Charles University
Faculty of Pharmacy in Hradec Králové
Department of Pharmaceutical Technology

STUDY OF COATING MIXTURE COMPOSITION ON QUALITY OF TABLET COAT

Diploma Thesis

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Statement of originality

I declare that the content of this thesis is original work. All literature, data, and resources used are cited and found in the references section.

Mehrdad Mirzaei
August 6, 2024

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1 Abstract

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The objective of this study is to develop a titanium dioxide-free coating for pharmaceutical tablets. Therefore, the study focuses on the impact of coating mixture composition on the quality of tablet coats, utilizing two placebo core types: standard convex-shaped (lenticular) and flat-shaped, both 9 mm in diameter. Two coating compositions were examined: lactose-based and calcium carbonate-based, with an orange colorant and green colorant, respectively. Key parameters assessed included coating process dynamics, coating thickness, tablet crushing force, and disintegration time.

The study found significant differences in the mechanical properties and performance of tablets based on the core shape and coating composition. Lactose-based coatings provided smoother and more uniform coats regardless of the core shape. Additionally, the type of core influenced the crushing force and disintegration time, with flat-faced cores exhibiting better mechanical strength but longer disintegration times; the higher disintegration time was noted for the lactose coat. The findings suggest that lactose-based coatings are more effective for achieving a high-quality coat compared to calcium carbonate-based coatings, while core shape significantly impacts the tablet's mechanical properties and performance. Finally, both types of green-coated tablets showed less intense darkening due to corrosion compared to the orange-coated tablets, indicating an advantage in terms of visual stability.

2 The aim of study

Titanium dioxide, a common excipient material, generally used in tablet coating, should be reduced and replaced with the other acceptable excipient due to a potential risk of DNA damage (EMA 2021). Although these findings were primarily focused on its use in food, they have significant implications for its use in pharmaceuticals as well. Therefore, this experimental work deals to the development of the titanium dioxide free coating for tablets.

Two compositions of a coating material will be studied for two types of placebo cores, i) standard convex-shaped cores (lenticular) and ii) flat-faced cores both 9 mm in diameter. The lactose-based and/or calcium carbonate-based coating with ferric oxide colourant (orange) will be used. The effect of core shape as well the composition of the coating dispersion on coating process dynamic, the coating thickness, the tablet crushing force, and the disintegration time will be studied.

Finally, the green pale coating will be used for the flat-faced cores with the active substance.

In the theoretical part, the review of pharmacy coating will be shown.

3 List of abbreviations

Abbreviation	Unit	Explanation
CC	-	calcium carbonate
CF	N	crushing force
DF	-	dosage form
DT	min	disintegration time
Fe	-	ferric oxide colourant (orange)
GR	-	green colourant (combination of blue and yellow)
H	mm	thickness of tablet (height)
L	-	lactose monohydrate
m	g	mass
Max	-	maximum
Min	-	minimum
MU	-	Mass uniformity
P	Pa	pressure
RH	%	relative humidity
SD	-	standard deviation
T	°	temperature
t	s	time
A	-	Lenticular (biconvex) shaped tablet
B	-	Flat surface tablet
B_{API}	-	Flat surface with perindopril
FCT	-	Film coated tablet
HPMC	-	Hydroxypropyl Methylcellulose
PVA	-	Polyvinyl Alcohol
CAP	-	Cellulose Acetate Phthalate
PVAP	-	Polyvinyl Acetate Phthalate
HPMCP	-	Hydroxypropyl Methylcellulose Phthalate

4 Introduction

Oral solid medications have been used around for centuries and remain the go-to choice for convenience in pharmacies. Their ease of production and patient-friendly nature significantly boost compliance (Augsburger & Hoag, 2016). Among oral solid medications, tablets are the most prevalent form, and they have seen considerable advancements over the past few decades. Innovations such as tablet coating, double compression, and osmotic systems have been introduced to enable controlled and targeted drug release. Various coating techniques have been developed to achieve these desired effects (Sastry et al. 2000).

Film coating (FC) stands out as the leading and versatile method in both the pharmaceutical and food industries. It is a contemporary process widely adopted for coating a variety of oral solid dosage forms (DFs), including tablets, capsules, pellets, and granules. FC involves the precise spraying of a thin, uniform polymer-based layer onto the surface of these dosage forms. This technique is categorized into two main classes: nonfunctional FC and functional FC.

Nonfunctional FC is primarily utilized to enhance the appearance, organoleptic properties, and ease of swallowing of tablets. Additionally, it serves to protect tablets from environmental factors such as humidity, oxidation, and light exposure, thus improving the stability and shelf-life of the medication (Suganya and Anuradha 2017; Paulo and Santos 2017). On the other hand, functional FC not only offers the benefits of the previous coating but also enables the modification or delay of drug release, thereby enhancing the therapeutic effects of the medication (Pinto et al. 2020).

The application of FC has revolutionized the field of oral solid dosage forms by providing a means to tailor drug release profiles to specific therapeutic needs. This has led to the development of advanced drug delivery systems that can target specific sites within the gastrointestinal tract, reduce dosing frequency, and improve patient adherence to treatment regimens (Roy et al. 2014). Furthermore, the versatility of FC allows for the incorporation of multiple active pharmaceutical ingredients (APIs) into a single dosage form, facilitating combination therapies that can address complex disease states more effectively (Thombre 2018).

In recent years, the pharmaceutical industry has also explored the use of novel polymers and coating technologies to further enhance the functionality of FC.

Innovations such as biodegradable and bioadhesive coatings are being investigated to improve drug absorption and reduce side effects (Marucci et al. 2013). Additionally, the integration of nanotechnology with FC is opening new avenues for the development of smart drug delivery systems that can respond to physiological conditions and release drugs in a controlled manner (Mishra et al. 2018).

Overall, the continuous evolution of FC technologies highlights the importance of this method in the development of modern oral solid dosage forms. By improving drug stability, patient compliance, and therapeutic efficacy, FC plays a crucial role in advancing pharmaceutical science and improving public health outcomes.

Titanium dioxide was a common excipient material, generally used in tablet coating. The European Food Safety Authority (EFSA) conducted a review and published a scientific opinion in May 2021, concluding that titanium dioxide could no longer be considered safe as a food additive due to unresolved concerns about genotoxicity. These concerns are primarily associated with the presence of nanoparticles, which have been shown to pose a potential risk of DNA damage (EMA 2021). As a result, it should be avoided and reduce of its usage in the pharmacy. This thesis aims to replace a titanium dioxide tablet coating with the titanium dioxide free one.

5 Theoretical section

According to Ph.Eur (European Pharmacopoeia 10th edition, 2020) coated tablets are divided in several groups:

Film-Coated Tablets (FCT)

- **Description:** Tablets coated with a thin polymer-based film.
- **Purpose:** To mask taste, provide physical and chemical protection, control drug release, and improve mechanical properties.
- **Examples:** Immediate-release film-coated tablets, modified-release film-coated tablets.

Sugar-Coated Tablets (SCT)

- **Description:** Tablets coated with a layer of sugar and other ingredients.
- **Purpose:** To mask unpleasant tastes and odors, protect the drug from light and moisture, and enhance appearance.
- **Examples:** Multivitamin tablets, certain over-the-counter medications.

Gastro-Resistant Tablets

- **Description:** Tablets coated with substances that resist the acidic environment of the stomach but dissolve in the intestines.
- **Purpose:** To protect acid-labile drugs from stomach acid, reduce gastric irritation, and target drug release in the intestines.
- **Examples:** Enteric-coated aspirin, certain proton pump inhibitors.

Modified-Release Tablets

- **Description:** Tablets with coatings that control the rate and location of drug release.
- **Purpose:** To provide sustained, controlled, or delayed drug release.
- **Examples:** Extended-release formulations, delayed-release formulations.

5.1 Tablet coating and its function

This chapter focuses on how the tablets are coated and main reasons of coating of tablets are discussed.

As mentioned above in the Introduction section, tablet coating serves multiple essential functions in pharmaceutical manufacturing, playing a pivotal role in ensuring the stability, efficacy, and patient acceptability of oral dosage forms. One of the primary functions of tablet coating is to protect the active pharmaceutical ingredient (API) from environmental factors such as moisture, oxygen, and light. Exposure to these factors can degrade the drug and reduce its efficacy over time, which is particularly critical for sensitive APIs that are prone to oxidation or hydrolysis. By applying a protective coating, the tablet's surface is shielded from such external factors, thereby extending the product's shelf life and maintaining its therapeutic potency throughout storage and transportation processes (Haleem et al., 2014). This aspect of tablet coating is crucial for ensuring that the drug retains its intended efficacy until it reaches the patient.

Beyond protection, tablet coating plays a significant role in controlling the release profile of the drug. Different coating materials and techniques enable pharmaceutical manufacturers to achieve specific release profiles, such as modified-release, prolonged-release or delayed-release formulations. For example, polymer-based coatings can be designed to dissolve rapidly in the stomach, allowing for immediate drug release, or to dissolve gradually in the gastrointestinal tract, providing sustained release over an extended period (Nokhodchi et al., 2015). This control over drug release kinetics is essential for optimizing therapeutic outcomes. Immediate-release formulations are beneficial for drugs that require rapid onset of action, while extended-release formulations help maintain steady drug levels in the bloodstream, reducing dosing frequency and minimizing side effects associated with fluctuating drug concentrations (Rao et al., 2017).

In addition to enhancing drug stability and controlling release profiles, tablet coatings also play a critical role in improving patient compliance. The physical appearance of a tablet, including its color, texture, and taste, can significantly influence a patient's willingness to take the medication as prescribed. Coatings can mask the bitter taste or unpleasant odor of certain drugs, making them more palatable and easier to swallow (Felton 2013). Furthermore, the use of color coatings can help in the identification of

different medications, reducing the risk of medication errors and enhancing patient adherence to their treatment regimen (Heinicke et al., 2020).

Aesthetic improvements provided by coatings also extend to branding and product differentiation. The appearance of a coated tablet can be customized with colors, logos, and other markings that distinguish it from generic or competing products. This not only helps in preventing counterfeiting but also aids in brand recognition and loyalty among patients and healthcare providers (Nielsen et al., 2017).

Moreover, tablet coatings can improve the mechanical properties of tablets, enhancing their durability during manufacturing, packaging, and transportation. Coated tablets are less likely to chip, crack, or break, which helps maintain the integrity of the dosage form from production to administration (Reynolds et al., 2018). This mechanical robustness is particularly important for large-scale production and distribution, where tablets must withstand significant handling and environmental stress.

Finally, the use of advanced coating technologies, such as functional coatings that respond to environmental conditions, offers new possibilities for targeted drug delivery. These coatings can be engineered to release the drug in response to specific physiological triggers, such as changes in pH, temperature, or enzyme activity, providing more precise and effective treatment options for various medical conditions (Siepmann & Siepmann, 2013). For instance, recent advancements in mucoadhesive and biodegradable coatings are designed to interact with specific tissues, thereby enhancing localized drug delivery and minimizing systemic side effects (Gandhi et al., 2015).

5.2 Excipients used in tablet coating

Excipient for coating can vary according to type and use of coating. In this chapter focus is on the excipients which are used for coating tablets, particularly for this study.

5.2.1 Film-forming agents

Film-forming agents are essential components in the tablet coating process. They create a continuous, uniform film around the tablet core, which serves various purposes such as protecting the tablet from environmental factors, masking the taste, and enhancing the tablet's appearance.

The primary function of film-forming agents is to produce a protective layer that can control the release of the active pharmaceutical ingredient (API), ensure stability, and improve the mechanical strength of the tablet. They help in maintaining the integrity of the tablet during handling, transportation, and storage (Rowe et al., 2009). Some examples include:

Hypromellose (Hydroxypropyl Methylcellulose, HPMC): It is one of the most widely used film-forming agents due to its excellent film-forming properties, solubility, and safety profile.

Ethylcellulose: This polymer is used when a water-insoluble coating is required, often for controlled-release formulations.

Polyvinyl Alcohol (PVA): Known for its strength and resistance to oils and greases, PVA is used in film coatings where these properties are beneficial.

5.2.2 Plasticizers

Plasticizers are substances added to film-forming agents to enhance the flexibility, to reduce brittleness, and to improve the overall characteristics of the film. The use of plasticizers is critical in preventing the coated film from cracking or breaking during the manufacturing process or while handling. They work by embedding themselves between the polymer chains of the film-forming agent, reducing intermolecular forces and increasing the flexibility of the polymer film (Zarmpi et al., 2017). These plasticizers comply with standards set by regulatory authorities such as the European Pharmacopoeia (Ph.Eur 10.0 2020) and the FDA. This compliance ensures that they meet strict safety, quality, and efficacy requirements. Some examples include:

Macrogol 6000 (Polyethylene Glycol 6000): Widely used due to its effectiveness in improving flexibility and its compatibility with many polymers.

Triethyl Citrate: A commonly used plasticizer in the pharmaceutical industry, known for its non-toxic nature and compatibility with various polymers.

Diethyl Phthalate: Effective in reducing brittleness and increasing the toughness of the film.

5.2.3 Anti-caking agents and glidants

Anti-caking agents and glidants are added to tablet coatings to improve the flow properties of the powder and prevent clumping. These agents ensure a smooth

application of the coating solution and prevent the formation of lumps. They improve the manufacturing process's efficiency and ensure that the coating is uniformly applied (Saha & Shahiwala, 2009).

Talc: Commonly used as an anti-caking agent and glidant due to its excellent flow properties and ability to prevent clumping.

Colloidal Silicon Dioxide: Used to improve the flowability of powders and prevent clumping.

Magnesium Stearate: Often used as a lubricant to prevent sticking and to ensure uniform coating application.

5.2.4 Colorants

Colorants are added to tablet coatings to provide a distinctive appearance, which can aid in product identification, brand differentiation, and patient compliance. Colorants not only enhance the aesthetic appeal of the tablets but also help in masking any unattractive colors of the core tablet and can aid in the identification of different strengths or types of medication (Carter, 2016). Some examples include:

Iron Oxide Red: Commonly used to provide a red hue to the tablets.

Iron Oxide Yellow: Used to give a yellow coloration.

Titanium Dioxide: Frequently used as a white pigment and opacifier in tablet coatings.

5.2.5 Opacifiers

Opacifiers are used in tablet coatings to make the tablet surface opaque, preventing light from penetrating through and potentially degrading the active ingredients, particularly the light-sensitive ones, thus enhancing the stability and shelf life of the product. They also improve the visual appeal of the tablet by providing a consistent, uniform appearance (Jones, 2008).

Calcium Carbonate: Used as an opacifier to provide opacity and whiteness.

Titanium Dioxide: Apart from its role as a colorant, it is also an effective opacifier used in many pharmaceutical formulations.

Zinc Oxide: Known for its opacity and ability to provide UV protection.

5.2.6 Solvents

Solvents are used in the preparation of coating solutions to dissolve the film-forming agents and other components, facilitating their application onto the tablets. They play a critical role in ensuring that the coating dispersion can be evenly sprayed onto the tablets and that it dries quickly and uniformly. The choice of solvent can affect the drying time, film formation, and overall quality of the coating (Niazi, 2004).

Purified Water: The most commonly used solvent in pharmaceutical coatings due to its safety and effectiveness.

Ethanol: Used for its fast-drying properties and ability to dissolve a wide range of film-forming agents.

Isopropanol: Often used in combination with other solvents to enhance the solubility of coating components and improve drying times.

5.2.7 Excipient used for gastro-resistant tablets

Gastro-resistant excipients, also known as enteric coatings, are specialized film-forming agents designed to protect the API from the acidic environment of the stomach. As mentioned briefly in the previous chapter these coatings ensure that the API is released in the more neutral pH environment of the intestines, which can be crucial for drugs that are sensitive to stomach acid or that can cause irritation to the gastric mucosa. Other use of gastro-resistant excipients can be mentioned by their ability to target delivery of drugs to the intestines, which can be essential for the treatment of certain conditions such as Crohn's disease or ulcerative colitis (Chourasia & Jain, 2003).

Gastro-resistant coatings work by remaining intact in the acidic pH of the stomach and then dissolving or disintegrating when they reach the higher pH of the small intestine. This pH-dependent solubility is achieved through the use of specific polymers that are insoluble at low pH but become soluble at higher pH levels. Some examples include:

- **Methacrylic Acid Copolymers:** These polymers, such as Eudragit L and S, are widely used in enteric coatings due to their pH-dependent solubility. Eudragit L dissolves at pH 6.0, while Eudragit S dissolves at pH 7.0, making them suitable for targeting different sections of the gastrointestinal tract.

- **Cellulose Acetate Phthalate (CAP):** This polymer is commonly used for enteric coating because it remains insoluble in the acidic environment of the stomach but dissolves readily at a pH above 5.5.
- **Polyvinyl Acetate Phthalate (PVAP):** Similar to CAP, PVAP provides effective gastroresistance and dissolves at a slightly higher pH, making it another reliable option for enteric coatings.
- **Hydroxypropyl Methylcellulose Phthalate (HPMCP):** Known for its excellent film-forming properties, HPMCP is soluble at a pH of 5.0 to 5.5, making it suitable for protecting drugs in the stomach and releasing them in the upper intestines.

While gastroresistant excipients offer significant benefits, their application can present challenges. Gastro-resistant coatings are applied using techniques similar to those used for regular film coatings but require precise control of process parameters to ensure the integrity of the coat. Ensuring uniform coating thickness and avoiding defects like cracks or pinholes is crucial to maintaining gastroresistant properties. Additionally, the choice of plasticizers and other formulation components must be carefully considered to avoid compromising the enteric coating's performance (Lecomte et al., 2003).

5.2.8 Role of titanium dioxide in coating and reason for it's limitation

Titanium dioxide (TiO_2) is a commonly used additive in tablet coating, primarily used as a white pigment to provide opacity and color to the coating layer. It enhances the aesthetic appeal of the tablets and facilitates their identification by patients and healthcare professionals. Additionally, TiO_2 serves as a coating agent, contributing to the mechanical strength and integrity of the coating film. Its inert nature makes it compatible with a wide range of pharmaceutical formulations, and its low cost makes it an attractive option for manufacturers (Salamanca et al., 2020).

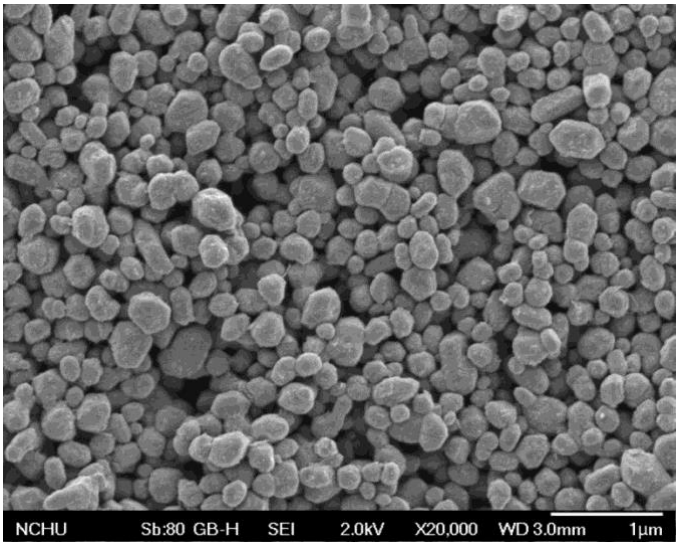


Fig. 1: SEM image of titanium dioxide particles at magnification of 20,000x (Hu et al., 2014).

Besides being predominantly used in the pharmaceutical industry for tablet coatings, TiO_2 also finds applications in various other sectors (Gernand 2014):

- Cosmetics which is used in sunscreens and cosmetics for its UV-blocking properties.
- Food industry where acts as a food additive (E171) to enhance the whiteness and brightness of products
- Paints and coatings as utilized for its high opacity and brightness.

However, TiO_2 has come under scrutiny due to concerns regarding its potential health risks, particularly its carcinogenicity. Several studies have suggested that TiO_2 nanoparticles may induce inflammatory responses and oxidative stress in cells, leading to adverse health effects, including cancer (Ghazy et al., 2019). As a result, there is growing pressure to find alternative coating materials that can provide similar functionality without posing potential health risks to consumers.

One promising alternative to TiO_2 in tablet coatings is the use of natural pigments and colorants derived from plant sources. For example, spirulina extract, curcumin, and beetroot extract have been explored as potential replacements for TiO_2 in tablet coatings due to their natural origin and safety profile. These natural pigments not only provide color to the coating but also offer additional health benefits, such as antioxidant and anti-inflammatory properties. Moreover, plant-based pigments are

biodegradable and environmentally friendly, aligning with the growing demand for sustainable pharmaceutical formulations (Li et al., 2018).

The other alternatives include lactose and calcium carbonate which are discussed below.

5.3 Coating techniques

Drum coating, fluid-bed coating, and press coating are pivotal techniques in the realm of pharmaceutical and industrial applications for coating particulate materials. **Drum coating**, also known as pan coating, involves placing the product in a rotating drum where a coating solution is sprayed and evenly distributed due to the drum's motion. (Porter 2016) This method, while simple and suitable for batch processing, can be time-consuming and requires precise parameter control for uniformity. It is commonly used for coating pharmaceutical tablets and in food industries (Ghebre-Sellassie & Martin 2006).

In this study focus is mainly on technique of film coated tablets using drum coater (Glatt GC 1), to produced desired coated tablets from differnet coating suspensions.

The process of film coating tablets primarily involves the application of a thin, continuous layer of polymer-based coating materials onto the surface of the tablets. The Glatt GC 1 is a high-performance coating machine designed to facilitate this process efficiently and uniformly. The Glatt GC 1 utilizes a perforated drum system which allows for optimal air flow and precise temperature control, essential for achieving a high-quality film coat. The machine ensures that the coating solution, typically composed of polymers, plasticizers, and pigments, is evenly distributed over the tablet surfaces as they tumble within the rotating drum. The controlled environment within the Glatt GC 1 minimizes variability in the coating thickness and enhances the uniformity of the final product.

The film coating process using the Glatt GC 1 is characterized by several critical stages: the spraying of the coating solution, drying, and cooling. During the spraying stage, the coating solution is atomized through precision nozzles and sprayed onto the moving tablet bed. The drying stage is crucial, as it involves the evaporation of solvents from the coating solution, facilitated by the heated air that flows through the perforations in the drum (Salunkhe et al. 2019). The efficient drying mechanism of the

Glatt GC 1 prevents agglomeration and ensures that each tablet receives a smooth and consistent coat. Finally, the cooling stage stabilizes the coated tablets, readying them for subsequent packaging or use. The combination of precise control over process parameters and the advanced design of the Glatt GC 1 makes it a preferred choice for pharmaceutical manufacturers aiming for high-quality, uniform film-coated tablets (Vogeleer et al. 2017).

There are important factors influencing the drum coating process; understanding these factors is essential for optimizing the coating process and achieving the desired product specifications (Porter & Bruno 1990):

Coating Solution Properties:

The viscosity, solid content, and composition of the coating solution play a crucial role in determining the coating quality. High-viscosity solutions can lead to uneven coating and potential clogging of spray nozzles, while low-viscosity solutions may result in inadequate coating thickness.

Drum Speed and Angle:

The rotation speed and angle of the coating drum affect the mixing and movement of the tablets. Optimal drum speed ensures uniform distribution of the coating solution over the surface of the particles, preventing agglomeration and ensuring consistent coating thickness.

Spray Rate and Nozzle Position:

The rate at which the coating solution is sprayed and the position of the spray nozzles relative to the drum interior are critical parameters. Uniform spray distribution and appropriate droplet size are essential to avoid over-wetting or under-coating the particles. Additionally, the number of nozzles and their distance from the cores are vital for achieving a consistent and uniform coating. Multiple nozzles can provide better coverage and reduce the risk of over-concentration of the coating solution in specific areas, while the distance between the nozzles and the cores affects the droplet size and spray pattern. If the nozzles are too close, the spray can become too concentrated, leading to over-wetting. If they are too far, the spray may become too diffuse, resulting in uneven coating

Drying Air Temperature and Flow:

Proper drying is necessary to prevent sticking and ensure that the coating adheres well to the particles. The temperature and flow rate of the drying air must be controlled to facilitate rapid evaporation of the solvent without causing thermal degradation of the active ingredients.

Batch Size and Loading:

The amount of material loaded into the coating drum can impact the coating uniformity and process efficiency. Overloading can lead to poor mixing and uneven coating, while underloading may result in excessive exposure to the drying air, causing brittle coatings.

Environmental Conditions:

Ambient conditions such as humidity and temperature in the coating room can influence the coating process. High humidity can slow down the drying process, while low temperatures may affect the viscosity and flow properties of the coating solution.

Fluid-bed coating, on the other hand, suspends solid particles in an upward-flowing stream of air while spraying a coating solution onto them. The continuous movement ensures uniform coating, and the hot air facilitates rapid drying of the solvent, leaving a dry coat on the particles (Parikh 2016). This method is widely used in the pharmaceutical industry for coating granules, pellets, and tablets to achieve controlled release or taste masking. Despite its efficiency and suitability for continuous processing, fluid-bed coating involves more complex equipment and higher operational costs compared to drum coating (Davies & Feddah 2003).

Press coating, also known as compression coating or dry coating, entails compressing a coating material around a core tablet, allowing for the creation of multilayer tablets with precise control over the core and coating composition (Augsburger & Hoag, 2016). This technique is particularly advantageous for developing controlled release profiles and protecting sensitive ingredients, though it necessitates specialized equipment and incurs higher material costs (Turco & King, 1974).

6 Experimental section

6.1 Materials

Lactose monohydrate M200, Meggle GmbH and Co., Germany

Lactose anhydrous – DEE Pharma, Netherland

Calcium carbonate – SPI Pharma, USA

Hypromellose 2910/5 – Rettenmaier and Soehno GmbH, Germany

Macrogol 6000 – Croda Chocques SAS, France

Avicel 112 – JRS Pharma -Microcellulose Weissen, Germany

Avicel 200 – JRS Pharma -Microcellulose Weissen, Germany

Tabletose 80 – Meggle GmbH, Germany

Ac-Di-Sol (croscarmellose sodium) – Mingtai Chemical Co.Ltd., Taiwan

Aerosil 200 – Evonik industries AG, Germany

Magnesium stearate – Undesa, Spain

Talc – Elementis minerals, USA

Iron oxide red – Neelicon food dyes & Chemicals, India

Iron oxide yellow – Neelicon food dyes & Chemicals , India

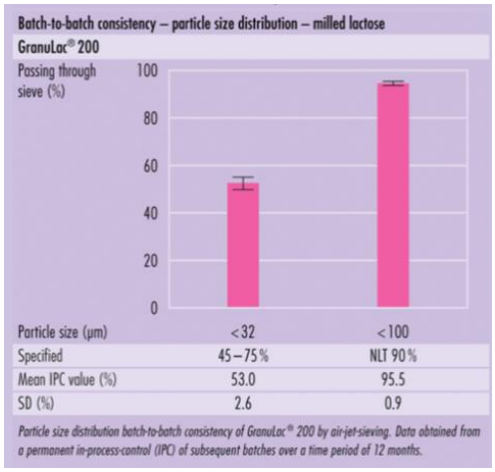
Quinoline yellow – Sensient colors, USA

Indigotin blue – Colorcon, USA

Characterisation of coating material

A)

B)



C)

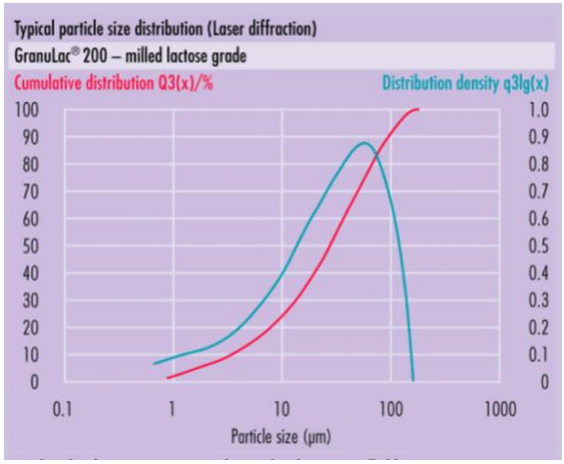
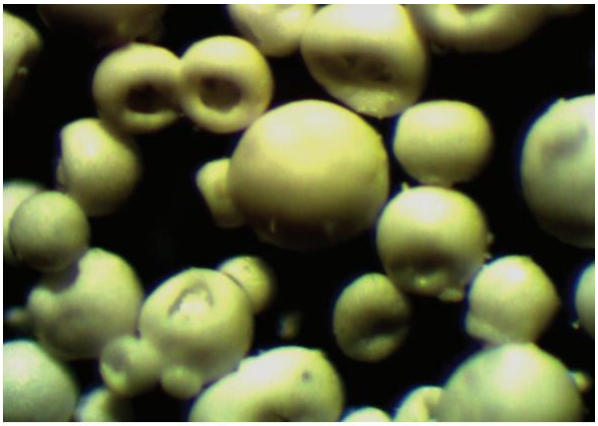
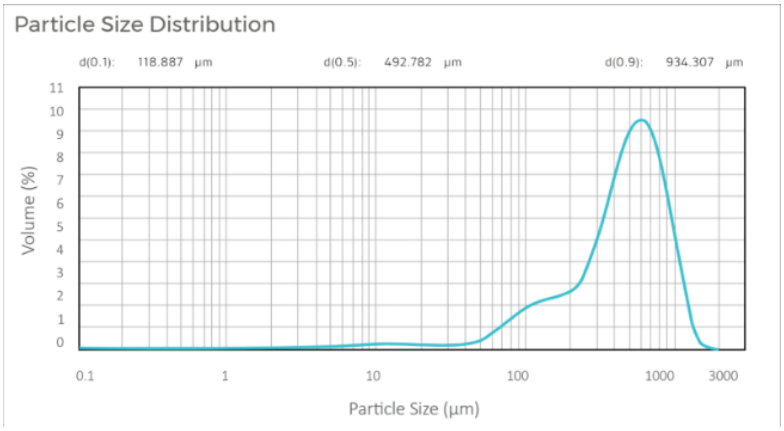


Fig. 2: Lactose monohydrate crystals and size distribution according to distributer site (https://www.meggle-pharma.com/en/lactose/3-granulac-200.html.)



A)



B)

Fig. 3: A) SEM image of calcium carbonate B) particle size distribution of calcium carbonate (SPI Pharma 2019).

6.2 Equipment

Scale Sartorius universal (d = 0.01 g) (GOETTINGEN, Germany)
Tablet press Pressima AX (IMA Kilian GmbH a Co. KG, GERMANY)
Analytical scale OHAUS® Eplorer (d = 0.1 mg) with a printer OHAUS® SF 40A (OHAUS Corp., USA)
Drum coater Glatt GC 1 (Glatt GmbH, Germany)
Vortex mixer POLYTRON® PT 2500 E (Kinematica GmbH, Germany)
Mixer Heidolph RZR 2050 Heidolph Instruments (GmbH & CO, Germany)
Disintegration apparatus SOTAX DT50 (Sotax, Switzerland)
Crushing force equipment Pharmatron MultiTest 50 (Pharmatron, Switzerland)

6.3 Methods

6.3.1 Preparation of cores

The tablet cores were manufactured using the direct compression method with the Pressima Ax tablet press. The powder mixture comprised Avicel 112, Avicel 200, Ac-Di-Sol (croscarmellose sodium), Lactose SD 14, Tabletose 80, lactose anhydrous, Aerosil 200, and magnesium stearate. The tablet batches weighed 6 kg each, and a premix placebo was utilized in the manufacturing process.
For tablet production, four punches with a 9 mm diameter were employed. The punch set, designated as 9C, had a radius of 8 mm, a track size of 12 mm, and was positioned in the middle. The pre-compression force applied was 2.6 kN and under this pre-compression force, the material was compressed to a height of 5.47 mm, followed by the main press force of 11.1 kN (height of material is reached to 3.20 mm). The cores were filled to a depth of 7.50 mm. The tableting machine operated at a speed of 12000 tablets per hour.
Throughout the tableting process, the average weight of the tablets was 260 mg, and the average crushing force of 10 random cores is 98 N. Two tablet shapes were produced: lenticular and flat. The lenticular-shaped tablets had a diameter of 9.06 mm, a height of 4.42 mm, and a mass of 260 mg. In contrast, the flat-shaped tablets exhibited a diameter of 9.05 mm, a height of 4.01 mm, and a mass of 290 mg.

In the production of green-coated tablets, the cores were manufactured using a similar apparatus, however with some distinct parameters. Specifically, the process involved utilizing 8 punches with a diameter of 9 mm, subject to a pre-compression force of 1.9 kN. The material was then compressed to a height of 5.47 mm, followed by the main press applying a force of 12.7 kN, reducing the height to 1.8 mm. These cores were subsequently filled to a depth of 6 mm. Notably, the core composition included the active pharmaceutical ingredient (API), perindopril, alongside other excipients. The tableting machine operated at a speed of 30,000 tablets per hour.

6.3.2 Preparation of coating material

As illustrated in the preceding Figure 4, the tablets can be categorized into two distinct shapes: lenticular (A) and flat surface (B). note that green-coated tablet contain different core composition and there is perindopril as API.

The tablets were coated with the similar coating material but the coats differ in the main substance as follows. The coating process for both types of tablets involves two distinct materials: either lactose monohydrate (A1, B1) or calcium carbonate (A2, B2). Moreover, it is noteworthy that the flat surface tablets are available in two distinct colours, orange and green. In contrast, lenticular tablets are available only in an orange color. The coding of samples is illustrated in Fig. 5.

It should be noted that The Core B composition was different for the orange and/or green coat.

A) B) B_{API})

Fig. 4: Illustration of shape; A) lenticular, B) flat surface B_{API}) flat surface with core contain perindopril

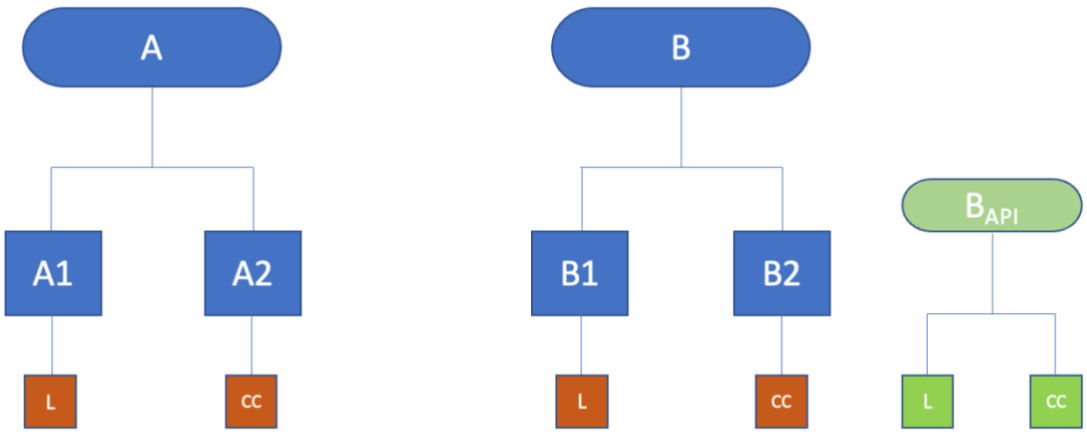


Fig. 5: Coding of coated tablet samples

Two different coating materials were used for coating of cores.

1. Lactose coating

First, water was poured into a suitable glass beaker and heated to about 90 °C. When the temperature was set, macrogol 6000 was slowly added and stirred for about 5 min until completely dissolved. Temperature was maintained at 80 - 90 °C and hypromellose was added to the hot mixture slowly to prevent sticking and held until complete dispersion was created. After that, stirring continued for about 15 min to let it cool down to room temperature for approximately 40 – 50 min to reach the clear solution. Finally, lactose was added to the cooled solution and the solution was mixed for another 10 minutes very slowly so air does not suck in to create foam.

In another glass beaker, purified water, talc, and a ferric oxide blend (pre-mixed from iron oxide yellow and red one in advance in a ratio 2:1) were stirred with vortex mixer POLYTRON® and mixed well to destroy the clusters.

In the end, both of these solutions were mixed carefully to avoid forming any clusters until a homogeneous dispersion was obtained.

To make green colour tablets, the same procedure was repeated but instead in a second glass beaker purified water, talc, quinoline yellow, and indigotin blue blend (pre-mixed from quinoline yellow and indigotin blue in advance in a ratio 1:1) were stirred with vortex POLYTRON®.

2. Calcium carbonate coating

The macrogol and hypromellose solution was prepared the same way as described above without the lactose addition.

In another glass beaker purified water, talc, and ferric oxide, were stirred with vortex mixer POLYTRON®, and mixed well to destroy the clusters, finally calcium carbonate was added in this step because it's not soluble and vortex POLYTRON® helps to mix it well.

In the end, both of these solutions were mixed carefully to avoid forming any clusters until a homogeneous dispersion was obtained.

To make green color tablets, the same procedure was repeated but instead in a second glass beaker purified water, talc, quinoline yellow, and indigotin blue (pre-mixed from quinoline yellow and indigotin blue in advance in a ratio 1:1) were stirred with vortex POLYTRON®.

6.3.3 Coating of tablets

Each time coating procedure has 3 steps: preheating, spraying (coating), and drying.

Preheating

After producing the coating suspension, amounts of cores between 1000-1500 g have been taken (the exact weight was registered) and loaded into a coater. A drum rotation was started in low speed (2-4 rpm) and inlet temperature 50 °C inserted to make tablets heated. By inserting inlet temperature to 50 °C, outlet temperature will reach approximately to 35 - 39 °C and air flow set at 50 m^3/min. By this way tablets will lose humidity and are prepared for spraying phase.

After 10-15 min, tablets average weight was measured to consider mass of tablets after preheating to be able to check how much coating was applied during spraying.

Spraying

Changing inlet temperature to 50-60 °C to let outlet temperature reach a maximum of 44 °C, suspension was sprayed into cores settling a spraying pressure to 1.2/1.4 bar and a pump speed between 7-10 ml/min. In this spraying phase, the drum speed between 12 - 16 rpm and airflow at 50 m^3 /min were controlled.

Every 15 - 20 minutes average weight was checked to see if the target value is reached, the theoretical mass of the coating should be 7.54 mg. It is imperative to include a thorough assessment of the tablet temperature alongside the routine check for average weight. This precaution is crucial due to the potential consequences of tablet overheating, such as capping or uneven distribution of coating suspensions. Furthermore, after each weight control procedure, it is essential to diligently clean the nozzle with a cloth before proceeding with spraying. This precautionary step is necessary to prevent nozzle clogging caused by suspended particles, ensuring a smooth and efficient coating process.

Drying

After reaching 7.54 mg of mass of coat on cores, drum speed was set between 3 – 8 rpm and inlet temperature between 32 - 35 °C so outlet temperature cooled between 28 - 30 °C. This process continued for 10 - 60 min (recommended time is 40 min) until the tablets got cooled and dry. Then, tablets were removed from a drum, put in the labeled box and sealed with a proper name tag.

6.3.4 Evaluation of tablet properties

Mass uniformity

The estimation of the average weight of tablet cores involved placing 10 tablets on the analytical scale and conducting five repetitions of the measurement. This process was repeated until a total of 50 tablets were measured to determine the overall average weight.

Following the completion of the coating process, all tablets underwent a drying procedure. Subsequently, all tablets were gathered, and mass uniformity testing was performed. This involved placing 10 tablets on an analytical scale and conducting five repetitions of the measurement. This process was then repeated with another set of 10 tablets. In the end, the average tablet weight from the device was obtained, and the standard deviation (SD) was expressed.

Disintegration time

Disintegration time of tablets DT (min) was tested according to the monograph for normal sized tablets and capsules (Ph Eur. 11.3) but with a slight difference. Three

tablets were tested using a basket apparatus. The tablets were placed in the basket and lowered into purified water heated to 37°C ±0.5°C. The apparatus raised and lowered tablets. The time of disintegration of last tablet was recorded when the complete tablet had disappeared from the basket and there were no fragments left on the bottom mesh of the basket. Between each batch of tablets, the apparatus was cleaned, and fresh medium was added and heated.

Crushing force

The height and diameter measurements for all tablets were conducted using the Pharmatron MultiTest 50 device. The setup for measuring 10 tablets involved a systematic process. Initially, the device measured the diameter with the tablet positioned horizontally, where one arrow extended to the opposite end and touched the tablet corner. Following this, the tablet was repositioned vertically, and the arrow made contact with the tablet's middle part. Finally, the tablet was once again placed horizontally, and this time the arrow approached until it caused the tablet to break, after which the tablet was disposed of.

It is noteworthy that all measurements, from diameter assessments to the final breaking point, were seamlessly executed using the Pharmatron MultiTest 50. The data generated during these measurements were automatically printed from the device's printer after the completion of the entire process for the last tablet.

6.3.5 Data processing

Data were processed by Microsoft Excel (version 16.83); statistical analysis was carried out using single factor analysis of variance (ANOVA) at the significancy level $\alpha = 0.05$.

7 Results and discussion

Titanium dioxide (TiO_2) has been a widely used ingredient in pharmaceuticals, often added to give medications a white color. However, new research has raised concerns about its safety, suggesting it could potentially be linked to cancer (Ghazy E et al 2019). This uncertainty means that the availability of TiO_2 for pharmaceutical use may no longer be guaranteed. Therefore, it is crucial to explore alternative options for ensuring the safety and effectiveness of drug products.

In this study, dynamics of coating with two different coating materials (the solution of lactose monohydrate and/or the suspension of calcium carbonate, respectively) for two different core shapes (round or flat-faced) were studied. The coding of tablets in experimental runs is shown in Fig. 5. The effect of coating material on coating process fluency and some parameters of tablets were investigated during this experiment.

7.1 Characterization of substances

There are two types of lactose from the list of substances: lactose anhydrous is available in cores as the filler, and act as a solution in aqueous media. lactose monohydrate M200 is used to coat tablets. According to Figure 2 (Meggle Pharma 2024), lactose monohydrate M200 particles are achieved by milling, and particles are soluble in water. At room temperature (20°C), its solubility is approximately 18.9 g/100 mL of water. As the temperature increases, the solubility also increases, reaching about 37 g/100 mL at 60°C.

The particles of lactose monohydrate M200 are usually crystalline in nature. They are often described as having a regular, angular, and somewhat prismatic shape. As described in Fig 2B two particle size ranges allow the manufacturer to compare and control the proportion of very fine particles (<32 μm) versus slightly larger particles (<100 μm). This helps in understanding the distribution of particle sizes within the product more comprehensively (Meggle Pharma 2024):

Particle size < 32 μm:

- Specified range: 45-75% which means that for this particle size category, the acceptable percentage of particles passing through the sieve should be between 45% and 75%.

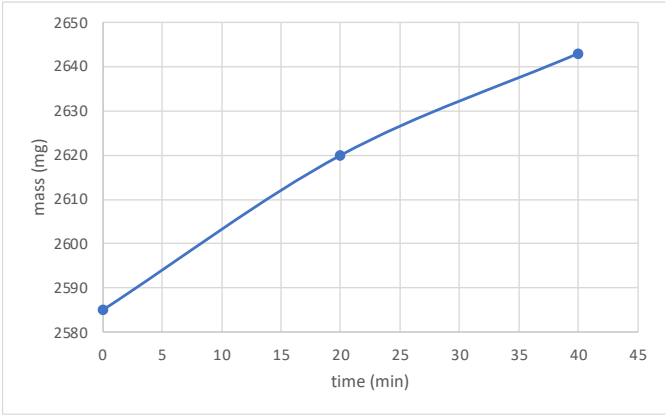
Particle size < 100 μm:

- Specified value: Not Less Than (NLT) 90% which means that for this particle size category, at least 90% of the particles should pass through the sieve.

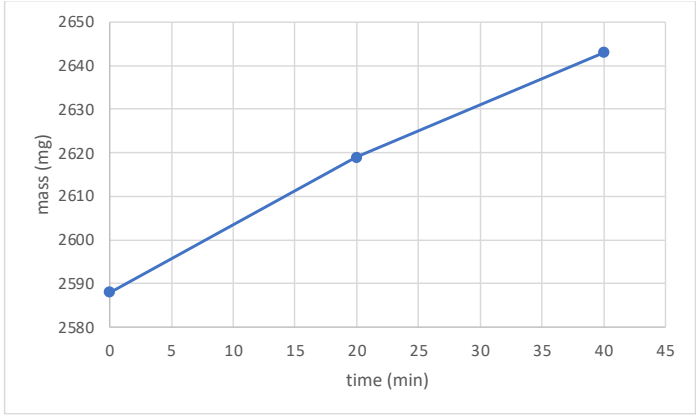
Figure 3A (SPI Pharma 2019) illustrates the SEM (Scanning Electron Microscope) image for a collection of calcium carbonate particles. These particles predominantly exhibit a roughly spherical shape with a range of sizes. The surface morphology appears smooth, which is characteristic of typical calcium carbonate precipitates. This smooth surface and spherical shape are likely indicative of the precipitation process used in the synthesis of these particles. The Figure 3B (SPI Pharma 2019) presents the particle size (µm) distribution of calcium carbonate. This distribution reveals a wide range of particle sizes, from sub-micron levels to over 1000 µm. Such a broad size range can often result from the production process used. A significant peak in the graph suggests a high concentration of particles in the size range of approximately 600 to 1000 µm. This peak indicates that while there is a broad overall size distribution, there is a notable prevalence of particles within this specific size range, which can be critical for specific applications and performance characteristics.

7.2 Coating with an orange-coloured coat

The efficiency of coating was studied by the coating dynamics which represents an increase in the core mass per time. coating suspension contains lactose monohydrate or calcium carbonate and ferric oxide as a colorant.



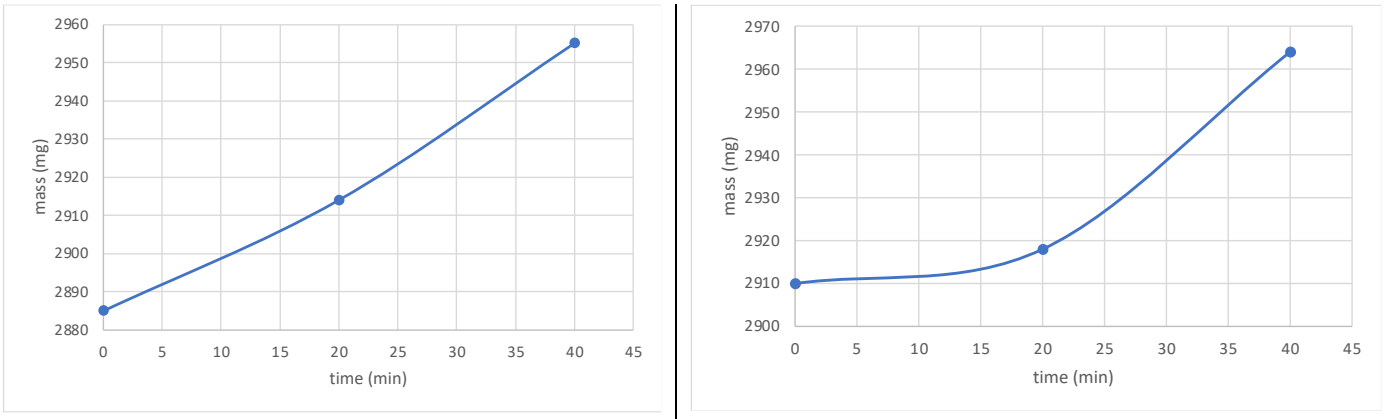
A)



B)

Fig. 6: Illustration of coating dynamics for the lentil-shaped core; A) A1, B) A2

Figure 6 illustrates the impact of the coating suspension on the weight gain of tablets until they reach the final target, which is a 3% increase in mass compared to the mass of the lentil-shaped cores. After reaching to needed mass the A1 tablets had better visual appearance and coat homogeneity compare to A2. By scratching two tablets together manually, the darkening in the color of tablets in place of scratch was observed which was more visible for A2 tablets, containing calcium carbonate. This could suggest that during coating in the larger scale there is a high abrasion between tablets and this could result in inhomogeneity of color between tablets. Such inconsistency could diminish the tablet's appeal in the market and raise concerns from the perspective of patients, who may perceive it as indicative of poor quality or potential issues with the tablet's composition.



A) B)

Fig. 7: Illustration of coating dynamics for the flat-shaped core; A) B1, B) B2

Accordingly, Figure 7 shows change in mass of tablets based on spraying of coating suspension on flat-shaped cores; the target value of the mass higher by 3% compare to mass at time 0 was the same as for the lenticular cores. In B2 sample, the significant increase in mass observed between time intervals 20 min and 40 min suggests the likelihood of uneven distribution of calcium carbonate suspension on the flat-shaped cores during the coating process. Two tablets were subjected to abrasion once more to observe if the color changes. The B2 tablets, containing calcium carbonate, exhibited a more intense color change. This difference can be attributed to the larger surface area of flat tablets, resulting in a broader spread of color alteration compared to the lentil-shaped tablets, where the darkening was primarily focused on the center.

Apart from the mass increase, the tablet diameters were also changed after coating as summarized in Table 1 for the lenticular tablets. Note that all the results for coated tablets are from the final coated tablets and after drying process. The application of coating on the tablet cores resulted in an increase in both diameter and height in both coatings, however, the results from Table 1 show that the calcium carbonate coat (A2) is approximately 0.16% thicker than the lactose coat (A1). This could arise from the difference in particle size and coating dispersion nature.

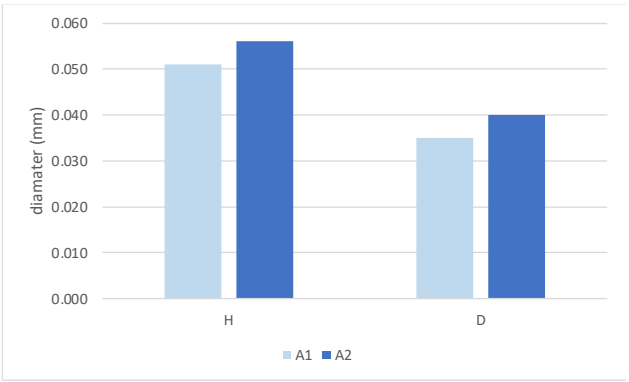
Table 1: Effect of coating material on diameters of lentil-shaped core, A1 and A2 tablets

	core		A1		A2	
	H (mm)	D (mm)	H (mm)	D (mm)	H (mm)	D (mm)
	4.42	9.04	4.46	9.11	4.48	9.07
	4.42	9.12	4.47	9.09	4.47	9.12
	4.43	9.07	4.49	9.10	4.50	9.11
	4.43	9.05	4.47	9.08	4.48	9.11
	4.45	9.04	4.46	9.07	4.50	9.10
	4.41	9.07	4.50	9.09	4.46	9.10
	4.41	9.06	4.45	9.11	4.47	9.10
	4.41	9.04	4.51	9.11	4.49	9.10
	4.44	9.05	4.48	9.08	4.49	9.09
	4.41	9.04	4.45	9.09	4.45	9.08
AV	4.42	9.06	4.47	9.09	4.48	9.10
SD	0.014	0.025	0.021	0.014	0.017	0.015

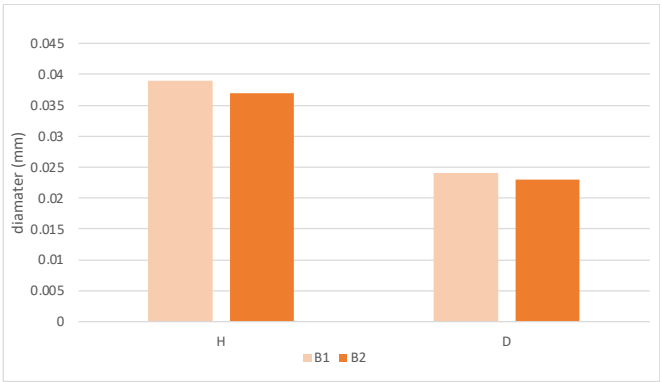
Table 2: Effect of coating material on diameters of flat-shaped core, B1 and B2 tablets

	core		B1		B2	
	H (mm)	D (mm)	H (mm)	D (mm)	H (mm)	D (mm)
	3.89	9.13	4.05	9.08	4.03	9.08
	4.01	9.05	4.04	9.07	4.06	9.07
	4.04	9.04	4.11	9.09	4.04	9.08
	4.02	9.04	4.01	9.07	4.04	9.08
	4.02	9.05	4.07	9.09	4.04	9.07
	3.97	9.04	4.07	9.08	4.09	9.09
	4.04	9.04	4.04	9.07	4.01	9.07
	4.03	9.05	4.01	9.07	4.07	9.08
	4.00	9.04	4.04	9.07	4.07	9.07
	4.04	9.05	4.05	9.08	4.02	9.07
AV	4.01	9.05	4.05	9.08	4.05	9.08
SD	0.046	0.028	0.030	0.008	0.025	0.007

Effect of the coating material on diameters of the flat-shaped core, is summarized in Table 2. The average diameters of coated tablets for both coating dispersions is similar to each other, indicating a consistent increase compared to the core.



A)

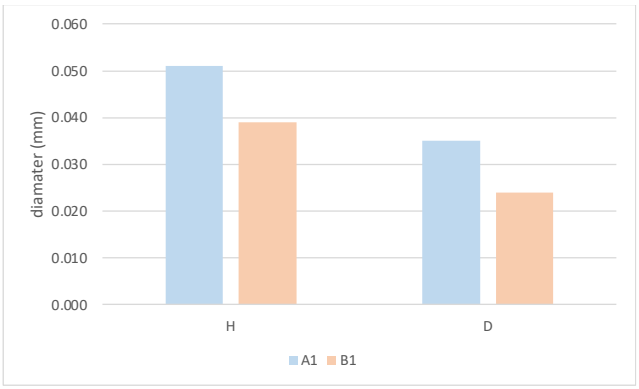


B)

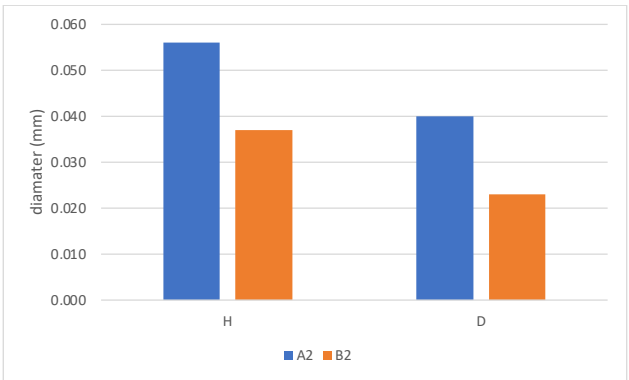
Fig. 8: Comparison of diameters after coating with different coating mixtures for the lentil-shaped core (A) and flat-shaped core (B); A) A1, A2, B) B1, B2

Based on the data presented in the Figure 8, it is evident that a greater amount of coating suspension is required to achieve the target value for lentil-shaped cores containing calcium carbonate (A2), in comparison to those containing lactose monohydrate (A1). However, this trend does not hold true for flat-shaped cores (Fig. 8B), where both height and diameter for lactose monohydrate coated tablets (B1) exhibit approximately slightly higher values compare to (B2), i.e, the calcium carbonate coat. The analysis of variance (ANOVA) showed that the difference between A1 and A2 is statistically highly significant ($p < 0.01$), while the difference between B1 and B2 is statistically insignificant ($p > 0.01$).

As depicted in Figure 9, it is visible that the lentil-shaped tablets A undergo a more pronounced change in both height and diameter compared to the flat-shaped tablets B, regardless of the coating dispersion type. This observation suggests that the center of lentil-shaped tablets may be more susceptible to the influence of coating suspension during the spraying process, thus leading to a greater alteration in dimensions. The analysis of variance (ANOVA) showed that the difference between A1 and B1 is statistically highly significant ($p < 0.01$); additionally, the difference between A2 and B2 is also statistically significant ($p < 0.01$).



A)



B)

Fig. 9: Illustration of influence of a core shape on the coating thickness of lentil-shaped core (A) and flat-shaped core (B); A) A1, B1 , B) A2, B2

7.2.1 Mechanical properties of orange-coloured coated tablets

In the next part, the effect of shape as well as the coating material on the mechanical properties (the crushing force, CF) of tablets was evaluated.

Table 3: Effect of coating on crushing force CF (N) of lenticular tablets A1 and A2

	CF (N)		
	Core	A1	A2
	103	132	131
	100	144	127
	114	143	129
	103	135	130
	97	129	124
	106	145	115
	106	142	125
	110	151	137
	96	135	128
	101	136	121
AV	103.60	139.20	126.70
SD	5.602	6.828	5.982

The coating process led to an increase in crushing resistance in both A1 and A2, with A1 demonstrating a more significant impact. The CF increased from 103.6 N to 139.2 N. This suggests that the lenticular tablets coated with the lactose mixture exhibit the significantly ($p < 0.01$) higher resistance to crushing compared to calcium carbonate coating.

The crushing resistance for both B1 and B2 flat-faced tablets (Table 4) is quite similar, and both are however greater than the core CF value 201.8 N. This suggests that the coating process increased the crushing resistance of the tablets, regardless of the coating dispersion used, i.e. with B1 and B2 exhibiting comparable levels of strength, both surpassing the resistance observed in the uncoated core. This hypothesis is supported statistically because the difference between B1 and B2 Orange coated tablets is statistically insignificant (p-value higher than 0.01).

Table 4: Effect of coating on mechanical resistance of flat-faced tablets B1 and B2

	CF (N)		
	Core	B1	B2
	161	284	252
	229	257	238
	173	253	276
	228	257	273
	196	236	266
	140	246	253
	234	271	224
	235	179	284
	234	239	263
	188	242	143
AV	201.80	246.40	247.20
SD	35.181	27.913	40.811

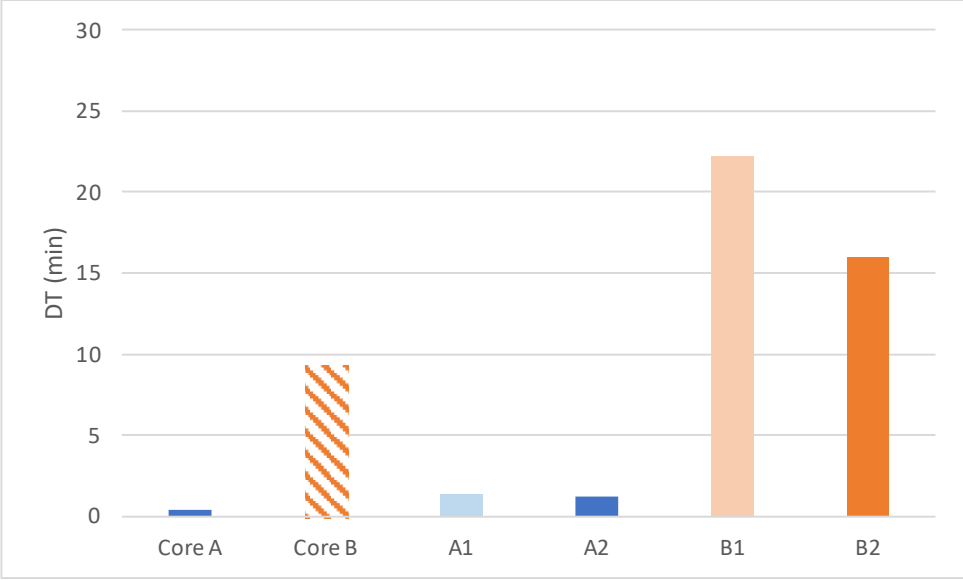


Fig. 10: The comparison of disintegration time of cores and coated tablets

Figure 10 illustrates the outcomes of the disintegration process of cores and coated lenticular and flat shaped tablets, presenting the time taken for the last tablet to

disintegrate completely within the apparatus. This disintegration apparatus employed distilled water maintained at a temperature of 37°C as the medium.

Core A and core B exhibit significant differences in the disintegration time, possibly attributed to the higher crushing force (and mechanical resistance) of flat core B, which is approximately 94.72% greater than core A. As the cores composition was the same, containing croscarmellose sodium as a disintegrant, this could be explained as the effect of the shape and different effect of punches throughout the core surface (Jange et al. 2023). The effect of compression force is probably lower for the convex-shaped cores (lenticular) than for the flat-shaped ones leading finally to the shorter DT.

Furthermore, the disintegration time of A1 is marginally longer than A2 (1.40 min compare to 1.20 min), despite A2 possessing a larger diameter and height of a coat. Nevertheless, the difference between A1 and A2 is statistically highly significant ($p < 0.01$). This would result from the fact that being composed of calcium carbonate (A2), the coat is less soluble than lactose monohydrate one (A1). However, A1 exhibits a higher crushing force, indicating greater tablet consistency, which could account for the slightly prolonged disintegration time.

As shown in Figure 10, the disintegration time of both B1 and B2 is longer than the DT of a core. In contrast to lenticular cores, the disintegration time of B1 differs significantly from B2. This variance may be due to the different solubility of the last tablet in disintegration apparatus for the B series, which dissolved over a longer period.

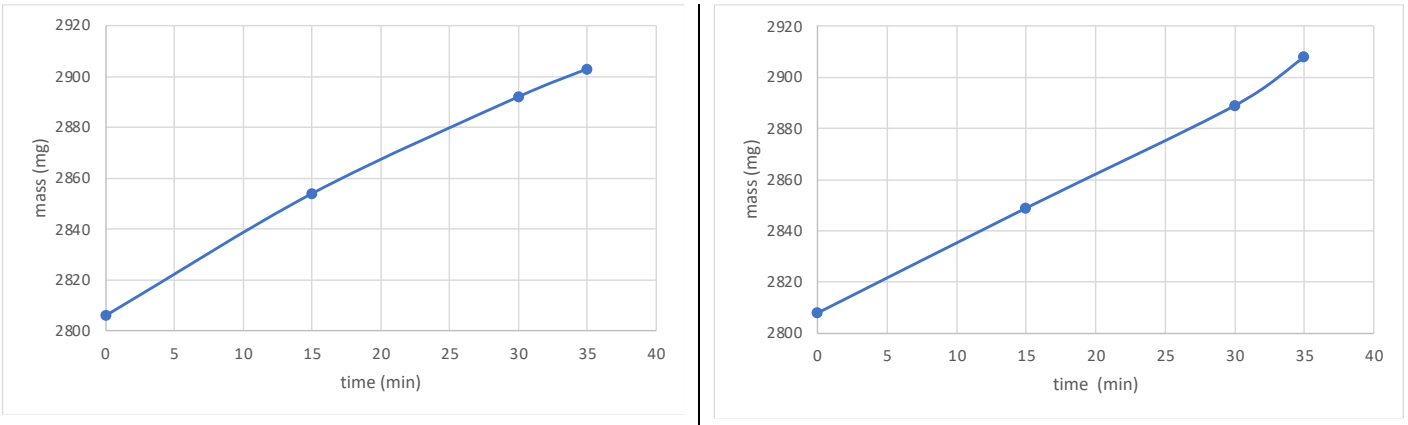
Higher disintegration time of lactose monohydrate coated tablets compare to calcium carbonate could be confusing, because of the solubility of lactose and insolubility of calcium carbonate in aqueous environment. According to mechanical resistant of tablets in table 3 and 4, tablets coated with lactose monohydrate demonstrated higher crushing resistance compared to those coated with calcium carbonate. This higher mechanical strength can prolong the disintegration time as the tablet structure is more resistant to breaking apart. Beside, lactose monohydrate coated tablets exhibit a more uniform coating from optical point of view, which can contribute to a slower disintegration as the coat provides additional structural integrity.

In conclusion, orange-coated tablets with coatings CC and L exhibit similar risk to show darkening of the tablets due to surface corrosion, indicating poor quality of the coats. Additionally, CC has lower solubility compared to the lactose coating material.

As calcium carbonate is alkaline in nature, when it disperse in water, it raises the pH of the solution. This higher pH environment can affect the stability of pH-sensitive APIs. Some APIs may degrade or lose efficacy in an alkaline environment. For instance, certain antibiotics, vitamins, and hormones are more stable in acidic or neutral conditions. can be incompatible with various active pharmaceutical ingredients (APIs) due to its different pH profiles. (Smith and Doe 2020)

7.3 Coating with a green-coloured coat

This section explores into the properties of flat-shaped green coated tablets. As the composition of B and B_{API} cores was different as detailed in the methodology, it is important to note that due to this fact, the direct comparison of the properties with the orange coated tablets is not possible.



A) B)

Fig. 11: Illustration of coating dynamics for the green flat-faced cores (B_{API}); A) Coating with L, B) Coating with CC

Figure 11 demonstrates the influence of the coating suspension on the weight gain of tablets until they attained the final target, which is a 3% increase in mass compared to the core mass. The scale of production for green tablets was relatively smaller than that for orange tablets (500 g). As observed visually for both lactose monohydrate and calcium carbonate coat, the homogeneity of the green coating was improved compared to orange tablets. Additionally, the degree of color darkening due to scratching was less pronounced, possibly attributed to a lower color intensity. The pale green hue of

the tablets might effectively mask any darkening during surface friction in the large-scale production.

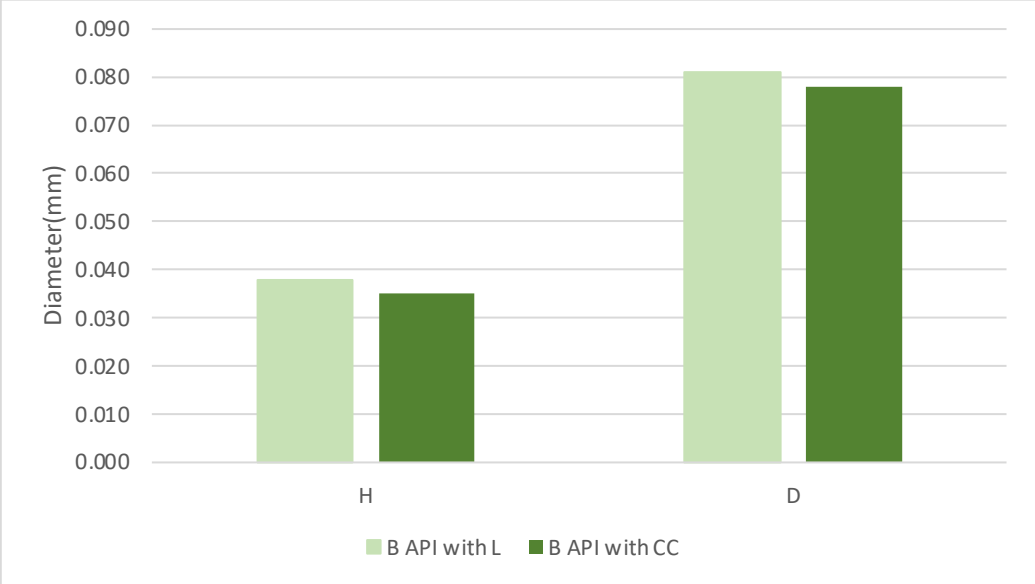


Fig. 12: The influence of the coating material on the coat thickness for green coated tablets.

Based on Figure 12, it is evident that the thickness of both coatings is quite similar, however, the coated tablet B_{API} with L showed slightly higher values compared to B_{API} with CC tablets. Interestingly, despite B_{API} with CC having a slightly higher final weight (290.8 mg) compared to B_{API} with L (290.3 mg).

Thickness of tablets with lactose monohydrate in orange coated tablets (B1) shows greater numbers compare to calcium carbonte coated tablets (B2). Final weight of of B1 (295.5 mg) is lower than B2 (296.4 mg). This means that this behaviour is same regardless of core composition in orange and green coated tablets.

7.3.1 Mechanical properties of the green-coated tablets

The tablet coating process enhances the resistance of cores to crushing forces for both coating materials (Table 5). However, B_{API} with L tablets exhibit a greater increase in resistance compared to B_{API} with CC, indicating that lactose monohydrate coat is more resistant to crushing forces. Mechanical resistance of the orange coated flat-shaped tablets, in other words B1 and B2 (Table 4), contrary, shows that CC-coated ones slightly has higher resistance. The analysis of variance (ANOVA) showed that the

difference between B_{API} with L and B_{API} with CC is statistically insignificant ($p > 0.01$); additionally, the difference between B1 and B2 is also statistically insignificant ($p > 0.01$).

Table 5: Effect of coating on mechanical resistance of green-coated B_{API} with L and B_{API} with CC

	CF (N)		
	B_{API} Core	B_{API} with L	B_{API} with CC
	65	89	80
	58	98	99
	65	99	98
	61	102	88
	55	89	85
	59	91	80
	55	96	92
	65	94	96
	52	98	86
	58	88	86
AV	59.30	94.40	89.00
SD	4.644	4.926	6.960

In conclusion of green-coated tablets, those coated with lactose monohydrate exhibited the greater diameter and height, and demonstrated the higher crushing force. Additionally, both types of green-coated tablets showed the less intense darkening due to corrosion compared to the orange-coated tablets, which is a notable advantage.

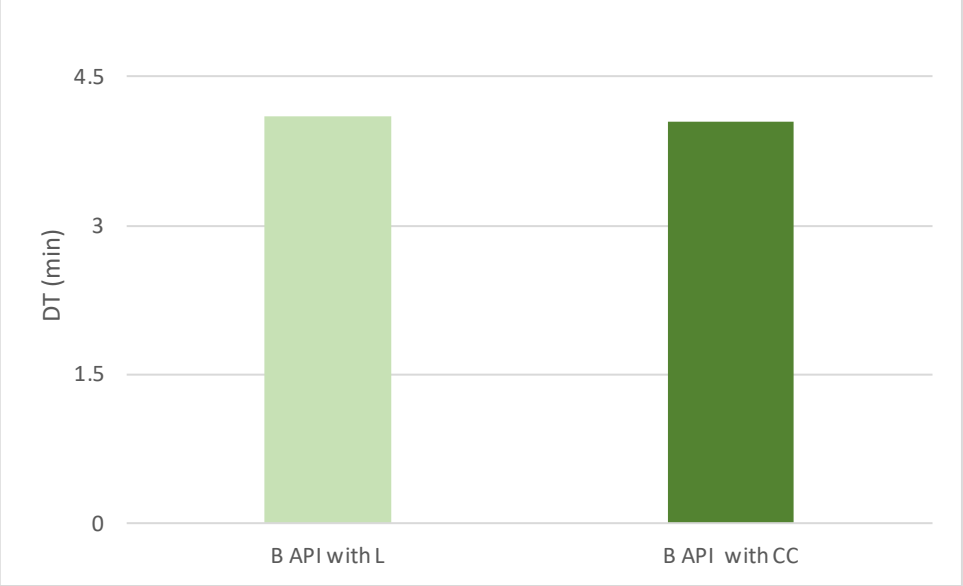


Fig. 13: Disintegration time of green coated B_{API} tablets

As may it is not fully visible from Figure 13 but lactose coated tablets (B_{API} with L) has slightly higher disintegration time (4:10) compared to calcium carbonate (B_{ApI} with CC) (4:05). This behaviour is same in flat-faced orange coated tablets.

8 Conclusions

The study aimed to develop a titanium dioxide-free coating for pharmaceutical tablets and evaluated the effects of two coating materials, lactose monohydrate and calcium carbonate, on different core shapes (lenticular, A, and flat-faced, B). Based on the experimental results achieved in the diploma thesis, the conclusions can be summarized as follows:

Orange coat colour

1. Coating dynamics:

- The coating process required a larger amount of coating suspension for lenticular-shaped cores, particularly with calcium carbonate. Apart from B2, which showed some regular pattern in the calcium carbonate suspension distribution, the dynamics of the coat increase was linear.
- Despite similar preparation methods, statistically significant increase in the diameter and height of a coat were observed for lenticular tablets but not for flat tablets.

2. Coating efficiency and appearance:

- Lactose monohydrate coatings (A1, B1) provided smoother and more uniform coats compared to calcium carbonate coatings (A2, B2).
- Tablets with lactose monohydrate coatings exhibited better visual appearance and coat homogeneity, especially in lenticular-shaped cores. Contrary, the calcium carbonate-coated tablets showed greater abrasion and inhomogeneity during the coating process.

3. Mechanical properties:

Both coatings increased the crushing resistance of the tablets compared to the uncoated core.

- For the lentil-shaped tablets, A1 demonstrated significantly higher resistance over A2.
- For the flat-faced tablets, B1 showed slightly higher values than B2, although the difference was statistically insignificant.

4. Disintegration time:

Disintegration times varied significantly between the different coatings and core shapes.

- Lactose monohydrate-coated tablets (A1, B1) generally had longer disintegration times than calcium carbonate-coated tablets (A2, B2), likely due to the higher mechanical strength and uniform coating of the former.
- The flat-faced cores (B series) had longer disintegration times compared to the lenticular cores (A series), attributed to their higher crushing force and mechanical resistance.

Green coat colour:

- A regular coating pattern dynamics was noted. Both types of green-coated B_{API} tablets showed less intense darkening due to corrosion compared to the orange-coated tablets, indicating an advantage in terms of visual stability.
- The lactose monohydrate green-coated tablets (B_{API} with L) showing higher crushing resistance than calcium carbonate coatings (B_{API} with CC), but the differences were not statistically significant.
- Among the green-coated tablets, B_{API} with L exhibited a slightly longer disintegration time compared to B_{API} with CC.

9 References

AUGSBURGER LL, HOAG SW. Pharmaceutical Dosage Forms-Tablets. CRC press; 2016. ISBN-13: 978-1498702387

CARTER, J. C. The role of color in pharmaceutical development. *Pharm. Technol.* 2016, 40(11), 36-43. ISSN 0031-6873.

CHOURASIA, M. K., & JAIN, S. K. Pharmaceutical approaches to colon targeted drug delivery systems. *J. Pharm. Sci.* 2003, 6(1), 33-66. ISSN 1735-7777.

DAVIES, N. M., & FEDDAH, M. R. A novel method for assessing dissolution of rapidly dispersing oral dosage forms. *Pharm. Dev. Technol.* 2003, 8(4), 405-412. ISSN 1083-7450.

European Medicines Agency. Annex I on the use of titanium dioxide as an excipient in human medicines: Industry feedback on QWP experts' questions. Retrieved July 2, 2021 Available at: https://www.ema.europa.eu/en/documents/other/annex-i-use-titanium-dioxide-excipient-human-medicines-industry-feedback-qwp-experts-ema-questions_en.pdf.

European Pharmacopoeia Commission. (2020). *European Pharmacopoeia* (10th ed.). Council of Europe.

FELTON, L. A. Film Coating of Oral Solid Dosage Forms. *AAPS Pharm. Sci. Technol.* 2013, 14(2), 309–321. ISSN 1530-9932. doi:10.1208/s12249-013-0016-8.

GANDHI, S. P., NAIR, R., & NAIR, P. D. Advances in mucoadhesive drug delivery systems. *Res. J. Pharm. Technol*. 2015, 8(2), 119-126, ISSN 0974-3618.

GERNAND, J.: Are Titanium Dioxide Nanoparticles in Food a New Health Risk? Retrieved Jun 2, 2014, Available at: https://www.progressiprocity.com/home/are-titanium-dioxide-nanoparticles-in-food-a-new-health-risk-1242.htm.

GHAZY E, GAD S, EL-NAHHAS T, HASSAN R, AZIZ R: Titanium dioxide particles: a review of current experimental and toxicological data. *Drug Delivery Sci. Technol.* 2019, 51, 494-500, ISSN 1773-2247.

GHEBRE-SELLASSIE, I., & MARTIN, C. Pharmaceutical Coating Technology. CRC Press. 2006, ISBN 978-0-8493-3147-7.

HALEEM, I., JAVAID, Z., SOHAIL, M. Coating technologies for tablet manufacturing: A review. *J. Basic and Clinic. Pharm.* 2014, 5(2), 27–33. ISSN 0976-0105. doi:10.4103/0976-0105.141942.

HEINICKE, G., BÖHM, R., & BONGAERTS, J. Color coatings on tablets for improved identification and compliance. *J. Pharma. Sci*. 2020, 109(1), 545-555, ISSN 0022-3549.

HU, YU-CHIH & DAI, CHING-LIANG & HSU, CHENG-CHIH. Titanium Dioxide Nanoparticle Humidity Microsensors Integrated with Circuitry on-a-Chip. Sensors. 2014,14, 4177-88. ISSN 1424-8220. doi:10.3390/s140304177.

JANGE, C.G., WASSGREN, C.R., & AMBROSE, K. The Significance of Tablet Internal Structure on Disintegration and Dissolution of Immediate-Release Formulas: A Review. *Powders*, 2023, 2(1), 99-123. ISSN 2674-0516.

JONES, D. S.. Pharmaceutical Applications of Polymers for Drug Delivery. Cambridge: RSC Publishing. 2008, ISBN 978-0-85404-915-7.

LECOMTE, F., SIEPMANN, J., WALTHER, M., MACRAE, R. J., & BODMEIER, R. Polymer blends used for the aqueous coating of solid dosage forms: Importance of the type of plasticizer. *J. Controlled Release*, 2003, 89(3), 457-471. ISSN 0168-3659. doi:10.1016/S0168-3659(03)00155-0.

LI, J., CHEN, D., CHEN, J., & HUANG, Y. Recent progress in natural pigments for sustainable food packaging materials. *Critical Reviews in Food Sci. and Nutrition*, 2018, 58(13), 2117-2134. ISSN 1549-7852.

MARUCCI, M., RAGNARSSON, G., & AXELSSON, A. Coated pharmaceutical dosage forms: fundamentals, materials and techniques for extended release. *J. Controlled Release*, 2013, 166(2), 126-139, ISSN 1873-4995.

MISHRA, P. R., JAIN, N. K., & DUBEY, P. Nanotechnology-based approaches for oral delivery of biologics: strategies and challenges. *Critical Reviews in Therap. Drug Carrier Sys.* 2018, 35(4), 327-381, ISSN 0743-4863.

NIELSEN, L. H., KELLER, S. S., & BOISEN, A. Microfabricated Devices for Oral Drug Delivery. *Lab on a Chip*, 2017, 17(9), 1406–1433. ISSN 1473-0197. doi:10.1039/C6LC01513K.

NOKHODCHI, A., RAJA, S., & PATEL, P. Coating of oral solid dosage forms: *A review. Drug Dev. Ind. Pharm.* 2015, 41(9), 1395–1409. ISSN 1520-5762. doi:10.3109/03639045.2014.964800.

PARIKH, D. M. (Ed.). Handbook of Pharmaceutical Granulation Technology. CRC Press. 2016, ISBN 978-1-4398-6087-1.

PAULO F, SANTOS L. Design of experiments for microencapsulation applications: a review. *Mater. Sci. Eng. C*. 2017, 77, 1327–1340. ISSN 0928-4931. doi:10.1016/j.msec.2017.03.219.

PINTO, J. T., PERES, C., & SILVA, J. P. Functional coatings in pharmaceutical tablets: *an overview. Intl. J. Pharm.* 2020, 576, 119025, ISSN 1873-3476.

PORTER, S. C. Coating of Pharmaceutical Dosage Forms. In Remington: Essentials of Pharmaceutics. Pharmaceutical Press. 2016, 303-320, ISBN 978-0-85711-362-3.

PORTER, S. C., BRUNO, C. H. Coating of Pharmaceutical Dosage Forms. *Pharm. Dosage Forms: Tablets.* 1990 (Vol. 3, pp. 77-159). Marcel Dekker, Inc. ISBN 978-0824783340.

RAO, R. N., MANDAPALLI, P. K., & GANNU, R. Development of fast dissolving tablets for poorly soluble drug by solid dispersion technique using factorial design. *Research J. Pharm. Technol*. 2017,10(4), 1423-1429. ISSN 0974-360X.

REYNOLDS, T. D., GEHRIS, A. S., & HERBIG, S. M. Advances in Coating Technology for Solid Oral Dosage Forms. *Pharm. Dev. Technol*. 2018, 23(3), 223–234. ISSN 1530-9932. doi:10.1080/10837450.2017.1337795.

ROWE, R. C., SHESKEY, P. J., & QUINN, M. E. Handbook of Pharmaceutical Excipients (6th ed.). London: Pharmaceutical Press. 2009, ISBN 978-0-85369-792-3**.**

ROY, P., SHAHIWALA, A., & MISRA, A. Controlled release approaches for orally administered drugs. *J. Controlled Release*, 2014, 190, 151-163. ISSN 0168-3659.

SAHA, S., & SHAHIWALA, A. Multifunctional coprocessed excipients for improved tabletting performance. *Expert Opinion on Drug Delivery*, 2009, 6(2), 197-208. ISSN 1742-5247. doi:10.1517/1742524080263140.

SALAMANCA, C. H., LÓPEZ, B. L., & MÉNDEZ, J. A. New alternatives for titanium dioxide in pharmaceutical coatings. *Acta Farmacéutica Bonaerense*, 2020, 39(1), 19-26, ISSN 0326-2383.

SALUNKHE, S. S., BHATIA, N. M., & BHATIA, M. S. Advances in film coating technology: A review. *J. Drug Delivery Sci. Technol*. 2019, 50, 145-155. ISSN 1773-2247. doi:10.1016/j.jddst.2019.02.012.

SASTRY SV, NYSHADHAM JR, FIX JA. Recent technological advances in oral drug delivery–a review. *Pharm. Sci. Technol. Today*. 2000; 3 (4),138–145. ISSN: 1461-5347.

SIEPMANN, J., & SIEPMANN, F. Mathematical modeling of drug release from lipid dosage forms. *Intl. J. Pharm.* 2013, 454(2), 160–173. ISSN 0378-5173. doi:10.1016/j.ijpharm.2013.01.063.

SMITH, J. A., & DOE, J. R. Stability of pH-Sensitive APIs in Alkaline Environments. *J. Pharm. Sci*. 2020, 109(4), 1234-1245. 10.014. ISSN 0022-3549. doi:10.1016/j.xphs.2019.

SPI Pharma Retrieved October 1, 2019 Available at: https://www.spipharma.com/en/products/mineral-supplement-ingredients/vitasmooth-dc-calcium-carbonate-with-excipients.

SUGANYA V , ANURADHA V. Microencapsulation and nanoencapsulation: a review. *Int. J. Pharm. Clin. Res*. 2017; 9 (3), 233–239. ISSN: 0975 1556. doi:10.25258/ijpcr.v9i3.8324.

THOMBRE, A. G. Oral delivery of medications to chronic patients: A focus on development of gastroretentive drug delivery systems. *J. Drug Delivery Sci. Technol.* 2018, 43, 43-53. ISSN: 1773-2247.

TURCO, S. J., & KING, R. E. Compression coating for controlled release of active ingredients. *J. Pharm. Sci.*1974, 63(3), 487-489. ISSN 0022-3549.

VOGELEER, J. D., GIL, M., & SUAREZ, M. Tablet coating with the Glatt GC1. *Pharm. Technol. Eu.* 2017, 29(4), 24-30. ISSN 1356-3252.

ZARMPI, P., FLANAGAN, T., MEEHAN, E., MANN, J., & FOTAKI, N. Biopharmaceutical aspects and implications of excipient variability in drug product performance. *Eu. J. Pharm. Biopharm*. 2017, 111, 1-15. ISSN 0939-6411. doi:10.1016/j.ejpb.2016.11.015.