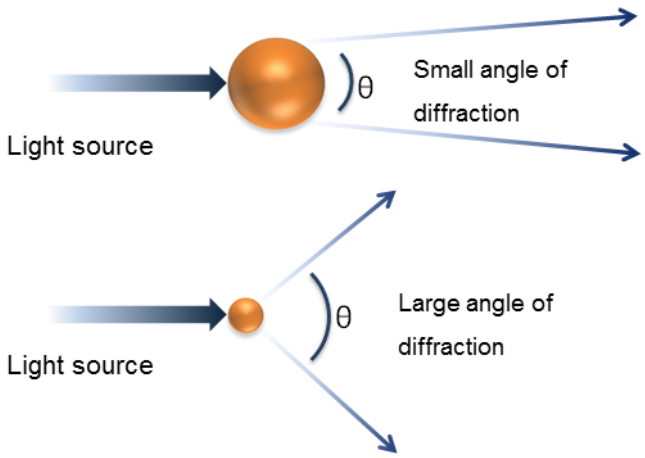


Figure 14. Laser diffraction after incidence in particles of different sizes.

The particle size distribution was measured by the laser diffraction technique using the Mastersizer™ 3000 laser diffractometer (Figure 15) provided with Malvern's Hydro EV dispersion unit (Malvern Instruments, Worcestershire, UK). The operation was carried out at room temperature. The material type was chosen as non-spherical, with refractive index 1.4 for CW, 1.54 for lactose, 1.5 for CSD, and 1.619 for paracetamol. The absorption index was 0.01 for paracetamol and lactose, 0.2 for the wax, and 0.1 for CSD. Water was used as a dispersant with a refractive index of 1.33 (Table IX).

Table IX. refractive indexes and absorption indexes for the used materials

Material	Refractive index	Absorption index
CW	1.4	0.2
Paracetamol	1.619	0.01
Lactose	1.54	0.01
CSD	1.5	0.1

Figure 15. MastersizerTM 3000 laser diffractometer with Hydro EV dispersion unit.

The sample was added to the water until reaching a laser obscuration interval between 5% and 10%. Using the scattering model Mie under the premise of lowest residual and weight residual values, it was possible to determine the particle size distribution based on the equivalent sphere volume. For lactose and paracetamol, saturated solutions of each one were used as dispersant medium, while for the CW, a 1% solution of sodium lauryl sulfate was used as a surfactant to lower the surface tension and reduce the wax agglomerations, which is an obstacle in particle size measuring. Each material was measured in triplicate. Data were collected with Malvern's software (version 3.63, Malvern Instruments, Worcestershire, UK).

The distribution in this apparatus is a volume-weighted distribution, that is the contribution of each particle in the distribution relates to the volume of the particle. The results are reported in percentiles and represented in a volume (%) vs particle size (µm) graph in the three most common percentile values of the volume distribution: Dv10, Dv50, Dv90. These values represent respectively 10%, 50%, 90% of the particles below a specific size value (85).

2.7.4 Tablets preparation

One formulation of matrix tablets was prepared to contain 10% of drug (paracetamol) with different ratios of drug/excipients (CW as a lipid matrix/lactose as a diluent). CSD was used in a small ratio 0.75% of lactose amount, to improve the flowability. The formulation ratios are given in Table X. The formulations were mixed for 15 minutes using the Turbula shaker mixer (WAB, Switzerland), then directly compressed into tablets (400 mg each) using a hydraulic press (P/N 15.011, Specac; Orpington, UK) with 10 tons for 30 seconds.

Table X. Main excipient ratios of the different used formulations

Wax	Paracetamol	Lactose
70 %	10%	20%
60%		30%
50%		40%

2.7.5 Compaction behavior of the final mixture

This study was done through direct compression of the mixture using an instrumented compression machine (DOTT Bonapace, model CPR-6, Italy) (Figure 16) connected to a computer. This instrumentation aims to measure the forces acting on the upper and lower punches during the compression and extraction processes. The *Costal-write* (to record the data), *Costal-read* (to read the recorded data), and FIMA Compression Data Analysis (to analyze the recorded data) software was used.

Figure 16. CPR-6 Automatic tablet press.

The compression chamber volume was maintained constant for all the tablets. While the upper and lower punches displacement was adjusted to get the desired weight and hardness, then were maintained during the whole test. The punches had a plane surface with an 11 mm diameter (Figure 17).

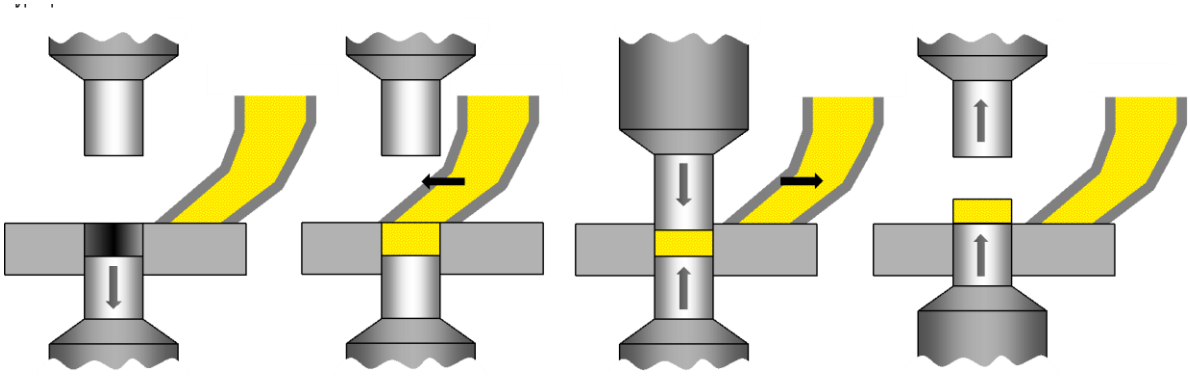


Figure 17. The working mechanism of the tablet press machine.

The compression curves were registered and analyzed with this software, and the used energies and applied forces during the compression, were calculated as well. The measured energies were used to calculate the plasticity index (PI) according to Stamm and Mathis equation, and lubrication coefficient (R) using the following equations (88):

$$PI\ (\%)\ =\ E_{LA}\ /\ E_S \times 100\ =\ (E_S\ -\ E_{EXP})/\ E_S\ x\ 100$$ *Equation 6*

$$R\ =\ F_I\ /F_S$$ *Equation 7*

where (E_S) is the total energy supplied by the upper punch, (E_{EXP}) expansion energy (energy lost in the elastic recovery), (E_{LA}) apparent net energy (the energy effectively needed to obtain a tablet), F_I is the applied force on the lower punch and F_S is the applied force on the upper punch. The parameter R refers to the lubrication capacity of the material and it is usually used to compare lubricants, and its maximum value is 1 (68, 88).

After setting the right adjustments to get tablets with 400 mg and acceptable hardness, 40 tablets of 60% CW were produced to undergo the hardness, friability, weight uniformity, and dissolution tests. Using the same parameters, 40 more tablets were produced, this time using only CW. Hardness, friability, and uniformity of weight were tested and compared with the previous tablets. The compaction behavior was studied for ten tablets from each group.

2.7.5.1 Force-displacement curve

This curve is used to calculate the consumed work in tablet compression and to determine the elastic and plastic behavior of a material (Figure 18). In this curve, the force (N) is presented on the y-axis, displacement (meter) on the x-axis and the area under the curve represents the work done (Joule). Thus, the area ABC represents the used-up work to compress the powder, and area DBC is the work returned to the upper punch by the tablet because of its expansion (elastic recovery). The ABD area, which is the difference between the two previous areas, is named net energy of compression (89).

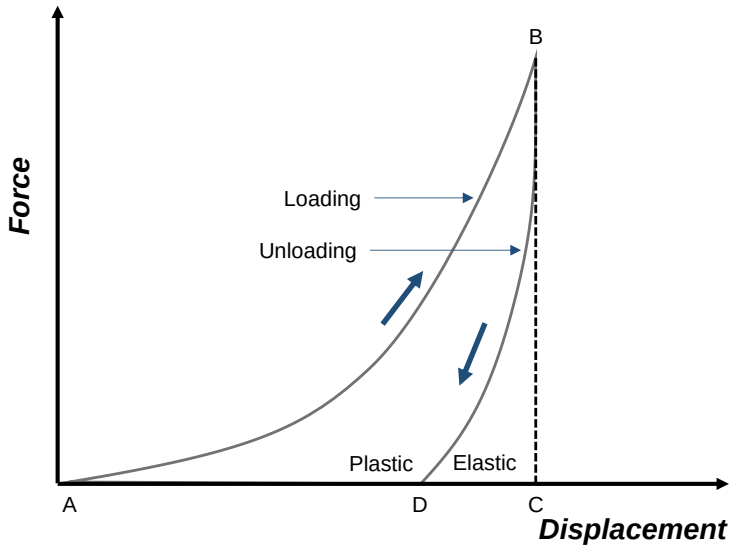


Figure 18. A force-displacement curve.

2.7.6 Matrix tablets characterization

2.7.6.1 Weight uniformity

The weight uniformity should be done by individually weighing 20 tablets and determining the mean weight. The deviation of its weight from the mean weight (as a percentage) should be determined, which should not exceed ±5% for a minimum of 18 tablets or ±10% for a maximum of two tablets (78).

2.7.6.2 Hardness

This test is done by a compression test using a Texture analyzer (TA.XT2*i*) for 10 tablets of each CW/drug ratio. The tablet was placed on a flat surface and a cylinder probe was placed down onto the tablet until it fractured, and the force (N) offered by the tablet was recorded. The probe diameter is 4 mm, the load cell is 30 kg, and the test speed was 1 mm/s. The results were obtained with a special macro, which was specially created for this work.

2.7.6.3 Friability

According to the Portuguese pharmacopeia, if the tablet weight is less than 650 mg, a sample equivalent to 6.5 grams should be taken and analyzed in a Friabilator (Electrolab, India). 16 tables were dedusted, accurately weighed and placed in the drum. The drum rotated 100 times (25 rpm) and then the tablets were removed and cleaned from any dust, then re-weighed, and the friability (F) is calculated in terms of weight loss (%) (Equation 8):

$$F = \frac{(w_1 - w_2)}{w_1} \times 100$$ *Equation 8*

where w_1 is the weight of the initial tablet (before test) and w_2 is the weight of the final tablet (after test). Friability lower than 1% is considered acceptable (68).

2.7.6.4 Thickness

Tablet thickness was measured using a digital micrometer with a sensitivity of 0.001 mm. Tablets' thickness were measured individually in three different points and then the mean was calculated.

2.7.7 Dissolution test

A spectrophotometric method was used to determine the paracetamol percentage released from the tablets. The UV spectrum of paracetamol was measured between 200 - 400 nm to select the optimal wavelengths in a spectrophotometer (Jasco V-650, Japan).

A calibration curve should incorporate five to eight points to cover the entire range of expected concentrations (90, 91). A different concentration series of paracetamol standards was prepared between 8 – 40 mg/L (20 -120%) according to the ICH guideline (92), and then their absorbance was measured three times (n = 3) in the selected wavelengths (217 nm and 243 nm) using quartz cells and water as a blank. A concentration *versus* absorption calibration curve was plotted. An amount equal to the quantities used in the tablet formulas of all different used materials was dissolved or dispersed in 100 mL of water, well stirred, and measured separately. This was done to determine their UV spectrum and analyze their possible interference in the paracetamol assay (specificity).

The dissolution test was done using a dissolution tester (SOTAX AT7, Switzerland) to verify the release of the drug from the CW matrix tablets. The apparatus was set at 37°C±0.5°C and 50 rpm. The test was carried out in 1000 ml of water. With these conditions, six tablets were placed, one in each dissolution cell. Samples of 5 ml were withdrawn in an interval time of 15 minutes for the first one hour, filtered, and analyzed using the same UV/Vis spectrophotometric method.

To explain the drug release mechanism, three models were used, zero-order (Equation 9), Higuchi (Equation 10), and Korsmeyer-Peppas (Equation 11) (62, 93). The in-vitro release data were, fitted to them, and the best model that describes the drug release was selected

based on the best fit expressed by the higher value of the determination coefficient (R^2) or the lower value of the residual sum of squares (RSS).

$$Q = Q_0 + K_0 t \qquad \textit{Equation 9}$$

$$Q = Q_0 + K.\sqrt{t} \qquad \textit{Equation 10}$$

$$Q = Q_0 + K.t^n \qquad \textit{Equation 11}$$

where *Q* is the amount of released drug (%) in time *t, Q_0* is the initial amount of drug(%), *t is* the time (hours), *k* is a constant and *n* is the release exponent.

Results

2.8 Powder characterization

To abide by the criteria described in Ph. Eur. 7.5, the time of 15 min was selected. The powder weights that retained in each sieve, expressed in percentage are shown in Figure 19. The results showed that the fraction with the highest amount of powder (%) was the CW > 710 (35%), followed by CW < 500 (32%).

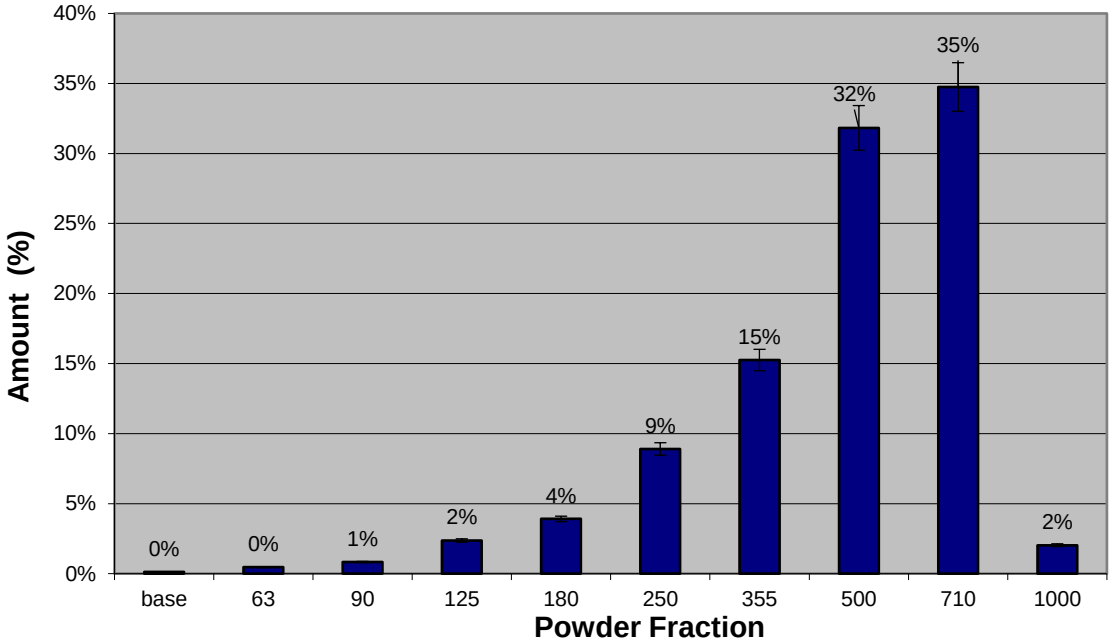


Figure 19. Weight (%) of different fractions.

2.8.3 Particle size analysis

The particle size distribution of the CW is shown in Figure 20 (a). The CW_{Total} had the widest size distribution, followed by CW < 500, while CW > 710 and CW > 500 had a narrower size distribution. The largest average size corresponded to CW > 710. As it is shown, the CW_{Total}, CW > 500 and CW > 710 have some particles larger than the upper limit of the particle size analyzer (0.01-3500 μm), wherefore they cannot be analyzed. The CW_{Total} incorporates almost all size classes of the fractions, but not the smallest and the largest particles due to their small amounts. In Figure 21 (a, b), also an overlapping between the size fractions can be noticed which is in concordance with bibliography (81).

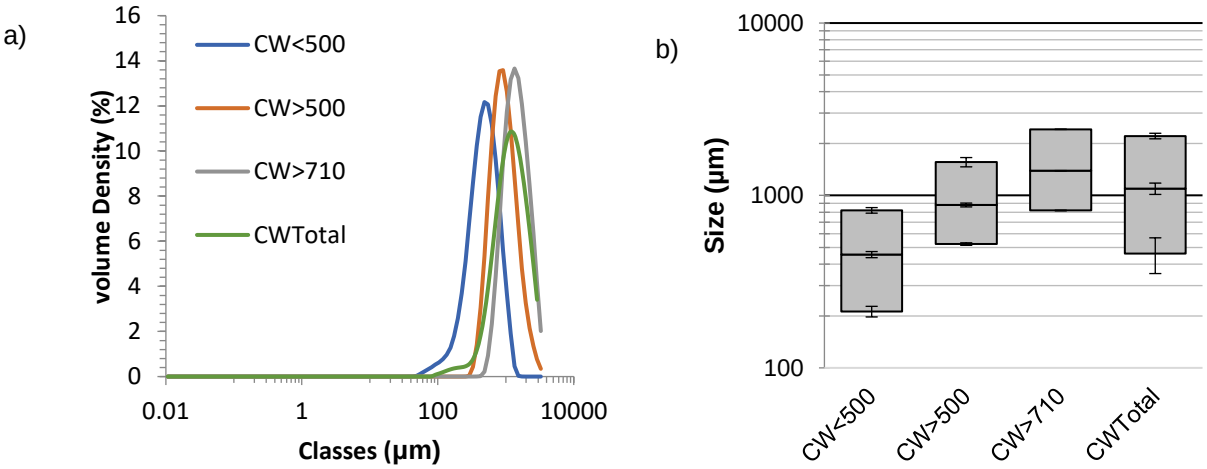


Figure 20. Particle size distributions for different fractions of CW: (a) volume density vs size classes and (b) size vs powder fractions (the three lines of the rectangles represent Dv90, Dv50, and Dv10, respectively from top to bottom).

Figure 21 shows the comparison of the particle size distribution for lactose, paracetamol, and CSD. Paracetamol had the widest size distribution after CW, CSD had the smallest average size, while paracetamol had the largest average size. Figure 21 (b) shows that there is no overlapping between CW and the other powders, which reflects the big difference in particle size between them. On the other hand, it can be seen the size convergence between lactose and paracetamol.

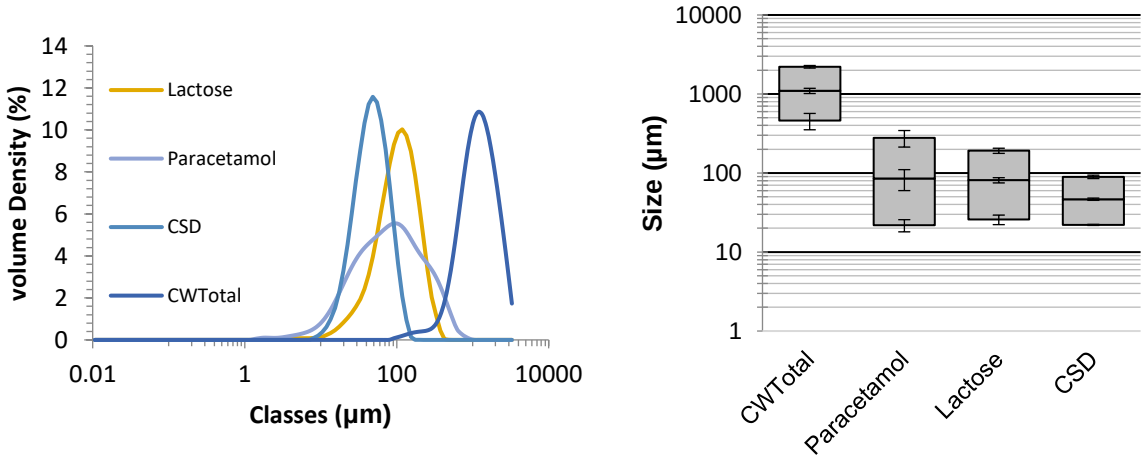


Figure 21. Particle size distributions: (a) volume density vs size classes and (b) size vs powder fractions (the three lines of the rectangles represent Dv90, Dv50, and Dv10, respectively from top to bottom).

2.8.4 Angle of repose

The values of this parameter for all the powders and each fraction are shown in Figure 22. The results showed the effect of particle shape and size on the flow behavior of different powders and fractions. Many factors, such as bulk density, moisture content, angle of internal friction (cohesive forces between particles), and angle of wall friction (particles sliding along a surface) can affect this test (81). The values obtained in this test were excellent for CW >710 (26.6 ± 0.3) and very, very poor for lactose (56.17 ± 2.1). For the other powders, the results were fair (35.7 ± 4.2) for CW_{Total} and very poor for paracetamol (53.06 ± 1.3), the opposite for all samples of CW, which flowed easily. After adding CSD to lactose, its flow behavior was better with a smaller angle of repose (39.9 ± 3) which corresponds to fair flow.

For the different fractions, we can see that the CW < 500 has a big angle of repose (41.2 ± 0.5) that corresponds to passable flow property, while CW > 500 has a very good flowability (29.2 ± 1.1), and as mentioned before CW > 710 has the best flowability (excellent flow property) with the smallest angle of repose (26.6 ± 0.3). CW_{Total} has good flow behavior with angle value (31.4 ± 1.1). The CW > 710 has a better flow than CW_{Total} , which probably happens because the smaller particles canceled the larger particles effect (adhesion of the particles with a smaller size to the surface of larger particles) (94).

Figure 22 demonstrates the flow capacity of the samples through the results obtained from the angle of repose test. CW total and in separated fractions flowed without any intervention, while for lactose and paracetamol, the use of a spatula was needed to force the powder to flow. This graph shows that the smaller the particle size of the powder, the more cohesive forces it has, leading to a reduced flowability. In other words, larger particle size (smaller surface area) increases the powder flowability and vice versa, (high surface area provides more cohesive and adhesive forces leading to poor flowability). Based on these results, it can be said that the angle of repose is inversely related to the particle size of the powder.

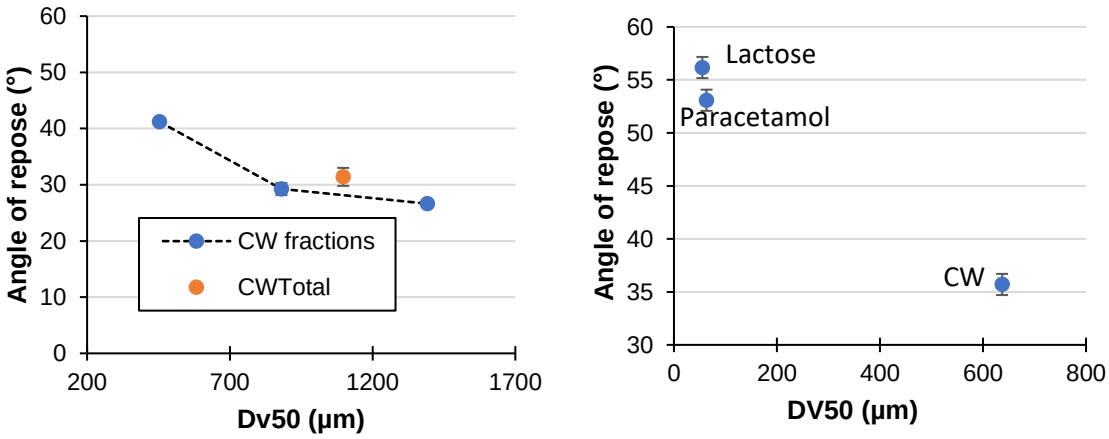


Figure 22. Angle of repose for each material versus Dv50.

2.8.5 Bulk and tapped densities

The bulk and tapped densities of the conventional method were used to calculate CI and HR parameters using Equations (3, 4). Paracetamol had the highest CI value = 42.44, which corresponds to very poor flowability, while CI values for CW > 710 and CW > 500 were 8.10 and 9.89 respectively, which corresponds to excellent flow characteristics. Followed by CW_{Total} with CI = 13 which matches good flow, and finally the 31.07 value for CW < 500 which corresponds to poor flow. Decreasing the particle size caused reduction in powder flowability and increase in CI value, this happens due to the larger surface area of the smaller particles. The HR values also showed that a larger surface area worsens the powder flowability, as paracetamol and lactose showed very poor flow behavior, their HR was 1.74, and 1.49, respectively. CW < 500 also had poor flow behavior with HR = 1.45. CW > 500 and CW > 710 had HR 1.10 and 1.08, respectively. And for CW_{Total} the HR value was 1.14 which represents good flow.

CI and HR values for lactose were calculated before and after adding CSD. Lactose showed high CI and HR values (39.50, and 1.49 respectively), which corresponds to a very poor flow character. Lower values appeared after adding CSD (30.38 and 1.44) for CI and HR, respectively, which means better flow characteristics.

The same parameters (CI and HR) were calculated using the results obtained from (FF and BD tests) of the PFT and then were compared to the ones from the conventional (Conv) method (Figure 21). From the results, the CI of the conventional method, and BD and FF tests showed similar values for CW (13.01 for Conv, 6.58 for BD, and 10.28 for FF) and were all in the range of excellent to good flowability. For lactose (39.5 for Conv, 45 for BD, and 40.20 for FF) also all the three values correspond to extremely poor flowability. The CSD role in improving lactose flowability was clearer in the values obtained by BD and FF tests than in the

conventional method (30.38 for Conv, 17.37 for BD, and 22.82 for FF). So according to these CI values, a mixture of lactose with CSD has fair flow behavior. However, for paracetamol, there was a significant difference in the CI result of the BD test (42.44 for Conv, 31.77 for BD, and 43.43 for FF) (Figure 23 (a)).

HR values for CW were approximately similar in the three methods reflecting its good flow properties (1.14 for Conv, 1.07 for BD, and 1.11 for FF). The same results were obtained for paracetamol, which showed close values in the three different methods (1.7 for Conv, 1.5 for BD, and 1.67 for FF). For lactose, there was a slight difference in BD result (1.5 for Conv, 2.75 for BD, and 1.7 for FF). For lactose and CSD mixture, (1.44 for Conv, 1.21 for BD, and 1.29 for FF), the effect of CSD on lactose flowability was not very clear in the conventional method value, this comparison can be seen in Figure 21 (a).

The same tests were carried out on the different fractions of CW with close results except for the smallest fractions < 500, where the HR values showed poor flow for Conv (1.45) and excellent flow for BD (1.08) and good flow for FF (1.14). Also, its CI values were uneven, it showed (31.07) for Conv which refers to poor flowability, (7.68) for BD which corresponds to excellent flowability and showed good flowability for FF (12.1). The other two fractions showed relatively close results, CW > 500 had CI (9.90 for Conv, 6.38 for BD, and 9.32 for FF) and its HR values (1.1 for Conv, 1.07 for BD, and 1.1 for FF). CW > 710 had CI (8.11 for Conv, 7.63 for BD, and 9.74 for FF) and HR values (1.08 for Conv, 1.08 for BD, and 1.11 for FF). The comparison of those values can be seen in Figure 23 (b).

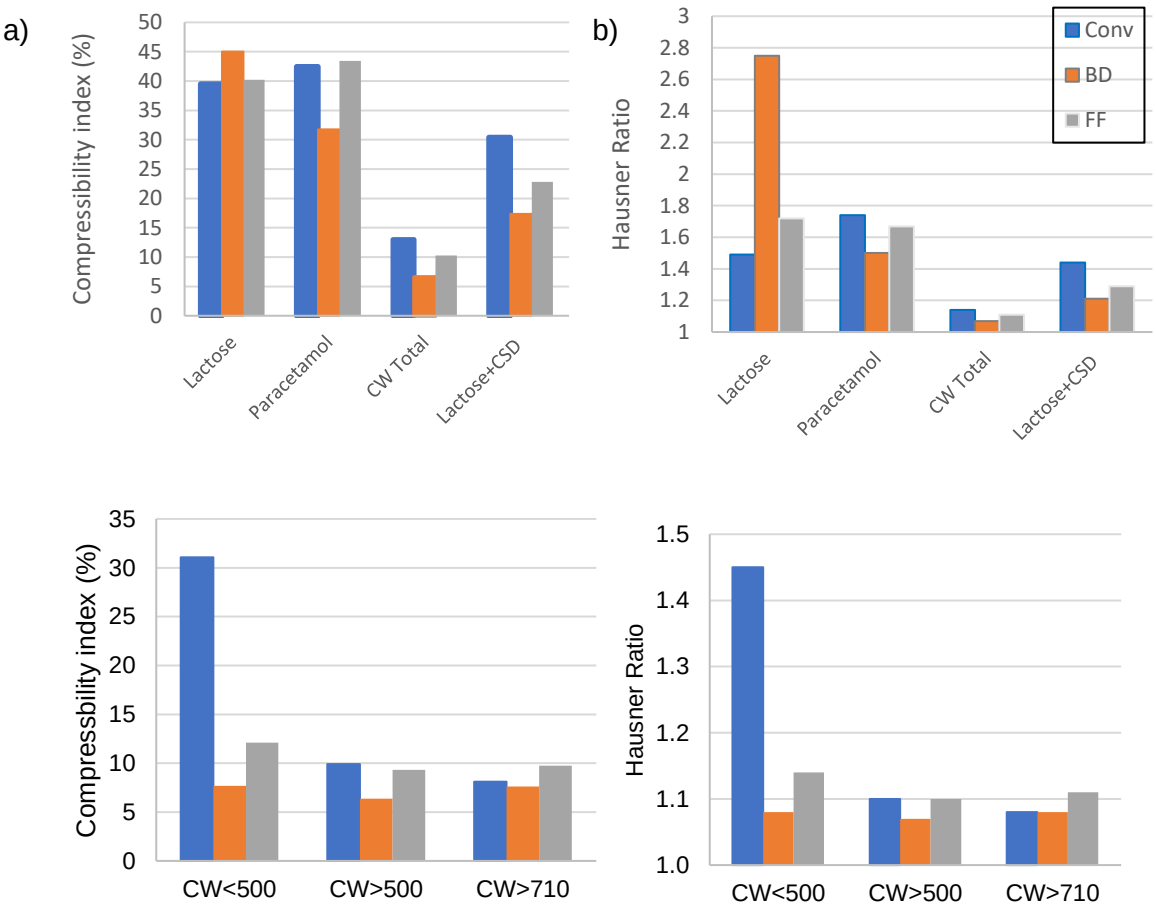


Figure 23. Comparison of Compressibility Index (a) and Hausner Ratio (b) for the different powders (top) and different fractions (bottom) using different methods.

It is also possible to display the bulk density results as a bulk density curve (Figure 24), which allows comparing the powders flow properties. Generally, free-flowing materials show a small increase in density with stress increasing, while the poorly flow materials show a large increase. From Figure 24 it is possible to see that CW is an incompressible material that showed a very small increase in density with stress, while lactose is a compressible material and showed a large increase in bulk density with increasing stress and paracetamol is also a compressible material, for the same reasons.

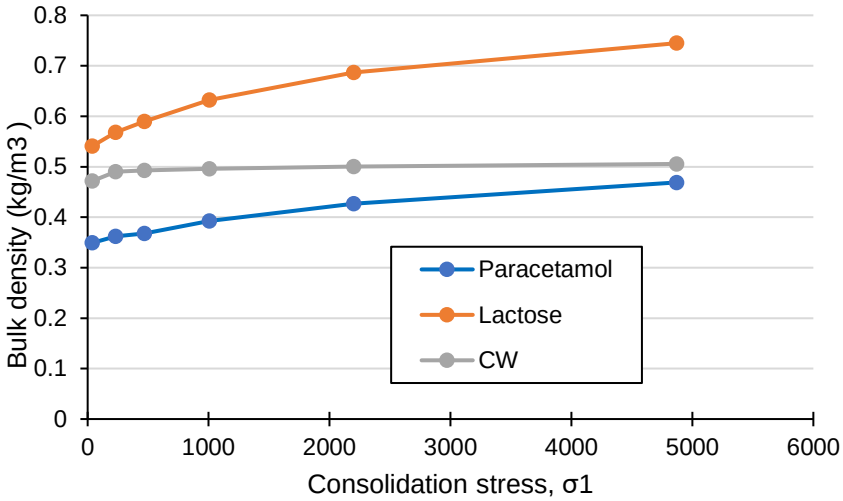


Figure 24. Bulk density curves.

2.8.6 Moisture content

The different powders presented moisture content between 0.23 and 0.33% (Table X). CW had the highest value (0.33 ± 0.08%), then paracetamol (0.30 ± 0.05%) and the lowest water content was for lactose (0.23 ± 0.02%). The different fractions of CW showed water content between 0.33% and 0.66% (Table XI). CW < 500 was the fraction with highest moisture content (0.56 ± 0.02%), most likely due to its larger surface area. On the other hand, CW > 710 was the fraction with the lowest moisture value (0.33 ± 0.01%), while the fraction in the middle (500 - 710) showed moisture content close to the average of the results (0.41 ± 0.01%). The moisture affects the flowability, but its effect is related to the amount of moisture (95). According to a study done on lactose, water content less than 3% does not show considerable changes in its flow behavior (96). In another study on paracetamol, the moisture will not affect its flowability until it is up to 6% (97). For CW, the finest particles have the highest moisture content (0.66%), and the largest particles have the lowest moisture content (0.33%).

Table XI. Moisture content of the different powders and different CW fractions.

Powders	***Moisture (%)***	
	Mean	**Standard deviation**
Paracetamol	0.30	0.06
Lactose	0.23	0.02
CW $_{Total}$	0.33	0.09
CW < 500	0.66	0.02
CW > 500	0.41	0.01
CW > 710	0.33	0.01

2.8.7 Flow properties

2.8.7.1 Instantaneous flow function

The σ_c *vs* σ_1 graph from the Flow Function test (FF), showed that the unconfined yield strength (σ_c) increased as the consolidation stress ($\sigma_{1)}$ increased (Figure 25). The figure shows a comparison in flowability of CW before dividing it into three groups according to the particle size, and the flowability of each fraction using the flow factor index, ff_c. It can be noticed that the CW_{Total} (total fractions) provides better flowability than the flowability of each CW fraction separately. It is possible to be noticed that all the fractions have the same profile in region $4 < ff_c < 10$ which refers to an easy flowing behavior. Their profiles are similar while the CW_{Total} is nearer $ff_c = 10$ which means better flow property.

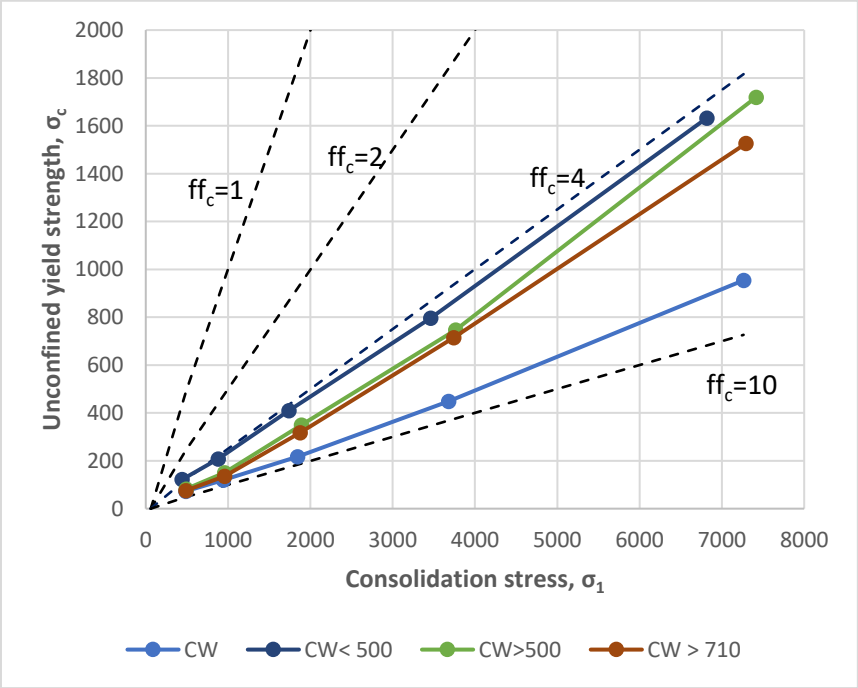


Figure 25. Instantaneous flow function for different carnauba wax fractions.

Figure 26 is a comparison of the flowability of all used powders. Lactose and paracetamol have the same flow properties and their profiles start in region 1 < ffc < 2 which correlates with a very cohesive behavior. However, with the σ1 increases (> 9482 N/m2) these curves passed to the 2 < ffc < 4 region which correlates with a cohesive flowing behavior. Adding CSD to the lactose as a glidant significantly improves the flowability of lactose. The lactose + CSD profile starts in the region of cohesive flowing behavior and then for higher than σ1 > 4628 N/m2, this profile passes to the region 4 < ffc < 10 that corresponds to an easy flowing behavior. As mentioned before, CW Total profile is in the region 4 < ffc < 10 referring

to an easy flowing behavior, and nearer to the boundary ffc = 10 which means better flowability.

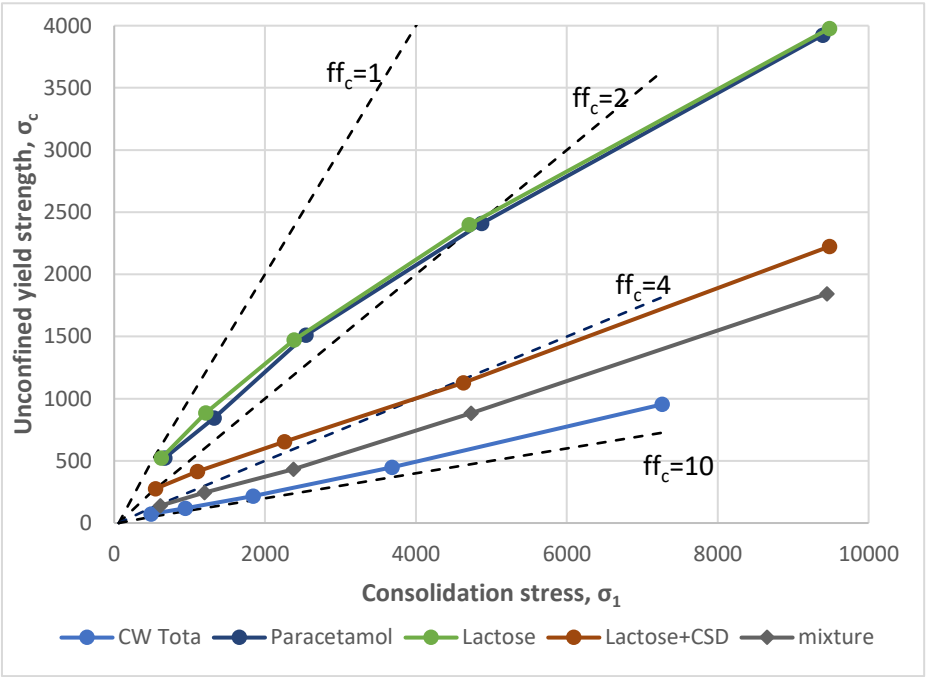


Figure 26. Instantaneous flow function of main raw materials.

2.8.7.2 Time consolidation flow function test

This test is like a flow function test, but gives results based on time consolidation flow function, meaning it is used to investigate if the powder gains strength during long time storage under different stresses. From the graphs, it is possible to say that CW fractions (CW < 500 and CW > 500) (Figure 27) and paracetamol (Figure 28) profiles for the CFF test are almost identical to the FF test profiles, meaning they were not affected by time consolidation. In other words, storing those materials in large amounts for a long time will not affect their flow properties.

That was not the same with the other CW fractions, where CW $_{Total}$ and CW > 710 (Figure 27) in addition to lactose (Figure 28), showed that storing them for a long time would affect their flow behavior. However, lactose with CSD will maintain the same flow behavior regardless of the storing period (Figure 28).

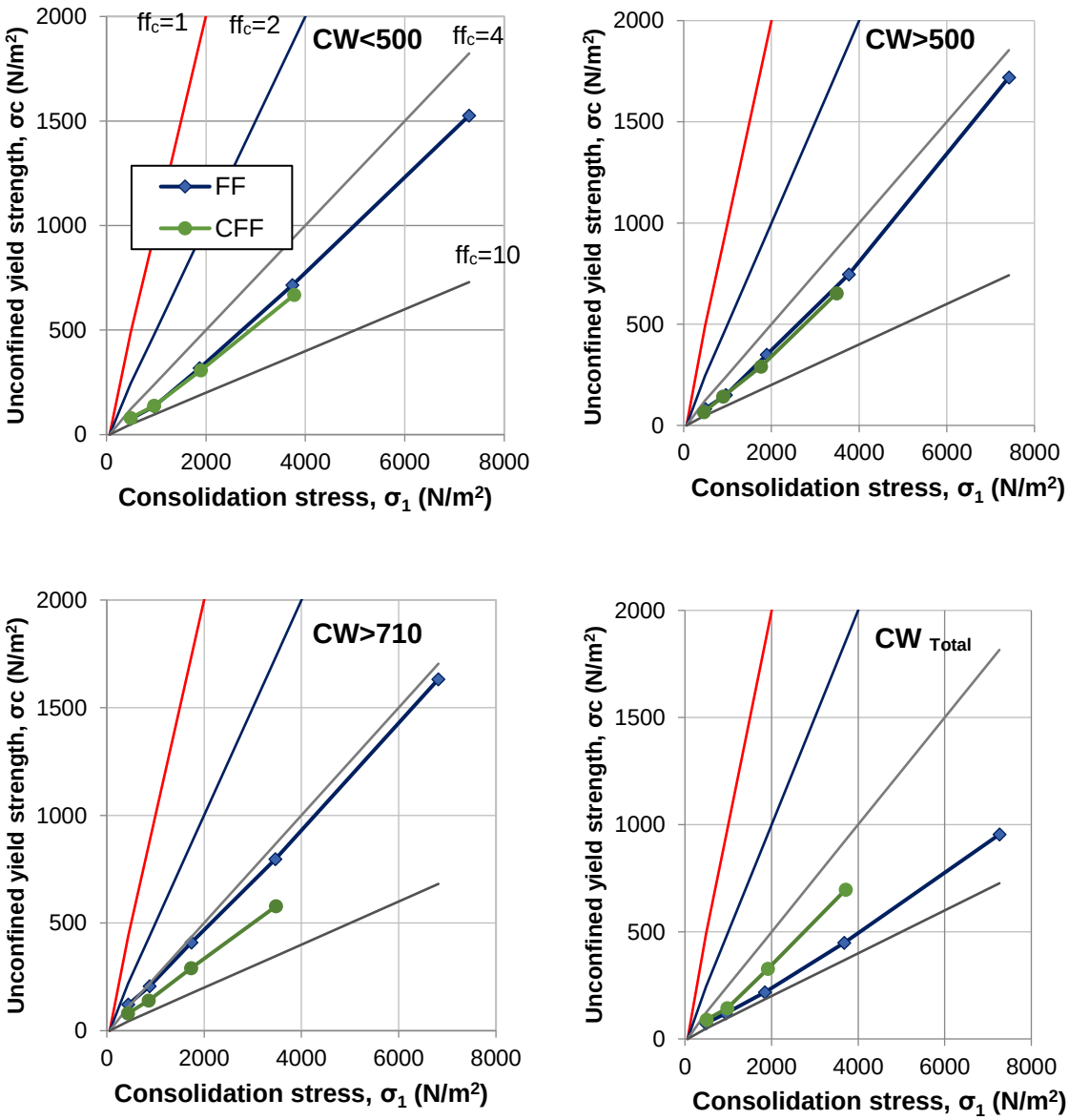


Figure 27. Influence of time consolidation on ff $_c$ of CW powders.

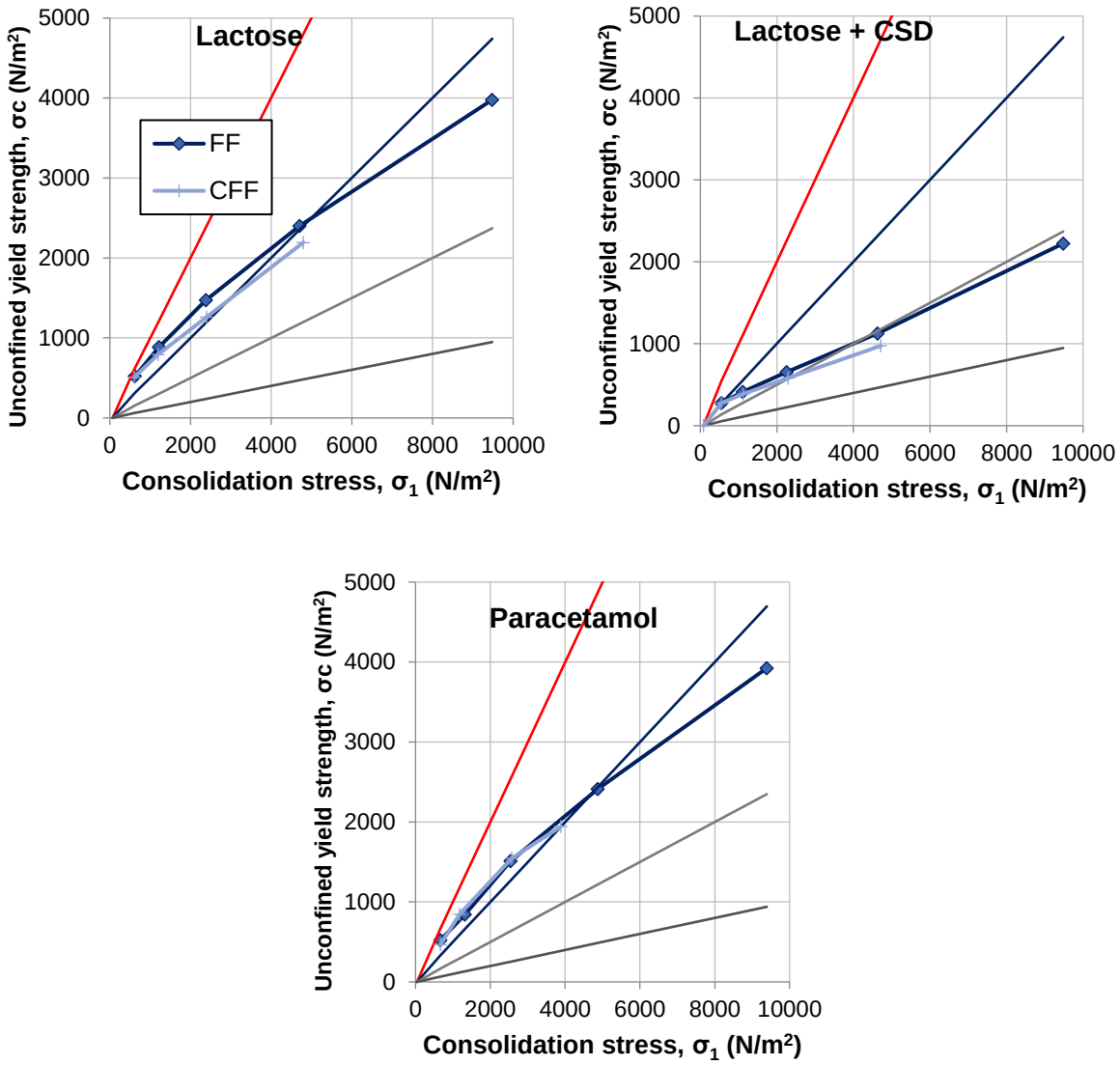


Figure 28. Influence of time consolidation on ff $_c$ of lactose (with and without CSD) and paracetamol.

2.8.7.3 Effective angle of internal friction and effective angle of wall friction

The effective angle of internal friction *(φe)* refers to the movement of the particles against each other. While the wall friction angle *(φx)* represents the adhesive strength or the external friction of the powder (between the powder and the hopper wall) (98). The angle of wall friction is affected by normal stress (σ_w). In all the powders, with increasing normal stress, the angle of wall friction decreases (Figure 29). The effective angle of internal friction is measured through the consolidation stress (σ_1). Like the angle of wall friction, the angle of internal friction decreases by increasing the consolidation stress (Figure 30).

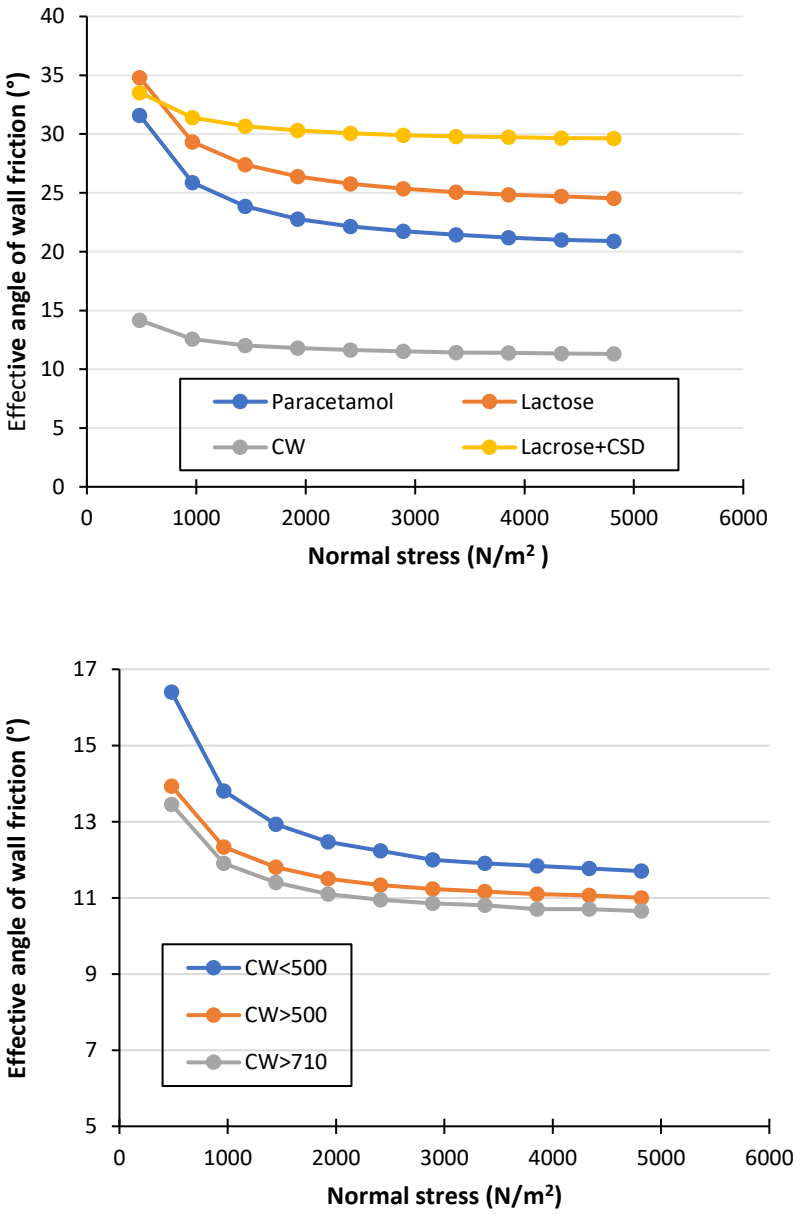
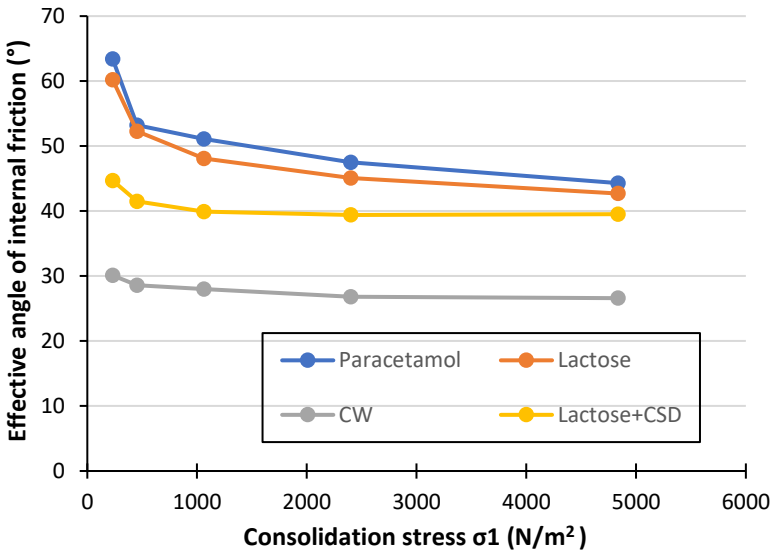


Figure 29. Effective angle of wall friction.



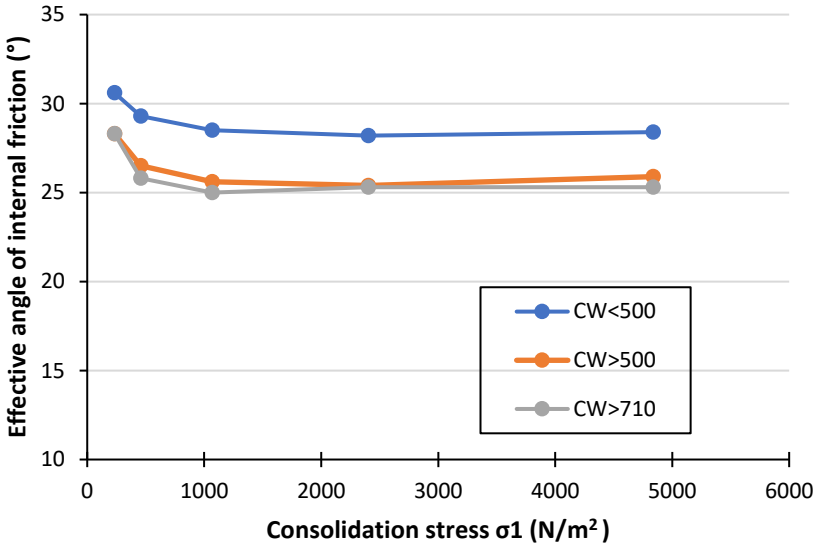


Figure 30. Effective angle of internal friction.

2.8.8 Friability test

This test was carried out for the three different CW/drug ratio tablets, and the weight loss was calculated. The friability values for all the formulations were above the official limit of not more than 1% (Table XI). Different concentrations of CW did not have a big impact on tablets' friability, this show that there is no relationship between the CW concentration in the formulation and the friability.

Table XII. Friability (%) for the different CW formulations.

CW (%)	Friability (%)
50 %	1.83%
60%	1.76%
70%	2.10%

2.8.9 Hardness test

As can be seen in Figure 31 there were no significant differences between the hardness of the three formulations (one-way ANOVA; p-value = 0.729). Using the mean values of the measured hardness, 50% and 60% CW tablets showed similar hardness values of 76.59 N, and tablets with 70% CW showed a slightly higher value of 79.69 N. According to these results, it is noticeable that the ratio of CW/drug did not have a significant effect on the tablet hardness.

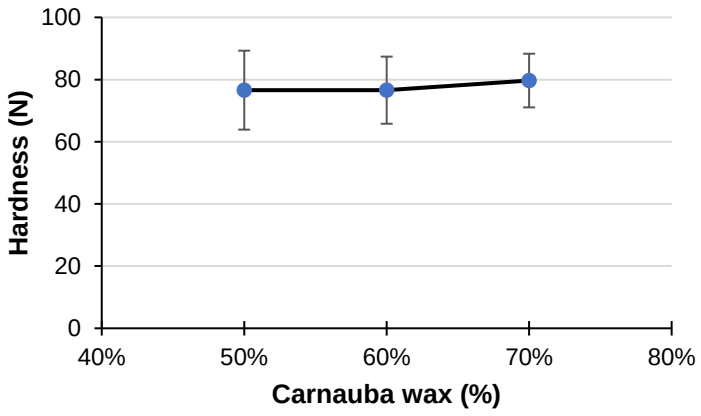


Figure 31. The hardness of the different CW formulations.

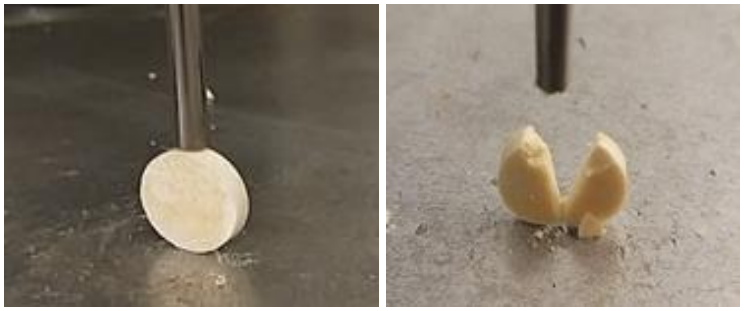


Figure 32. Hardness test using a Texture Analyzer.

2.8.10 Tablet thickness

Different CW/drug ratios gave different thicknesses. A higher percentage of CW provided thicker tablets (Figure 33). In the graph, the tablets' thickness and percentage of CW vary in a correlated way, that is why it is possible to use this graph to predict the tablet thickness for different CW proportions.

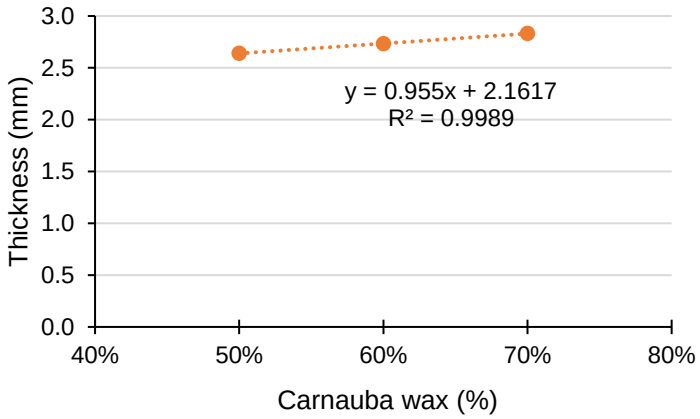


Figure 33. The thickness of tablets according to CW amount.

2.8.11 Dissolution test

A series of paracetamol solutions of known concentrations were prepared and a calibration curve of six points was obtained with a concentration range from 20% to 120%. The absorbance was measured using the spectrophotometer at a wavelength of 243 nm.

The drug response was linear with a regression equation y = 0.6217x + 0.0367 and a determination coefficient (R^2) of 0.9957. The correlation coefficient (R) was 0.9979, which indicates a good linear relationship (Figure 34 (a)). A concentration vs deviations plot is another graph that can be used to assess the linearity (Figure 34 (b)) and the good linearity of the method was confirmed by the random dispersion of the points in the residual plot.

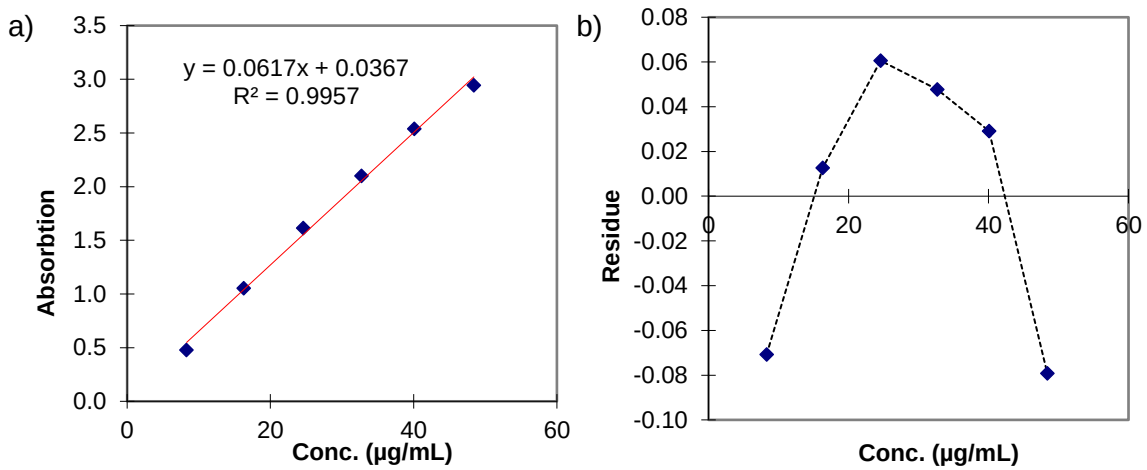


Figure 34. a) Abs versus concentration curve; b) Residuals curve.

To validate the specificity of the method, a solution of each excipient was scanned separately, to avoid any interference with paracetamol. Lactose (20mg/100ml), carnauba wax (16 mg/100ml), CSD (0.2 mg/100ml) and paracetamol (4 mg/100ml) solutions were prepared. Then their absorptions were measured on the same wavelength where paracetamol shows its optimal absorption. As it is presented in Figure 35, the only peak was for paracetamol, which gave the method a high specificity.

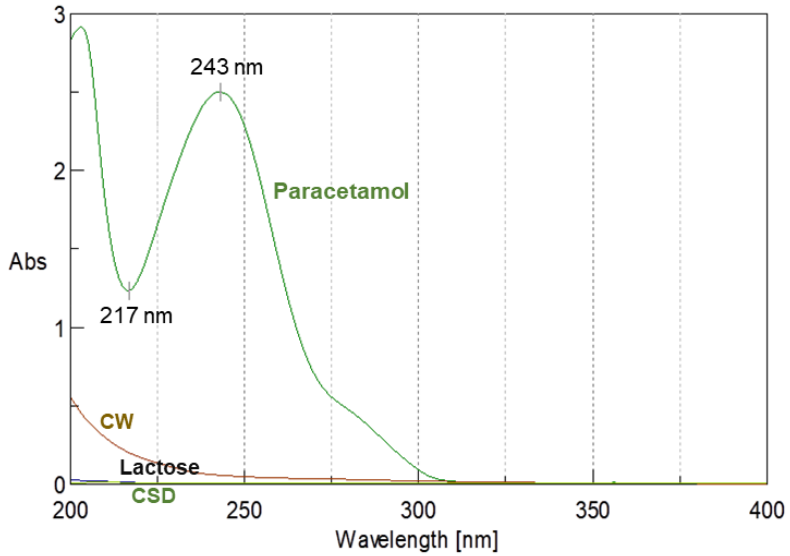


Figure 35. The absorption spectrum of paracetamol, carnauba wax, lactose, and CSD.

The dissolution study was done at 243 nm, where there was no interference from the other matrix materials. Six tablets of each CW /drug ratio 50, 60, and 70% (Table IX), were prepared and placed in the dissolution vessels that contained the dissolution medium (water at 37 °C, as referred). To detect the amount of drug in the medium, 5 mL samples were

collected, during specific time intervals, filtered, and measured to detect the paracetamol concentration using the UV spectrophotometric method.

The dissolved percentage vs. time curve showed a quantitative determination of released paracetamol at a specific time. From the dissolution profile for six tablets of 50% CW, the 100% of paracetamol was reached after 5 to 6 h. For tablets with 60% wax, the release was more prolonged, and the tablets needed 8 h to release the 100%. Tablets with 70% wax gave higher retention and prolonged the release for the longest period showing that after 11 h only 77% of paracetamol was released (Figure 36).

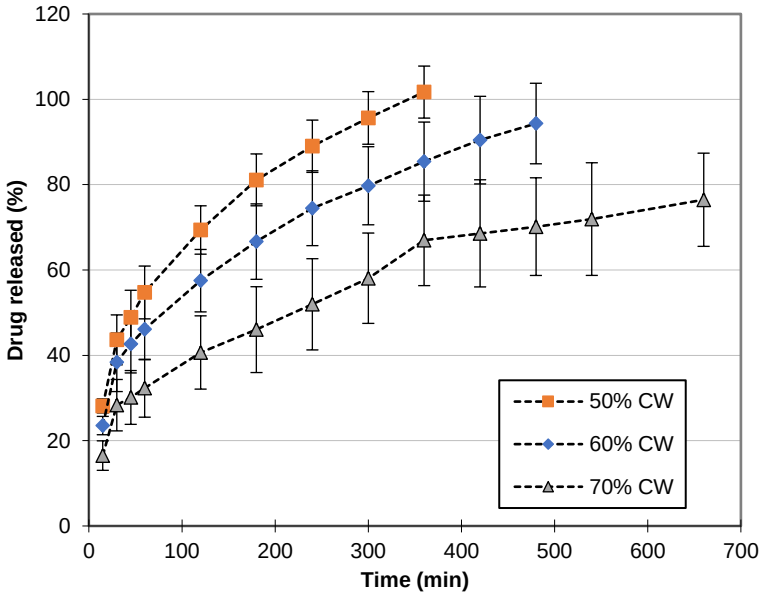


Figure 36. Dissolution profile for 50%, 60% and 70% CW tablets.

2.9 Final mixture characterization

After carrying out the previous tests, the CW/drug ratio with 60% CW was chosen to prepare the final tablets. Because of that, a 300 g of the mixture (60% CW, 10% paracetamol, 30% lactose) was prepared and underwent the flowability testes again. Then a larger number of tablets were prepared using an instrumented compression machine (circa 40) which allowed studying the forces that were involved in the compaction process (99).

2.9.3 Angle of repose

The mixture showed a mean angle of repose of (39.6 ± 1.2°) that corresponds to passable flow property. Since CW constitutes the highest proportion, so it is more likely to get

this angle because of the small influence of the other powders on it. A mathematical calculation for a predicted angle of repose of the mixture was done two times, with and without CSD. Excluded CSD showed a very close value to the experimental one (40.9°). However, doing the math with CSD included showed a very different value (36.1°). There is a type of interaction between the particles, but it is out of the scope of this work.

2.9.4 Tapped and bulk densities

CI and HR of the mixture were also calculated using three different tests. CI values were (Conv 14.9, BD 9.3, and FF 15.6), and HR values (Conv 1.12. BD 1.1 and FF1.12). The CI and HR values of the mixture refer to good powder flowability. These values are close to the ones of CW total (13.01 for Conv, 6.58 for BD, and 10.28 for FF) with the same flow behavior.

2.9.5 Flow properties

By undergoing the Flow Function test using the PFT, the *ff c* was calculated and placed on the σ_c *vs*. σ_1 diagram (Figure 37). Its profile was in region $4 < ff_c < 10$ which corresponds to an easy flowing behavior.

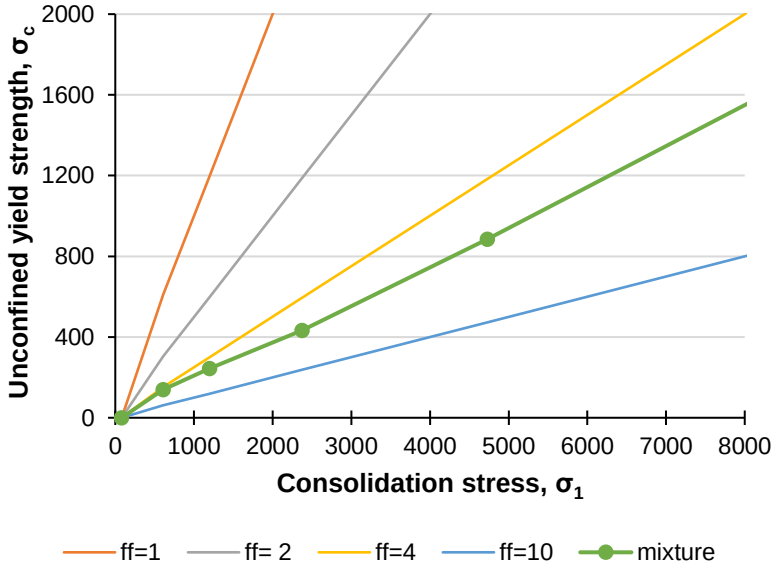


Figure 37. Flow function of the chosen mixture.

The mixture also underwent the wall friction test, and its effective angle of wall friction was calculated and plotted in a graph to compare with the other component. The mixture behavior under normal stress was very similar to the one of paracetamol (Figure 38).

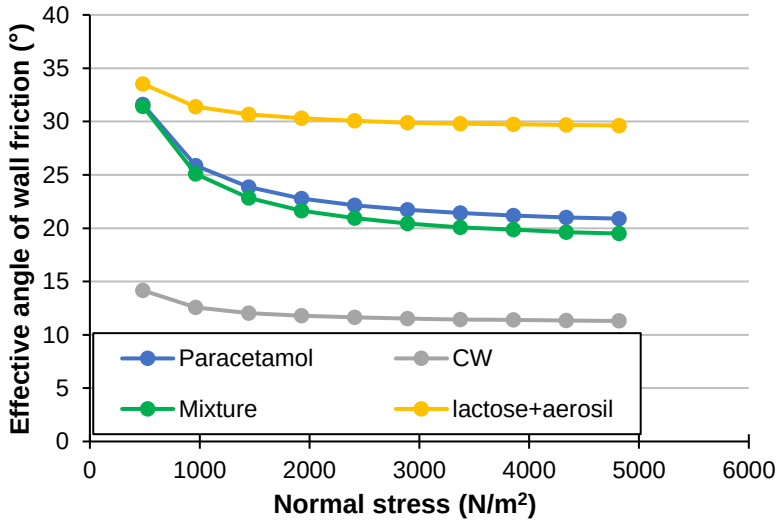


Figure 38. Effective angle of wall friction of the mixture compared to the initial materials.

From the flow function test of the mixture, its effective angle of internal friction was calculated and plotted in a graph to compare with the other components. It can be seen a decrease as the consolidation stress increases in almost the same behavior of lactose + CSD mixture (Figure 39).

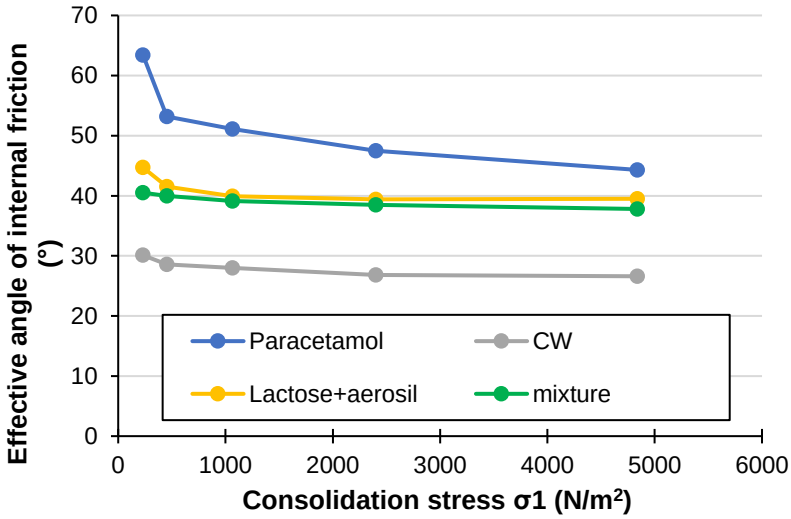


Figure 39. Effective angle of internal friction of the mixture compared to the initial materials

To determine the compressibility behavior of the mixture, the bulk density test was made. The mixture showed a very small increase in density, so it can be considered incompressible (Figure 40).

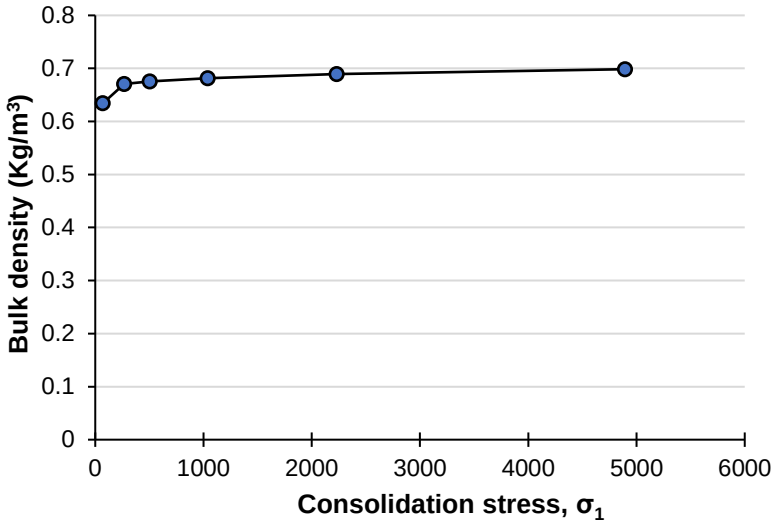


Figure 40. Bulk density curve of the used mixture.

2.9.6 Tensile strength

The produced tablets should be strong enough to handle further procedures such as packing and transport. The hardness test is a way to measure the strength of the compact. However, this test does not consider neither the dimension nor shape of the tablets. Tensile strength is a mathematical way to check if the tablet is strong enough considering tablet dimensions (100). It can be defined as the maximum stress a material can withstand before breaking (89). Tensile strength (TS) was calculated using Equation 12 (88):

$$TS = 2P / \pi DT \qquad \textit{Equation 12}$$

where P is the hardness (N), D is the diameter (mm), and T is the thickness (mm) of the tablet.

2.9.7 Compaction behavior

The registered compression curves (force/time and work/time curves) were used to obtain the required parameters (Es, $E_{EXP,}$ $F_{I,}$ and F_S) for each tablet (Figure 41). Then the (R) and (PI) were calculated (Table XIII and XIV). From the results, both Carnauba wax powder alone and the mixture, have a high Lubrication index (higher than 0.9), which indicate an adequate lubrication behavior. A higher value of PI (closer to 100%) refers to lower elastic recovery of the tablet after removing the compression load.

Table XIII. Results of the compaction behavior of the final mixture.

Parameter	Tablet										Mean	SD
	1	2	3	4	5	6	7	8	9	10		
Fs (KN)	25.06	23.93	26.41	25.05	25.03	22.48	22.97	23.02	24.14	25.10	24.32	1.23
FI (KN)	23.52	22.52	24.73	23.40	23.45	20.93	21.46	21.50	22.64	23.48	22.76	1.18
R	0.94	0.94	0.94	0.93	0.94	0.93	0.93	0.93	0.94	0.94	0.94	0.00
Es (J)	8.51	8.24	7.73	8.05	8.61	7.61	7.26	7.39	7.00	7.83	7.82	0.53
E EXP (J)	3.00	2.91	2.33	3.04	3.36	2.71	2.74	2.81	2.19	2.99	2.81	0.34
E LA (J)	5.51	5.33	5.40	5.01	5.25	4.90	4.52	4.58	4.81	4.84	5.02	0.34
PI (%)	64.75	64.68	69.86	62.24	60.98	64.39	62.26	61.98	68.71	61.81	64.17	3.01
Tensile strength (N/mm^2)	1.37	1.38	1.41	1.38	1.40	1.39	1.39	1.41	1.40	1.39	1.39	0.01

Table XIV. Results of the compaction behavior of CW tablets.

Parameter	Tablet										Mean	SD
	1	2	3	4	5	6	7	8	9	10		
Fs (KN)	6.61	6.37	5.32	7.31	5.64	7.72	9.71	8.96	7.82	6.97	7.24	1.38
FI (KN)	6.44	6.16	5.04	7.09	5.32	7.40	9.30	8.75	7.52	6.72	6.97	1.36
R	0.97	0.97	0.95	0.97	0.94	0.96	0.96	0.98	0.96	0.96	0.96	0.01
Es (J)	0.40	0.50	0.39	0.65	0.38	0.70	0.81	0.87	0.75	0.57	0.60	0.18
E EXP (J)	0.01	0.11	0.00	0.13	0.01	0.39	0.20	0.38	0.30	0.22	0.18	0.15
E LA (J)	0.39	0.39	0.39	0.52	0.37	0.31	0.61	0.49	0.45	0.35	0.43	0.09
PI (%)	97.50	78.00	100.00	80.00	97.37	44.29	75.31	56.32	60.00	61.40	75.02	19.34
Tensile strength (N/mm^2)	0.65	0.64	0.63	0.64	0.62	0.64	0.63	0.61	0.64	0.63	0.63	0.01

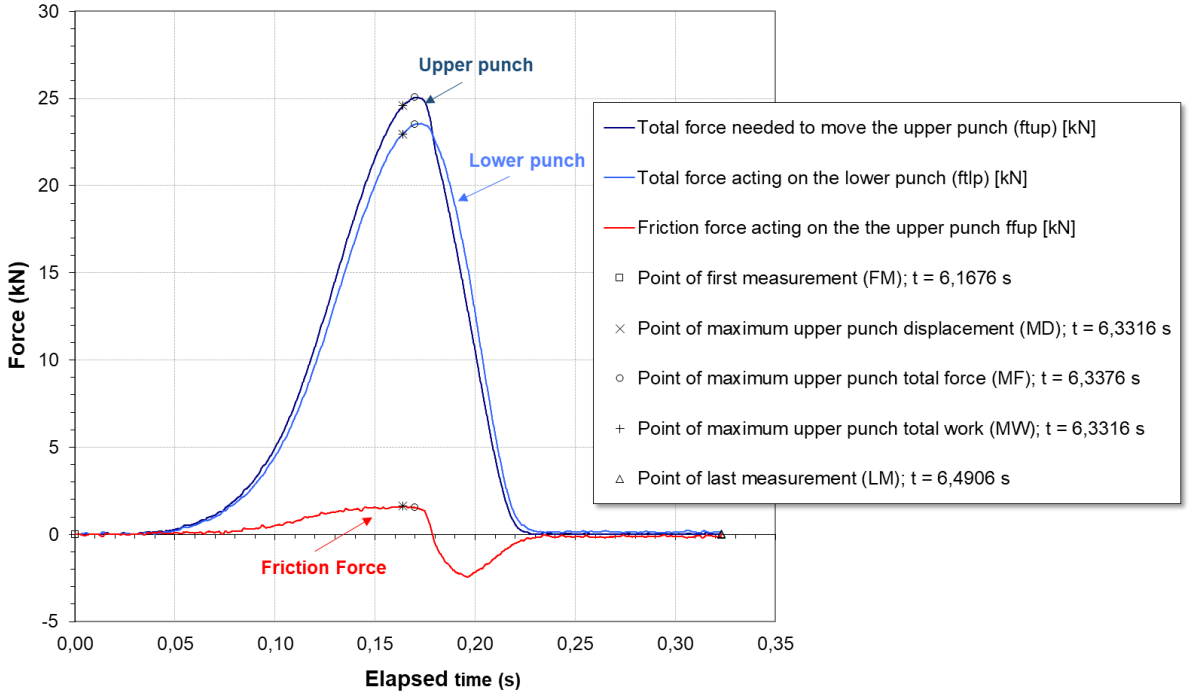


Figure 41. Force/time compression profile obtained from a tablet of the final mixture.

2.9.8 Weight uniformity

The deviation of individual weight for each tablet from the average weight did not exceed ± 5% for both mixture and CW tablets.

2.9.9 Hardness

The hardness of 10 tablets was obtained using pure CW and the other 10 using the final mixture was measured using the previously referred procedure (section 2.7.6.2). The final mixture tablets showed higher hardness than CW tablets (mean value of 90.02 and 33.58 N respectively) (Figure 42) and the differences were considered significant (t-test; p-value < 0.001).

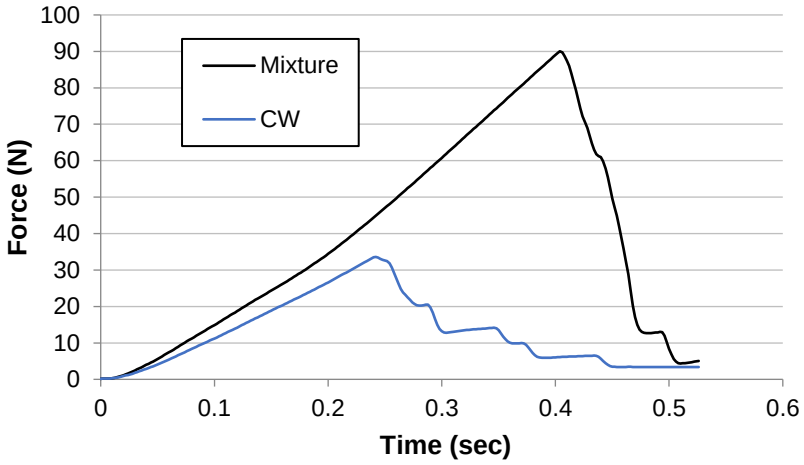


Figure 42. Hardness peaks showing the difference between CW and final mixture tablets.

2.9.10 Friability

CW tablets showed a very high friability F= 5%, while it was better for the final mixture tablets presenting an F value of 2% that was still not good enough.

2.9.11 Dissolution Test

The same steps were followed (section 2.7.7), six tablets were placed, one in each basket. Using 50 rpm and water with 36.5°C $\pm$ 0.5°C temperature. The samples have been taken each 15 minutes for the first hour then each hour for 9 hours. After that, the tablets were left all night and a 24-hour sample was taken the next day. The results were used to get the dissolution curve and determine when 100% of the drug was achieved. According to the curve, 100% was reached after 19 hours (Figure 43).

Figure 44 shows two tablets before and after the dissolution test. It is known that diffusion is the main mechanism of drug release in this type of tablet, which happens by dissolving the lactose first (the white spaces in the left tablet) by the surrounded medium (the water in this case), which forms channels (the right tablet) through which the paracetamol can diffuse.

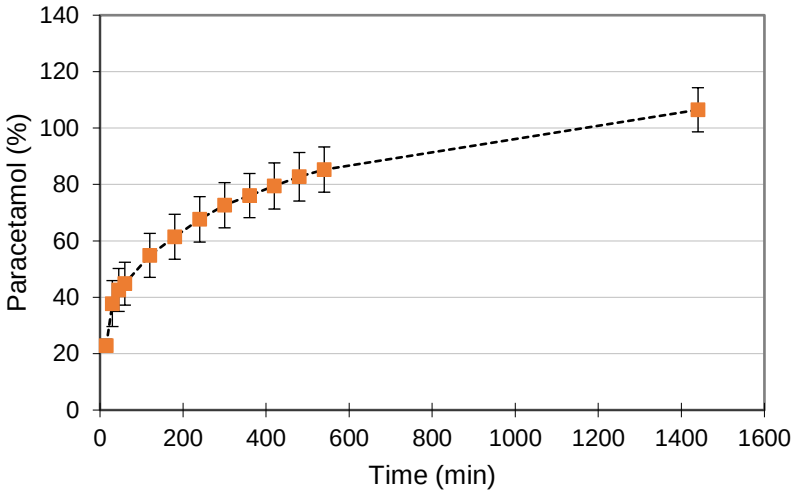


Figure 43. The dissolution profile of 60% CW instrumented tablets.

Figure 44. Tablets used in the dissolution test: on the left the tablet before the test and on the right after the test.

2.9.12 The effect of the tableting method on drug release

The same formulation with 60% CW was used to produce tablets using two different machines. One is the manual hydraulic press machine, and the other is an eccentric press machine. The release rate of each group was studied, and then their dissolution profiles were obtained. By comparing both dissolution curves (Figure 45), for the first hour, their release rate was identical, but after that, the release rate of the tablets produced by the eccentric machine started to decrease. This reduction in drug release can be explained by taking the hardness of each group into account. The hardness mean value was 90.02 N for eccentric machine tablets and 76.59 for hydraulic machine tablets and the differences were considered as significant (t-test; p-value < 0.001). This difference in hardness can affect the tablet's porosity, making harder tablets to have less porosity; thus, less amount of water can enter the tablet to dissolve the drug, therefore less amount of drug can diffuse out from the matrix.

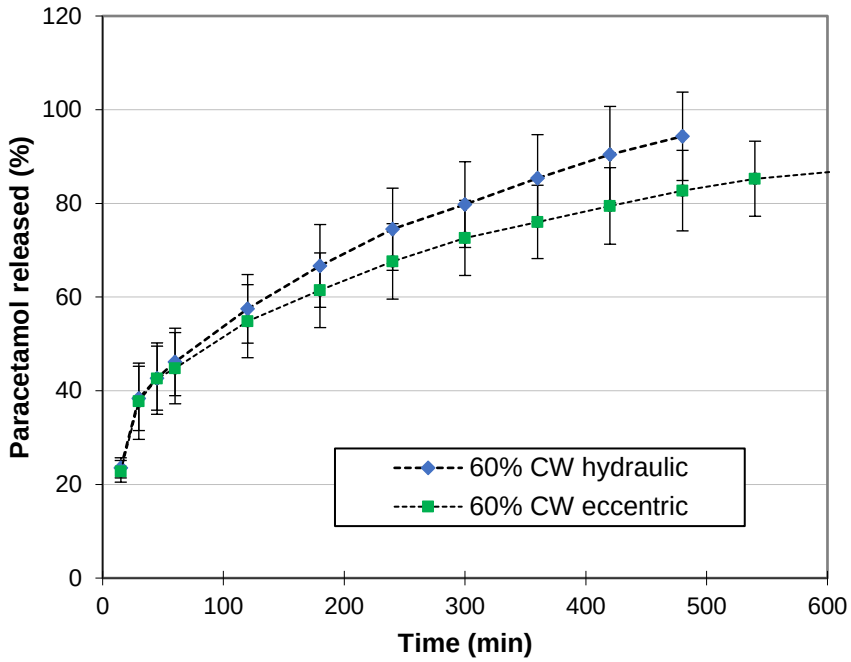


Figure 45. The dissolution profile of 60% CW tablets produced using two different machines.

The formulation with 60% CW was chosen to describe the dissolution curves to find the mathematical model that describes their release in the correct way. The results for the dissolution curves using the three models (zero-order, Higuchi, and Korsmeyer-Peppas) can be seen in Table XV.

Table XV. The released kinetics parameters of the selected formulas (60% CW).

	Parameters	Hydraulic tablets	Eccentric tablets
Zero-order	b	35.642	43.690
	K	0.137	0.068
	R^2	0.931	0.822
Higuchi	b	16.104	23.392
	K	3.667	2.660
	R^2	0.988	0.968
Korsmeyer-Peppas	b	11.255	17.387
	K	5.480	5.480
	R^2	0.991	0.982
	n	0.443	0.395

To choose the model that fits the release mechanism the best, the R^2 is going to be the considered parameter. The higher the R^2 value is, the better the model describes the dissolution curve. Therefore, the best fit, in this case, is the Higuchi model with $R^2 = 0.988$ and 0.968 for hydraulic and eccentric tablets respectively comparing to the ones of zero-order ($R^2 = 0.931$ and 0.882 for hydraulic and Eccentric tablets respectively). This may suggest that diffusion is the release mechanism in the tested tablets. *K* value is lower for eccentric tablets, which clarify that the release rate in eccentric tablets is slower than the one of hydraulic ones, as the curve in Figure 45 shows.

For a further analysis of the release mechanism, the Korsmeyer-Peppas model was used. It is normally used when the release mechanism is unknown or not so clear (62). The *n* value in this model is used to characterize the release mechanism. In this model $n < 0.43$ suggested diffusion mechanism (101). Then according to Higuchi and Korsmeyer-Peppas models, diffusion is the main release mechanism in these tablets.

Conclusions and future work

From this work, it can be concluded that CW can be used to produce matrix tablets by direct compression with prolonged release effect. By studying the dissolution profile of the different tablets obtained from different mixtures, the effect of CW concentration on the release profile was clear. The higher the concentration of the CW content of the matrix tablet, the slower the release rate of paracetamol due to the higher retardant effect provided by the CW. Using 60% of CW the release can be prolonged for more than 15 h.

The analysis of the results obtained in this work allows concluding that the different particle size fractions of CW showed different flow characteristics. The fractions of smaller particle size had a lower flow capacity because smaller dimensions facilitate accommodation, which negatively influences the flowability.

Studying the tablets' hardness, friability, and thickness for the mixture in different proportions and pure CW tablets showed the effect of the excipients in different proportions on the final characteristics of the product. The tensile strength of pure CW tablets was almost half of the value of the final mixture tablets (0.63 and 1.39 respectively).

Compression ability and compaction behavior of pure CW and final mixture were investigated by studying their compression cycle, and it was clear that the excipients had an important effect on the compressibility of the tablet.

By studying the release profiles of tablets with 60% CW obtained with different tableting methods and correlating these results with the hardness, it can be stated that there is a significant effect of the hardness of a tablet on the drug release.

Considering the crucial role of powder flowability on tablet production, it is important to make further studies on the solid bulk to avoid scaling-up problems. Rat-Hole and Arching are the main flow obstructions that can occur to prevent the flow. The critical rate-hole diameter and the critical arching diameter can be calculated using the PFT.

Based on the importance of controlled release technology and matrix tablets in specific, further studies using different methodologies to study the characteristics of matrix tablets are desirable, long term stability studies are necessary as well.

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