Oral formulations for children

The microstructure of functionalized calcium carbonate as key characteristic to develop age-appropriate and compliance enhanced formulations

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Dedicated to

my parents and my husband

“Don’t panic and carry a towel”

Hitchhiker’s Guide to the Galaxy by Douglas Adams

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Abbreviations

ADF	abuse deterrent formulation
API	active pharmaceutical ingredient
art.sal.	artificial saliva
BCS	biopharmaceutical classification system
CPI	critical path initiative
EMA	european medicines agency
EMLc	list of essential medicines for children
EU	European Union
FCC	functionalized calcium carbonate
FDA	food and drug administration
LMIC	low and middle income country
NSDS	nipple shield delivery system
ODT	orally disintegrating tablet
Ph.Eur.	European Pharmacopoeia
PCL	polycaprolactone
PDCO	European Medicines Agency's Paediatric Committee
PFI	pediatric formulation initiative
PIP	pediatric investigation plan
pMDI	pressurized metered-dose inhaler
PUMA	pediatric-use marketing authorization
QbD	quality by design
RDT	rapidly disintegrating tablet
TIC	tablet-in-cup
TOS	tablet for oral suspension
VAS	visual analogue scale
VHC	valved holding chamber

Summary

The development of age-appropriate formulation for children is a challenging task. Children cannot easily swallow a conventional tablet, therefore alternative dosage forms that can be administered orally are required. These are buccal tablets, oral films as well as orally disintegrating tablets or rapid disintegrating tablets. The age-appropriate formulations are contributing enormously to compliance, as such formulations ensure acceptable palatability. Therefore, there is a need of suitable excipients. Functionalized calcium carbonate (FCC) has already been investigated for different applications. It was used to develop orally disintegrating tablets (ODTs) because the tablets were characterized by high physical stability at low compressive stress. To ensure acceptable palatability, a taste masked and mouthfeel enhanced formulation based on FCC-granules was developed and tested for its acceptance in 20 healthy volunteers. This formulation was also analyzed with a novel *in vitro* model to determine rate constants for liquid sorption and disintegration as well as disintegration time. As a further step, the stability of the FCC-based granules combined with two model drugs were investigated in form of tablets for oral suspension (TOS). The influence of stress conditions on content, disintegration time and hardness was assessed. To understand and describe the distribution of drug in different drug loads, moxidectin containing mini-tablets were analyzed with synchrotron X-rays micro tomography. Moreover, a mineral polymer composite material (FCC-PCL) was developed and investigated for the use in geometry constrained sustained release formulation in form of a tablet-in-cup (TIC) device. The results show that the FCC-based ODTs with enhanced mouthfeel and taste-masking show good acceptability *in vivo* and the analysis with the *in vitro* model showed, that the ODTs do not need more liquid to completely disintegrate than available in the human mouth. The additional excipient in the formulation did not change the characteristics of the FCC under pressure. TOS were found to be stable in stress conditions and there was no chemical degradation detected. Humidity and temperature affected disintegration time, highlighting the importance of correct storage conditions. It was possible to analyze content distribution based on the data obtained from synchrotron X-ray micro tomography. The composite material was successfully used in the TIC device providing higher drug load than a commercial product by ensuring the same sustained release kinetic. The FCC, with the unique lamellar structure on its surface, is able to provide a novel formulation platform based on a ready-to-use granule that ensures fast disintegration times, whether formulated in ODTs, TOS or mini-tablets. It was also possible to compact mini-tablets with different drug loads. The composite material showed to have plastic flow under pressure which is based on the fact that the FCC particles are embedded in the PCL. Even though they were exposed to shear stress the lamellae stayed intact and resulted in stable compacts, whereas the pure polymer PCL is not compactable. It can therefore be concluded, that the microstructure is the key characteristic to the development of age-appropriate as well as compliance enhanced formulations.

1 Introduction

1.1 Pediatric patient population

The pediatric population is classified in five different age groups, these are [1]:

- Preterm newborn infants (born before 37 weeks of gestational age [2])
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 years to 11 years)
- Adolescents (12 years to 16-18 years, dependent on region)

These age groups are very heterogeneous and therefore each patient needs to be considered as an individual [3].

1.2 Physiological differences of children compared to adults– an overview

The physiological differences within the age groups are big. Organs such as the liver [4] or kidney undergo strong development through the whole childhood. The unique development of the liver is among other facts a reason that levels of xenobiotics that are safe for adults can be toxic for children. The liver of a neonate has less than 20% of the hepatocytes that are found in the adult liver [4]. The kidneys of a newborn have immature renal tubules and also the globular filtration rate is low. This has both anatomical and functional immaturity as a root cause [2]. Also the skin is developing heavily, in newborns it is much more permeable than in adults [5]. Moreover, the weight to surface ratio is higher compared to adults which can lead to systemic toxic effects if exposed to topic xenobiotics [2]. The gastrointestinal transit times in newborns can vary highly [6]. Differences in bioavailability are a consequence of this (see section Age-appropriate formulations).

Not only the organs crucial to drug metabolism and absorption are differing from the adult's situation but also organs of perception i.e. ability to taste and ability to smell. In a study where the quantity of fungiform papillae and taste pore densities were analyzed, researchers found out that children have substantially smaller papillae compared to adults and they have a significantly higher density of papillae. This seems to be the reason for the higher sensitivity to sucrose in childhood [7,8].

The olfactory function is proven to already be present in neonates, as breastfed infants were reacting to the smell of their lactating mother more intensively than to the smell of a lactating mother that was unknown to the infant [9]. Even though the newborn seems to be equipped with the ability to smell, affective responses to pleasant or unpleasant odors do not present until the child reaches the age of 5 [10].

Newborns have also been found to be able to distinguish sweet taste from non-sweet taste, sour from bitter as well as distinguish the aforementioned from salty taste [11]. This was measured by analyzing the facial expressions with a facial action coding system adapted to babies (Baby-FACS [11]).

1.3 Swallowing process of children

Particularly of interest when talking about oral formulations for children is the development of the swallowing process. The swallowing process consists of 3 phases and undergoes some development. Phase one is the oral phase, followed by the pharyngeal phase and the esophageal phase. Up to the age of 4 to 5 months, the infant is equipped with an extrusion reflex that is responsible for the infant being able to only swallow liquids. At the age of 4 to 6 months, the infant can process spoon fed semisolids [3]. A gag reflex can last up to the age of 7 to 9. Hence, eating is an active process for the infant and it requires the capability to coordinate sucking, swallowing and breathing.
Therefore, at the age of 4-6 months it is not possible for the infant to swallow a monolithic dosage form (such as a tablet or capsule) but using a vehicle like soft food, multi-particulate dosage forms might be administered. These multi-particulate dosage forms can be mini-tablets, pellets, powders or granules [3].

Swallowing difficulties are not only present in children [12], but also in adults [13] and geriatric patients [14]. Also, different illnesses can cause so called dysphagia, such as Parkinson's [15], Dementia [16] or Duchenne [17]. Different medication can also cause dysphagia. These are anticholinergics, tricyclic antidepressants, theophylline or calcium channel blockers [18] to only name some examples. As difficulties to swallow affect patients of all populations, it is important to address this problem in the public pharmacy [19] and by developing dosage forms that do not need to be swallowed as a whole (see section solid dosage forms). If patients cannot swallow the dosage form,

they are prone to crush or manipulate it [20]. In all cases, dysphagia can impair compliance [20,21] and effective treatment.

1.4 Regulatory challenges

The development of medicines for children faces several challenges as the pediatric population is very heterogeneous. Most of the time, there is also a necessity to develop several formulations, meeting the needs of different age groups in the pediatric population [22]. This is cost intensive [23]. Moreover, industrial companies are not conducting studies about the safety and efficacy in vulnerable populations such as pediatric or geriatric patients [6]. Therefore, a new Pediatric Regulation was introduced in the European Union in 2007, it includes a Pediatric Investigation Plan (PIP) that describes the drug product strategy. This PIP needs to be in accord with the European Medicines Agency's Paediatric Committee (PDCO) at an early stage of development (i.e. latest when the human pharmacokinetic studies in adults are completed) [24]. There are different rewards for such a PIP, e.g. EMA allows medicines that are authorized in the EU with results from the PIP to have an extension of 6 months for the supplementary protection certificate. In the case of an orphan medication, market exclusivity of additional 2 years is possible. If the medicine was especially developed for children and already on the market in an unprotected state without a patent, the medicine is eligible for pediatric-use marketing authorization (PUMA). If the PUMA is conferred, the product profits from 10 years market protection [25]. All these incentives should contribute to have more age-appropriate medicines available for children. The WHO has compiled a document with literature to consider when developing a pediatric formulation, where all aspects are covered [26].

In order to get license for medication in children, studies need to be conducted. As we talk about a vulnerable population, special guidelines are established [27]. Some of the differences lay in the ethical aspect of the trial conduct [28]. The ethical principles are anchored in the Declaration of Helsinki, the United Nations Convention on the Rights of the Child, as well as in the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine [28].

Trials in children are considered to be necessary by WHO, as it is the only way to ensure well-being, treatment and prevention in children (and all other patient populations). The particular necessity to investigate medicines in the vulnerable population of children is recognized by the Directive 2001/20/EC (i.e. clinical trial directive) whilst ensuring the child's protection [28]. A large difference to the studies in adults is the informed consent. In trials involving children, an informed consent of the legal representative is necessary. This consent needs to represent the presumed will of the child and can be revoked at any time. Additionally, the minor child needs to receive information that is understandable for the child in aspect of the age and developmental stage. This information needs to be given by a person experienced with minors and involved in the trial, therefore being fully informed about the risks and benefits of it.

The investigator in the trial has to consider it is also possible at any time throughout the trial, that the minor child can form an opinion and express the wish to refuse participation [28]. If possible, age-appropriate formulations should be used in order to reduce risks such as e.g. choking, and ensure accurate dosing. As it is not possible that children can give consent to the participation in studies, the use of placebo is more restricted in children compared to studies with adults [28].

If there are no trials conducted in children, off-label use and the use of non-licensed products continues to be some sort of normal practice.

Off-label drug use means, that the medicines are used outside of the market authorization (e.g. the use of a drug product in children, that is only authorized for adults) [29].

Non-licensed drug use means, that the particular product used does not have market authorization (this includes compounding or extemporaneous preparations [30]).

This can lead to adverse events, as the medication has not been studied systematically in children [31,32]. In the Netherlands, a study showed, that in 435 patient-days, 90% of the pediatric patients received one or more courses of unlicensed off-label medication [33] (in this study unlicensed was defined as "medicine modified" or "medicine homemade").

1.4.1 Situation in low and middle income countries

Medicine availability in low and middle income countries is already a problem for adult patients [34]. For children this is equally if not more problematic and has led to the list of essential medicines for children (EMLc) by the WHO [35]. These medicines are chosen by a committee that meets every two years [36]. The essential medicines on the EMLc are determined to be available in functioning health systems in sufficient amounts as well as in the appropriate dosage form in an ensured quality and at an affordable price [37]. At the moment, people in low and middle income countries expect medicine to be liquid (syrups). This thought needs to be directed in a new way as these liquid formulations (see corresponding section) are more expensive and not easy to ship; moreover, some of the medicines need refrigeration, which is a problem in these countries [38].

1.5 Requirements for dosage forms for children

1.5.1 Age-appropriate formulations

An age-appropriate formulation has to fulfill several conditions in order to be considered as such. On one hand, there is the pediatric population, where a formulation needs to be properly adjusted [10] but there is also the need to do so for the geriatric patient group [6]. The physiological differences are most present in very young and very old patients [6]. Hence, it can be stated that accordance with the requirements of age-appropriate formulations should be fulfilled in both cases. These requirements are adapted from [6]:

- Sufficient bioavailability (see section “Physiological differences”)
- Safe excipients (see section “Excipients for pediatric use”)
- Palatable/acceptable properties (see section “Taste masking”)
- Accurate and flexible dosing (see section “Liquid dosage forms”)
- Easy and safe administration (see section “Solid dosage forms”)
- Socio-cultural acceptability (see section “Rectal formulations”)
- Technological Manufacturability (see section “Technologies”)

1.5.2 Liquid oral dosage forms for children

There are several liquid formulations available. These are suspensions, solutions, syrups and drops. Liquid peroral dosage forms can be swallowed by the children already at young age [10] and they can be dosed flexibly to the desired amount [3]. But these formulations have drawbacks such as the problem of the stability of the drug [3] and microbiological stability [39] as well as higher costs than solid dosage forms [40] and more difficulties to transport them [38]. Moreover, the formulation needs to be palatable and dosing consistency has to be ensured [3]. Additionally, there is a risk of over- or under-dosing [39]. Another restriction is, that liquid formulations cannot be used in children that suffer from an illness that requires restricted intake of liquid [39]. In order to administer liquid formulations properly, a dosing device is necessary [3]. Dosing syringes were found to be more accurate than dosing cups or spoons [41,42]. But even when using oral syringes, it has been shown that dosing inaccuracy can occur when small volumes are used [43]. Drops seem to be a dosage form that can be accurately dosed by count, but they also bear the risk of overdosing as shown in a case study [44]. In this case, a child died from codeine intoxication due to the fact, that the drop weight of 10 drops varied from 494mg to 940mg. The weight of 940mg corresponds to a codeine dose of 23.5mg, which is in the toxic range. According to EMA, the correct choice of dosing equipment should depend on the therapeutic index of the drug, type, taste of the formulation and ease of administration in practice [10].

1.5.3 Solid oral dosage forms

Classic monolithic oral dosage forms are difficult to swallow for children [6]. Alternative formulations that can be administered perorally are buccal tablets [3,45], orodispersible [46,47] or fast dispersible tablets [48], soluble tablets [49], chewable tablets [50], sprinkle capsules [47] or “stickpacks” [3,51]. Also buccal films [52] and orally dispersible films [53] are counted as alternative solid dosage forms. Another alternative is the use of rapid disintegrating tablets (RDT) they can be dispersed or dissolved in water prior to administration [54].

All these alternative formulations have the advantage that they do not need to be swallowed as a whole monolithic dosage form. The mentioned alternative formulations need to be palatable so that the taste masking is an additional challenge (see chapter 1.7.2 Taste masking). Such alternative formulations

available on the market can be used in the pediatric population provided that there are products available in the right dose range.

1.5.4 Manipulation of existing oral dosage forms

As most of the time the right dose range is not available, the formulations for adults are manipulated [3]. Tablet crushing or opening capsules to be mixed with food is an option but with some formulations it can be dangerous when tampering with the dosage form prior to administration [3]. A study showed that the bioavailability was reduced by ~45% when Lopinavir/Ritonavir (Kaletra ®) tablets were crushed to be administered to children compared to the administration of whole tablets[55].

Most of the time, there is no information about the influence on absorption of the drug, when a tablet is crushed [55]. Some substances cause sensitization if in contact with the skin, this can occur after crushing a tablet containing e.g. chlorpromazinum [3]. Other substances like finasteride are toxic for women which is unsafe for the people in the surroundings, as the active pharmaceutical ingredient (API) can be present as an aerosol after crushing [3]. This is due to the fact that the protective coating is destroyed when crushed. This can also be disadvantageous when the coating acts as a taste masking. There is not only a risk for the person administering the drug but also for the patient. If modified release formulations are crushed prior to administration, the kinetics of the designed dosage forms can be completely changed. This can lead to a toxic blood plasma level, also called dose dumping [3].

One way to meet the need of individually dosed medicines is to compound the medication extemporaneous for a particular patient or patient groups [30]. These preparations bear some risks as they lack data on safety and tolerability as well as pharmacokinetic characterization and bioavailability [56] (see section “Regulatory Challenges”). There are even reports of fungal contaminations in compounded medicines that lead to infections and deaths [57].

There are products available on the market to prepare extemporaneous oral suspensions. These are the products ORA-Plus, ORA-Sweet or ORA-Blend [58]. Medicated powders can be suspended in ORA-Plus or ORA-Blend, whereas ORA-Sweet serves as a syrup vehicle. It has to be taken into account that these products contain parabens, which makes them not suitable for neonates and infants [59].

Alternative products are available in Portugal under the name of SUSY-system. These products do not contain parabens, propylene glycol or alcohol [60].

Administering the dosage form to the child often poses the question whether it can be mixed with food and beverages. It is attractive if the mixing contributes to a better palatability of the medicine [3]. Most of the time there is only limited information that supports the safety to do so. It is advisable to get the information about the influence of food on bioavailability if it exists. It needs to be assessed as well, how the medicine reacts to the change of pH when mixed with acidic products (e.g. orange juice) or food that is warm [3].

In England, a guideline (MODRIC) was established for healthcare professionals to provide guidance on how to safely deliver reproducible accurate doses to children if manipulation of such is unavoidable [61].

1.6 Other routes than peroral for administration of drugs– some examples

1.6.1 Rectal formulations for systemic treatment

Rectal formulations such as suppositories have some restrictions. They can be advantageous if the patient is in a condition where the oral route is not an option as while vomiting or being unconscious [3] or in status epilepticus [62]. Moreover, the pre-systemic first-pass metabolism can be circumvented when the drug is absorbed trans-mucosal in the rectum [63]. The drug administered rectally to the patient does not need to be palatable and hence, taste masking of bitter substances is not necessary [6]. But the acceptance of this dosage form can affect compliance because of privacy or cultural reasons [63]. In some situations, the ability to retain the suppository can pose a problem. Additionally, the correct positioning of the dosage form in the rectum is crucial, because the blood vessels that circumvent the first-pass metabolism are not equally present in all sections of the rectum [63]. It was shown that dosing with suppositories can lead to inaccurate plasma concentrations in children when administering acetaminophen [64]. Moreover, the onset of action is slower in case of acetaminophen when administered as a suppository compared to a tablet [64,65]. Hence, for fast acting antipyretic or analgesic therapy, a rectal formulation is not always favorable.

1.6.2 Formulations to inhale

Formulations to inhale are the preferred option to treat asthma. In the UK, 10% of the children are affected by this condition [3]. Most importantly, the ability to properly inhale the medication needs to be taken into account in order to guarantee the clinical effect [66]. To ensure effective treatment, the correct inhaler should be chosen. E.g. from birth to 4 years of age, a nebulizer or pressurized metered-dose inhaler (pMDI) with a valved holding chamber (VHC) and a facemask should be used. Only above 13 years of age all devices (also dry powder inhalers and breath-actuated pMDI) can be used. As an interface to inhale, a facemask is recommended for children under 4 years of age, whereas older children can use a mouthpiece [66]. The dose that is inhaled by the child can be influenced by device [6,67] and by the chosen spacer [67]. A thorough instruction for inhalation devices is necessary to ensure proper handling as many children apply an incorrect technique [68].

1.6.3 Administration of drug via skin

The *stratum corneum* of the skin is functional at the time of birth. However, the skin of a term newborn is more hydrated and perfused than the adult skin. In preterm newborns, the skin barrier is not efficient, this can lead to undesired uptake of substances. The large body surface to body mass ratio (cm^2/kg) [69] and the reduced volume of distribution lead to enhanced absorption [3]. Transdermal drug delivery can generally be considered as route of administration, but the product available cannot be easily adapted to the need of an infant, which causes a limitation of use [3,47].

1.7 Excipients for pediatric use

Choosing the fitting excipients for pediatric use is a challenge. Information about safety and risks cannot be directly transferred from adults to children. Tools like the ADI (Acceptable daily intake) established by the Joint Expert Committee on Food Additives, or PDE (permitted daily exposure), created by the ICH (International Conference of Harmonization) for solvent residuals are commonly used for risk assessment of excipients in drugs, but the special conditions of other patient populations such as physiological differences are not included in these values [6]. Safe excipients for adults have been associated with toxicological effects in children [70] (See Table 1). The knowledge about the use of excipients in particular age groups is distributed over different sources, therefore US and EU

Pediatric Formulation Initiatives (PFI's) are working together to create a database [70,71]. In this database, information about Safety and Toxicity of Excipients for Paediatrics (STEP) is collected.

The excipient should be inert, non- toxic and if absorbed by the body of a child, it needs to be metabolized without toxic effect. Sensitization or allergies should be avoided as well [3].

1.7.1 Excipients to be avoided for oral administration

Some excipients should be avoided in the pediatric population for oral administration, certainly in some patient groups. The appropriate selection of excipients depends on the child's age, condition and route of application. A retrospective study showed that critically ill neonates can already be at risk of being exposed to toxic levels of benzylalcohol and propylenglycol when administering routine medication by continuous infusions [72]. The excipients for the different groups are listed in Table 1 as well as the adverse reaction that would be caused by the excipient [3]. Most adverse reactions can be traced back to the insufficient metabolic capacity in the first month of life [6]. As discussed in the section "Regulatory Challenges", these adverse reactions were not investigated in clinical trials but are based on experience and observed cases [32].

Table 1: Excipients with higher risk of toxicological effect when administered orally to pediatric population adapted from [3].

Excipient	Adverse reaction
Neonates and infants younger than 6 months	
Benzyl alcohol	Neurotoxicity, metabolic acidosis
Ethanol	Neurotoxicity
Propylene glycol	Seizures, neurotoxicity, hyperosmolarity
Patients with reduced kidney function	
Aluminum salts	Encephalopathy, microcytic anemia
Propylene glycol	Neurotoxicity, hyperosmolarity
Hypersensitive patients	
Azo dyes	Urticaria, bronchoconstriction, angioedema
Benzalkonium chloride	Bronchoconstriction

Parabens	Allergies, contact dermatitis
Starches	Gluten-induced coeliac disease
Sulfites, bisulfites	Asthma attacks, rashes, abdominal upset
Patients with metabolic disorders	
Aspartam	Phenylketonuria
Fructose	Hereditary fructose intolerance
Lactose	Lactose intolerance, diarrhea
Sorbitol	Hereditary fructose intolerance
Sucrose	Hereditary fructose intolerance

1.7.2 Taste masking

Oral formulations that are either liquid or swallowed in a dosage form that has no coating, need taste masking if the taste is inacceptable. There are several methods to mask the taste, the following techniques represent examples. The easiest way is to add sweetener and aroma to a formulation in order to cover to the unpleasant taste of an API [73]. Another method is to use physical options, where the API is physically hindered by a barrier to be available in the mouth and hence the taste cannot be experienced [74]. This includes coated granules or mini-tablet as well as pellets. In order to successfully coat such particles, different polymers/lipids are used to prevent dissolution of the drug in the environment of the mouth. One option is to use pH-dependent coatings (Eudragit RS30 [74]), that do not dissolve in saliva. Another option is to use lipids like Gattecoat ® , where naturally derived mixed glycerides are applied in a molten stage using fluid-bed process [75].

Another way that yields successful taste masking is to modify the solubility of the API, so its unpleasant taste cannot be detected by the patient. For solubility changing, one can add a substance that changes the pH in the microenvironment (e.g. adding an alkalizing agent to a drug that dissolves best in acidic conditions). Of course this is only possible if the drug has a pH dependent solubility. Another option is to use substances that form a complex with the drug and are therefore not easily soluble any longer. Cyclodextrins are the most often used substances [74]. Of course there are even more options such as producing solid dispersions by melt extrusion, or spray congealing [74]. As an

alternative it is also possible to create a prodrug of the desired API that is less bitter than the original component [73].

Taste masking can also be achieved in a biochemical way, where substances interfere with the taste receptor or taste transducing mechanism. They obstruct the signal transmitted to the brain so the taste signal cascade is blocked [76]. They need to be administered prior to the administration of the drug and it is not clear to what extent they are able to affect the aftertaste of a bitter substance. These substances have only been tested in a few studies in human [76], and up to the year of 2014, no study with children has been conducted [76].

1.7.3 Sweeteners

There are different ways to differentiate sweeteners. The groups of sweeteners can be distinguished into the nutritive sweeteners and nonnutritive sweeteners. The first group encompasses all the sugars (sucrose, dextrose, fructose, lactose), corn syrup, high-fructose corn syrup and sugar alcohols (polyols, e.g. maltiol, mannitol and sorbitol as well as xylitol). The nonnutritive group includes highly intense artificial sweeteners such as aspartame or saccharin or intense natural sugars such as glycyrrhizin or thaumatin [3]. The sweeteners can also be divided in two groups referred to as bulk and intensive sweeteners, respectively [76]. The materials are either natural or artificial. As an example, glycyrrhizin is a natural intense sweetener which is nonnutritive [3]. Interestingly, not all the sweeteners are approved by the authorities in all countries. For instance, cyclamates are not approved in the US, but they are in Canada and the EU. The nutritive sweeteners such as sugars bear the risk to cause caries, therefore artificial intensive agents are sometimes more fitting in a formulation as they are used in very small amounts (saccharin is 300-500 times sweeter compared to sucrose [76]). Moreover, the nutritive sugars are caloric [77] which is not favorable for long-time treatment as well as intake before bedtime [3]. Formulations that contain caloric sugars also need to be considered if the patient is diabetic.

1.7.4 Flavors

Flavors originate from natural and artificial sources. The advantage of natural flavors is the better palatability, whereas the artificial flavors are chemically more stable, therefore less batch to batch

variability is occurring [76]. Several flavors are available to be used in particular ways, depending what character the product has and which condition is treated [10].

Acidic basic sensations are proposed to be covered with cherry, lemon, lime, mandarin, orange or strawberry; Alkaline basic sensations are suggested to be covered with banana, caramel, cherry, liquorice, passion-fruit or peach; Bitter basic sensations are recommended to be covered with cherry, chocolate, grapefruit, liquorice, strawberry, peach, raspberry or tutti-frutti; Salty basic sensations are proposed to be covered with caramel, grapefruit, lemon, orange or vanilla; and sweet taste is suggested to be covered with banana, caramel, cream, chocolate, grape or vanilla [10].

Three different conditions can be distinguished and flavors are recommended[10]:

i) Pain, fever, allergy and infection: Cherry, strawberry, banana, caramel.

ii) Vitamin deficiency: Blackcurrant, lemon, lime, mandarin, orange

iii) Indigestion (Antacids): Lemon, lime, orange, peppermint.

Additionally, there are also geographical preferences present. The US population favors the flavor "bubble-gum" and "grape", whereas "citrus" and "red berries" are the favorites of Europe and "liquorice" is the favorite in Scandinavia [10,78].

1.7.5 Colorants

The purpose of colorants in pharmaceutical formulations has its roots in esthetics [56]. They are used to make the drug product more attractive or to match the color with the product's taste (e.g. berry flavor with a red color) [3]. There are substances like riboflavin and cupric blue that have intrinsic color and are not considered as pharmaceutical colorant and there are synthetic colorants with the origin of either plant or mineral [56]. Colorants can bear toxicological risks when used in the pediatric population (e.g. azo-colorants). For example, a small amount of iron oxide is more preferable than an azo colorant because the oxide is generally considered as non-irritant and non-toxic [79]. The color of the drug product is important for identification. The identification is necessary for safety [80]. Moreover, the color implicates expectations that may support the therapeutic effect [81]. Using color

codes can also be beneficial for the use in countries where it is difficult to educate the patients in a written format.

1.7.6 Palatability testing

As already described, the palatability is crucial for medication administered to children. Several terms are used to describe palatability. For this work, palatability and perception are used as synonyms and consist of the components taste and mouthfeel. The latter includes the texture, cooling, heating or trigeminal response. Mouthfeel cannot be separated from taste sensation as taste stimuli are contributing to a pleasant mouthfeel [82] Palatability is one of the main aspects contributing to the acceptability of an oral medication and is determined by the active ingredient and the excipients.

The investigation of palatability particularly in very young children is challenging [83]. There are some options such as a hedonic scale [84], visual analogue scale (VAS) [85], verbal responses [85], ranking between products [85], evaluating the ease of administration [86] or registering the spontaneous verbal judgement after the child took the medication [84]. The different methods are either measured by addressing the question directly to the child or by asking the questions to the parents [85]. There are also combinations available, where a VAS is combined with a hedonic scale [87]. Another option is to use a hedonic scale and a two-score grouping where specific answers on the hedonic scale are related to either satisfactory or unsatisfactory sensation [88]. It is important to ensure that the method used is adapted to the age of the child. For example, the hedonic scale to address children is considered not to be suitable for children under the age of 3 years [84] and 5 years [89], depending on literature. The VAS for parents was already successfully used for children with the age of less than a year [90]. There are no international standards so far that could be used as a guideline. Even more challenges come with the palatability testing in children. It should be considered that a healthy child has a different perception than a child with a certain condition. Ethically it is difficult to say whether it is better to do palatability testing in healthy children or in children with the condition that will be treated with the medication [83]. Whether it is appropriate exposing a healthy child to API even for one dose needs to be assessed [85]. There is also the difference between acceptability and preference that needs to be taken into account, as the first describes what can be tolerated and the latter

describes what is liked better, this may differ from healthy children to children with a chronic condition and the necessity of repeated dosing [85]. Analyzing this differentiation is challenging compared to adults, that are trained to do palatability testing [91]. Very young children do also have a reduced time span of attentiveness [92] which can mean that the rating will be done by the child but may rather be connected to e.g. whether the mother is happy with the kid or whether the child is generally in a good mood instead of relating to the palatability of the formulation. Therefore, the assessor needs to be specially trained to conduct such studies with children in particular, the assessor needs to be competent to exclude external factors that could bias the results [85]. The reproducibility of palatability tests is also not a simple task, as there are several options to test for palatability but no definite international standard has been identified [82,93].

Of course it would be preferable to investigate perception at an early stage of development [24]. As mentioned above, human panel tests can be performed but at early stages of development enough information about the component is rarely available [24]. To save costs and time, the application of an e-tongue is possible to obtain some important data aside from a human panel test [94,95]. The electronic tongue is a multisensory device, that can automatically analyze complicated compositions based on their characteristics [96]. As the electronic tongue considers aspects of taste it does not allow to predict the whole aspects of palatability, therefore human panel tests are still necessary.

1.8 Compliance

The topic of compliance is a topic of research on its own. Therefore, for this work only a short summary is presented. Compliance is crucial for any medical treatment. It was shown, that children die from treatable diseases, because of the lack of suitable formulations. They are incompliant, because the medicines available are bitter or impossible to swallow [97]. This pinpoints the necessity of age-appropriate formulations (see corresponding section) to ensure compliance. Even the best drug cannot be effective, if the palatability is not acceptable. It has also been shown that palatability of a treatment is crucial to ensure compliance [87,92]. Also, the esthetics of a dosage form contribute to a good compliance [98]. If the color differs in generic drug products, compliance can be negatively influenced when switched to another brand of drug [99].

Furthermore, some medication plans are quite inconvenient for children such as the one for Ritalin. Therefore, a lot of effort was made to develop a formulation that leads to less intake per day, so stigmatization for the child in school to take several capsules per day is reduced [6].

Another important factor is the ease of administration of medication. If the parent or caregiver is not able to give the medication to the child, compliance is reduced [89]. Noncompliance has been identified to produce major costs to the health system and also increased morbidity [89].

This shows, that the medication would be available, but not in the format necessary for children. Whether this is ethically justifiable is up for debate.

1.9 Excipients

Excipients are used in all formulations and represent a large portion of the dosage form. In solid dosage forms excipients are used as fillers, binders, disintegrant, glidants or lubricants to only name some of the categories. The excipient needs to be pharmaceutically inert [100]. In the past it was shown that the safety was in most of the cases taken for granted but should be researched. Also, possible interactions of the API with the excipients need to be taken into account as chemical interactions can lead to adverse effects in patients [100].

1.9.1 Multifunctional excipients

Multifunctional excipients form a group of substances that can be used to serve more than one function in a formulation. Such an excipient is e.g. starch [101] used as a disintegrant and a binder or UICEL that can be used as a binder, disintegrant as well as a filler [102]. There is also Fujicalin which can take the role of a filler [103,104] and an excipient to load drugs in it [68]. The same is valid for Aerosil (colloidal silicon dioxide), it can be used as a glidant [105] or to be loaded with a drug [106]. In the same sense, pellets can be considered a multifunctional excipient as they can act as drug carrier [107] and filler because a considerable amount of a multi-unit pellet system consists of pellets [108].

Multifunctional excipients are advantageous as they allow to reduce the number of excipients that need to be used for a particular formulation [109].

1.9.2 Co-processed excipients

The creation of co-processed excipients had the goal to combine different advantageous attributes of existing excipients and minimize their hindering characteristics. Co-processing is defined as physically modifying one or more excipients without changing the chemical properties [110]. These excipients represent a beneficial application in direct compaction (see section Technologies).

Examples for co-processed excipients are Ludiflash ® or Pharmaburst [111]. Ludiflash ® consists of 90% mannitol (filler), 5% Kollidon (disintegrant) and 5% polyvinyl acetate (binder) and is supposed to be used to formulate orally disintegrating tablets. The advantageous characteristics of this excipient are good compressibility, fast dissolution and smooth mouth feeling [110].

Pharmaburst consists of mannitol (filler), crospovidone (disintegrant), sorbitol (sweetener), and precipitated silicone dioxide (glidant) [112]. It is as well, like Ludiflash ® , designed to prepare orally disintegrating tablets.

1.10 Technologies

To meet the criteria to formulate age-appropriate and compliance enhanced oral formulations, some requirements need to be fulfilled. As mentioned above, excipients are an absolute necessity. To process those adequately, suitable technologies need to be established. It has been shown, that there is a deficit of technologies to develop formulations for children [22]. The ideal requirements for such technologies and manufacturing processes should be simple, cost effective and easily scalable.

There have been some efforts made to develop novel technologies to formulate for children. These are e.g. dose sipping with a highly sophisticated straw where the child can sip the dose needed [6]. Another innovative device is the nipple shield delivery system (NSDS), that combines a nipple shield with an appropriate dosage form to administer drug to the infant while breastfeeding [113]. These two examples are rather special and do not fulfill the desired requirements mentioned above.

1.10.1 Granulation

If the excipients cannot be directly compacted because they show poor flow resulting in non-uniform tablet weight, the excipients can be processed. Different granulation options are standard in

pharmaceutical technology. These are e.g. wet granulation and dry granulation. Both processes are pursuing the same goal i.e. particle enlargement in a controllable size range. This leads to mixtures/excipients that show better flow and less dust. The narrow size range of the particle yields to less segregation effect in the end formulation [114]. In wet granulation, the enlargement of the particles is achieved by using a spray solution that is sprayed on a powder bed in case of fluid bed process or added stepwise to a high shear mixer. In both wet granulation processes, the size enlargement of the agglomerated particles (granule) is based on the formation of bridges between the particles. High shear granulation is followed by a drying step and if necessary milling step. Both mentioned processes are most of the times based on batch production [115,116]. Recent technological progresses presented continuous versions of both fluid bed [117] and high shear granulators [118]. Another option to granulate in a continuous process is twin screw granulation [119]. Continuous processes are easier in scale up and therefore more cost effective. Dry granulation such as roller compaction uses force to produce ribbons, that are subsequently milled. Also, this way the particle size can be enlarged. One drawback of roller compaction is the dust fraction, that cannot be used. This yields higher costs compared to direct compaction where all the material can be used [120]. Compared to wet granulation, dry granulation is a faster and therefore cheaper process [114]. It is also suitable for moisture or heat sensitive APIs [120]. In the case of roller compaction, it is also a continuous process [121].

1.11 Functionalized calcium carbonate as a novel pharmaceutical excipient

Functionalized calcium carbonate (FCC) consists of calcium carbonate and tribasic calcium phosphate. It has a highly sophisticated surface structure with lamellae and a porous core [122] (see Figure 1). It is a highly porous material, that has a surface area of up to ~60m^2/g and porosities of approx. 70% [122]. The apparent true density is between 2.50-2.73g/cm^3 [122]. A study of compaction behavior showed, that the compaction of FCC consists of two phases, first the lamellae interlock with each other (phase 1), this leads to stable compacts with a high tensile strength at low compaction pressures. This interlocking is followed by a densification by fracture of the lamellae and then a plastic deformation under higher compressive stress (phase 2) [122]. In previous research, it was shown that FCC can be used to prepare orally disintegrating tablets [123] and floating gastro-retentive drug

delivery systems [124]. Moreover, it was shown to be used to load drugs into the particle [125] and prepare mucoadhesive particles for colonic drug delivery [126]. The differences to ground calcium carbonate lay in the morphology of the particle [127].

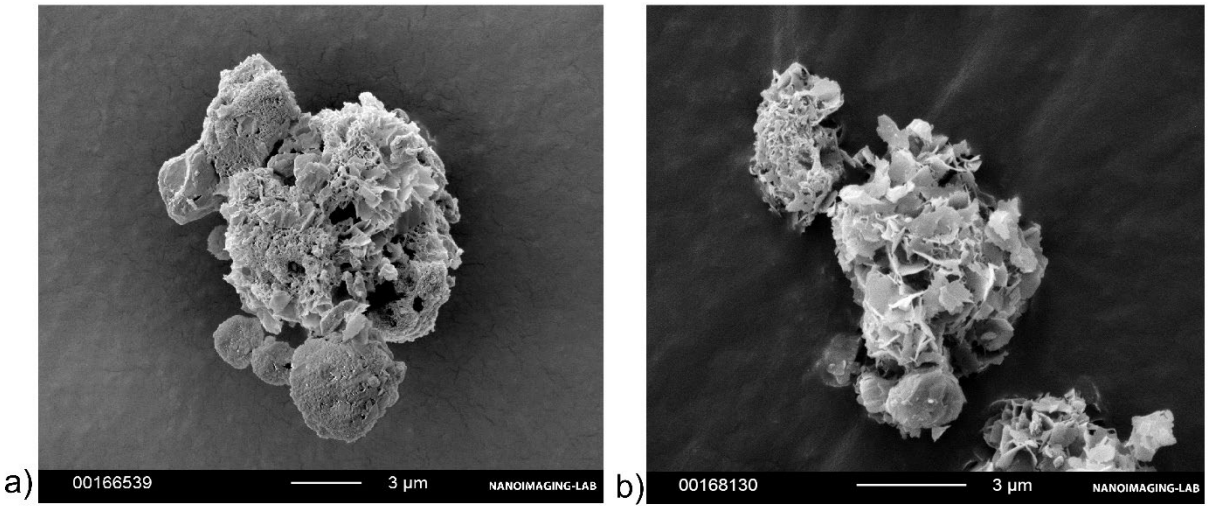

Figure 1: SEM picture of a FCC particle of batch SO3(a) and SO2 (b).

2 Aim

The main aim of this thesis is to establish new strategies for developing age-appropriate and compliance enhanced formulations for children based on the novel excipient FCC. It is of particular interest to bridge the gap between technological aspects and therapeutic optimization. Four projects were identified to reach this main aim:

I) Development of an ODT formulation and methods to characterize *in vitro* disintegration kinetics and *in vivo* acceptability in form of a human panel test.

II) Studies of stability of FCC-based TOS formulations containing model drugs for BCS1 and BCS4 type of drugs.

III) Establish a method for studying drug-distribution in low-dose formulations on the example of moxidectin containing orally disintegrating mini-tablets.

IV) Development of a mineral-polymer composite material (FCC-PCL) as a multifunctional excipient to be used in geometry constrained sustained release formulations. It was the aim to reduce the size of the dosage form by compacting it into a Tablet-In-Cup (TIC) device. This device can also be beneficial for children.

3 Publications in peer-reviewed journals

3.1 In vitro Characterization and Mouthfeel Study of Functionalized Calcium Carbonate in Orally Disintegrating Tablets

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Research Paper

In vitro characterization and mouthfeel study of functionalized calcium carbonate in orally disintegrating tablets

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ABSTRACT

Orally disintegrating tablets (ODT) are comfortable and safe drug delivery methods beneficial for all age groups of patients. ODTs are characterized by fast disintegration, high physical stability, taste masking and acceptable mouthfeel. In this work, the applicability of Functionalized Calcium Carbonate (FCC) to formulate ODTs with enhanced mouthfeel was elaborated and tested for acceptability on twenty healthy volunteers, using a 10-step visual analog scale Mechanical characteristics of the ODTs were examined using Heckel analysis, modified Heckel analysis and Leuenberger equation. Disintegration time was measured with the tensiometer method and analyzed for disintegration kinetics with a system of ODE. As a result, it was shown that the tablet was well accepted in healthy volunteers, disintegrated fast *in vivo* and correlates well with the mathematical model. Additionally, the compactibility and the physical stability were preserved yielding high porosity to absorb liquid necessary for disintegration. *In vitro* disintegration time was successfully linked to *in vivo* disintegration time. These findings lead to the conclusion that FCC is applicable to use in ODT dosage forms and mouthfeel was successfully enhanced to a pleasant result without losing the unique characteristics of FCC.

1. Introduction

Orally disintegrating tablets (ODT) gain more and more clinical importance as they can significantly improve effectiveness of treatment for people with dysphagia, acute allergic reactions (Rameesa and Drisya, 2015), or epileptic seizures (Poukas et al., 2011). ODTs offer the potential to change the pharmacokinetics of the existing therapies by reducing first-pass metabolism due to a changed absorption site (Rauck et al., 2009).

The main problem affecting wide application of ODTs is the necessity of a fast disintegration time, physical stability as well as taste masking, including an acceptable mouthfeel (Kimura et al., 2015). Moreover, a cost-effective formulation development and production are both challenging tasks (Badgujar and Mundada, 2011). ODTs are favored for applications in pediatrics (Orubu and Tuleu, 2017) and geriatrics (Abdelbary et al., 2005). However, there are challenges. Apart from manufacturing bottlenecks, the analytics of ODTs are often a challenge and lack a standardized method for disintegration time and behavior assessment despite several proposed techniques (Bi et al., 1996; Morita et al., 2002; Narazaki et al., 2004).

In vitro disintegration testing according to Ph.Eur., allows assessment of the disintegration time itself without any information about water uptake or disintegration kinetics. To address this challenge, several methods have been proposed, *e.g.*, simulated wetting test, where the time to completely saturate a tablet with liquid is defined as a tablet's disintegration time (Hooper et al., 2016); the Petri dish method, where the disintegration time measurement is visually observed (Gohel et al., 2004); or a texture analyzer method, where the disintegration time is estimated from a force-displacement profile (Dor and Fix, 2000). All these methods are highly accurate in registering a time necessary for a tablet to disintegrate, however they are not suitable for assessment of kinetics of the weight change in the tablet due to water sorption and disintegration. A microbalance method, where a tablet is placed on a grid and immersed into disintegration medium has been reported as suitable test set up for measurement of kinetic of disintegration (Stirnimann et al., 2013). In this work this method for disintegration time measurement and analysis is applied and extended with mathematical model to quantitatively estimate the disintegration kinetics and liquid necessary for disintegration.

In the publication of Stirnimann et al., along with the microbalance method to test the disintegration of the ODTs, a novel pharmaceutical excipient to produce ODT (Stirnimann et al., 2013) was presented. This

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ingredient, called functionalized calcium carbonate (FCC), consists of co-crystallized calcium carbonate and calcium phosphate. It was shown to consist of a porous meshwork with a lamellar surface structure (Stirnimann et al., 2014). Under compressive stress the lamellae interlock to form stable bonds within the tablet while keeping the compact highly porous (Stirnimann et al., 2014). The rough and grainy appearance of FCC particles suggest that pure FCC may have an unpleasant mouthfeel. This may hinder or severely impede an application of FCC as a main component of the ODT formulations since a good mouthfeel is of a high importance to ensure acceptability of the medication (Davies and Tuleu, 2008; Orubu and Tuleu, 2017). Mouthfeel is strongly connected with taste sensations (Batchelor et al., 2015). The chalky sensations in mouth left by calcium carbonate and calcium phosphates may necessitate additional actions to mask this unpleasant perception. Several options for taste masking are already established in industry (Douroumis, 2007), such as physical methods (Sohi et al., 2004), chemical methods (Douroumis, 2007), or admixing of sugars and aromas (Mennella et al., 2015). Mouthfeel enhancement can be achieved using substances that create pleasant sensations such as polyvinylpyrolidone (Metcalf et al., 1998) or effervescent agents *e.g.* citric acid in combination with sodium bicarbonate, to complement taste-masking (Sohi et al., 2004).

This study investigates a suitability and organoleptic acceptance of FCC as a main component in the enhanced mouthfeel fast disintegrating ODT formulations, characterized by excellent compactibility and high physical stability. The organoleptic acceptance of the proposed ODTs was assessed in an *in vivo* study with 20 healthy volunteers. Additionally, the correlation between *in vitro* measured disintegration time and *in vivo* data is presented.

2. Materials and methods

2.1. Granule production

For the production of the granules, Omyapharm FCC 500 OG (co-crystalized calcium carbonate and calcium phosphate) and Ac-Di-Sol® (croscarmelose sodium crosslinked, PHEUR) were sieved to < 500 µm fraction. The two excipients were mixed for 10 min with Turbula blender T2C (W.A.Bachofen, Switzerland) at 34 rpm in a ratio of 97% Omyapharm and 3% Ac-Di-Sol. This mix was then roller compacted with Chilsonator IR220 (Fitzpatrick,USA). The agitator was set at 21 rpm speed. The horizontal screw speed was set to 20 rpm. The vertical feed screw speed to 150 rpm. The roll gap was set at 0.5 mm and the roll pressure was set at 10 bar. The roll speed was set at 3 rpm and then during the process adapted to speeds between 1.5 rpm and 3.5 rpm. The force on the rolls was between 1.9 kn/cm and 2.2 kn/cm with corresponding roll thickness of 2 cm. The collected ribbons were milled with Fitz®Mill Comminutor L1A hammer mill (Fitzpatrick, USA) using the 1729-0001 type rasping screen (1.5 mm diameter of screen opening) and hammer at 300 rpm. The resulting granules were sieved to retrieve the particle size fraction between 180 µm and 710 µm. These granules are referred to as ReadyMix hereafter in this work. The second formulation is a mixture composed according to Table 1. This formulation is referred to ODTF hereafter in this work.

Table 1
Composition of the ODTF.

Excipient	Amount, %
ReadyMix(180 µm − 710 µm)	87.93
Citric acid monohydrate PHEUR	5.71
Sodiumhydrogencarbonate PHEUR	2.86
Sodium cyclamate/Sodium saccharine (10:1) PHEUR	2.5
Orange aroma permaseal (foodgrade)	1

2.2. Tablet preparation

The tablets were compacted with Styl'One Classic compaction simulator (Medel'Pharm, France). A Euro B 5 mm flat punch tooling and a Euro D 11.28 mm flat punch tooling at upper punch immersion depth of 4 mm were used. The compression cycle consisted of 5 sections: 1.5 s filling, 1.5 s upper punch approach, 3.0 s compression, 1.0 s relaxation, 5.0 s ejection. Filling height was set to 20 mm, to allow manual die filling; Compaction force was set to 5 kn and 25 kn, respectively. Tooling lubrication was carried out manually prior to tablet compaction with magnesium stearate PHEUR (Hänseler, Switzerland).

The tablets were weighed with the balance (Mettler Toledo, AX204, US). Height and diameter of the tablets were measured using a digital caliper. The tablets were stored in plastic bags in a plastic box with desiccant bags (desiccant silica gel, C. Roth AG, Switzerland).

2.3. Compactibility study

A deformation profile was carried out for the ReadyMix and the ODTF. The compression cycle had the following 5 sections: 2.0 s filling, 1.5 s upper punch approach, 1.5 s compression, 1.0 s relaxation, 5.0 s ejection. A flat round Euro D tooling with diameter of 11.28 mm was used, tooling lubrication was carried out manually using magnesium stearate PHEUR. Applied compaction pressures were in range from 10 MPa to 350 MPa; the ReadyMix tablets compacted at > 300 MPa showed a resulting hardness higher than > 400N (*i.e.* greater than upper detection limit of the hardness tester). Therefore, those tablets were not analysed, and the profiling was carried out for the range of 10–250 MPa. With the ODTF stable tablets were only formed starting at 30 MPa, therefore the profiling range for the ODTF is 30–350 MPa.

Compressibility of the two formulations was investigated by fitting the Heckel equation with experimental data (Eq. (1)) (Heckel, 1961):

$$\ln\left(\frac{1}{1-\rho}\right) = k\cdot\sigma + A \quad , (1)$$

where k is the Heckel parameter (MPa^{-1}), σ is the compressive pressure (MPa), ρ is the density of the tablet (g/cm^3), and A is a constant. The density of the tablet was calculated according to Eq. (2) (Ilkka and Paronen, 1993):

$$\rho = \frac{m}{\pi\cdot r^2 h}\cdot\frac{1}{\rho_{true}} \quad , (2)$$

where m is the mass of the tablet (g), r is the radius of the tablet (cm), h is the tablet height, and ρ_{true} is the true density of the material (g/cm^3) measured with Micromeritics AccuPyc 1330,USA. The yield pressure σ_y was calculated by taking the reciprocal of the Heckel slope k (Ilkka and Paronen, 1993) ($\sigma_y = \frac{1}{k}$).

The modified Heckel equation was used to investigate compaction susceptibility of the material (Kuentz and Leuenberger, 1999):

$$\sigma = \frac{1}{C}\left[\rho_{rc} - \rho - (1-\rho_{rc})\cdot ln\left(\frac{1-\rho}{1-\rho_{rc}}\right)\right] \quad , (3)$$

where σ is the compressive pressure (MPa), C is a constant (MPa^{-1}), ρ_{rc} is the relative critical density, and ρ is the relative tablet density.

Tensile strength was calculated according to Eq. (4).

$$\sigma_t = \frac{2\cdot F}{\pi\cdot d\cdot h} \quad , (4)$$

where σ_t is the tensile strength (MPa), F is the crushing force (N), d is the diameter (mm) of the round tablets, and h the height of the round tablet (mm). Powder compactibility was investigated by plotting tensile strength as a function of compressive pressures (Leuenberger and Rohera, 1986).

Deformation of the material under stress and bonding properties of the material were obtained through compactibility and compression

susceptibility parameters from Leuenberger equation (Leuenberger and Rohera, 1986).

$$\sigma_t = \sigma_{tmax} \cdot (1 - e^{(-\gamma \cdot \sigma \cdot \rho)}) \quad , (5)$$

where σ_t is the tensile strength, σ_{tmax} is the tensile strength when compressive pressure (σ) $\rightarrow \infty$ and relative density (ρ) $\rightarrow 1$, γ is the compression susceptibility (MPa^{-1}), and σ is the applied compressive pressure.

Numerical fitting was carried out with Levenberg-Marquardt and orthogonal distance regression algorithms (Origin Pro 2016).

2.4. Hardness testing

Hardness testing of the tablets was carried out using Dr. Schleuniger Tablet Tester 8 M (Switzerland) with n = 3 tablets per test.

2.5. Porosity

The porosity was calculated according to Eq. (6). The apparent true density was measured using helium pycnometer (Micrometrics Accupyc 1330, USA).

$$\varepsilon = \left(1 - \frac{m/(\pi \cdot r^2 \cdot h)}{\rho_{true}}\right) \cdot 100 \quad , (6)$$

where Ɛ is the porosity (%), m is the mass of the tablet (g), r is the radius of the tablet (cm), h is the height of the tablet (cm) and ρ_{true} is the apparent true density (g/cm^3).

2.6. Particle size disitribution

Particle size distribution (PSD) was measured using the sieves 90 µm, 125 µm, 180 µm, 250 µm, 355 µm, 500 µm, 710 µm, 1000 µm on a Retsch Vibro (Schieritz & Hauenstein AG, Arlesheim, Switzerland). The cumulative passage (%) and the cumulative residue (%) were plotted and the intersection of both curves was calculated. The x-coordinate of this intersection point yields the median particle size (µm).

2.7. Disintegration measurement

Disintegration time was measured with a Tensiometer K100 (Krüss, Germany). The grid was further developed from Stirnimann et al. (see Fig. 1). A 3D printer Formlabs Printer Form 2, Software Preform 2.10.0 was used to print the grid, designed on Solidworks®2016 Sp5.0, using a black photopolymer resin V2. The grid was immersed in the test liquid to the level of the notch (see Fig. 1). The measurement was carried out in demineralized water and artificial saliva (n = 3). The artificial saliva (art. sal.) consisted of 0.228 g/L calcium chloride dihydrate, 1.017 g/L sodium chloride, 0.204 g/L sodium phosphate dibasic heptahydrate, 0.061 g magnesium chloride hexahydrate, 0.676 g/L potassium carbonate sesquihydrate, 0.273 g/L sodium phosphate monobasic monohydrate and 1 g/L porcine mucin.

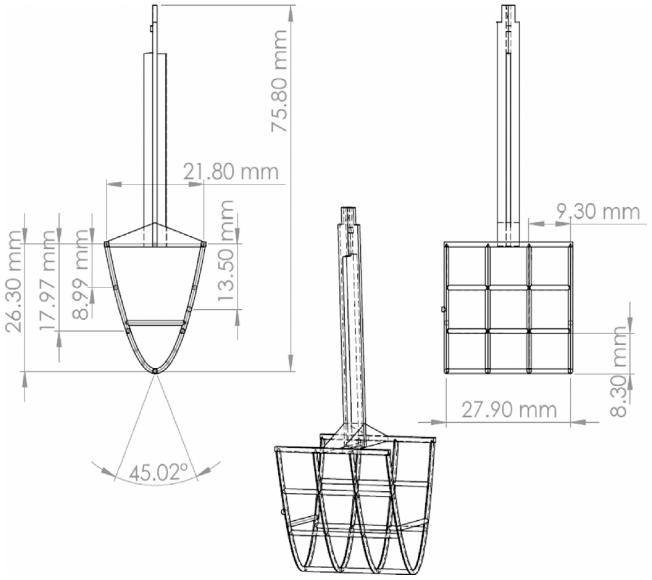

Fig. 1. 3D printed resin grid for disintegration measurement with the tensiometer.

First the grid is immersed in liquid, after automatic taring the tablet is put on the grid. What was measured is the tablet's net force *i.e.* the buoyancy force of the tablet subtracted from the weight force of the tablet. As we do not consider volume change of a tablet due to swelling in our model as significant, the net force change can be assumed as linearly proportional to mass change rate.

The water uptake was measured using Tensiometer K100 (Krüss, Germany). A glass tube, with a filter paper fixed on the liquid facing side, was used. The tablet was then placed on the paper prior to immersion in the liquid. After touching the water surface, the weight gain was registered. The maximal amount of adsorbed liquid was registered when a plateau was reached.

The total specific amount of water uptake (g/g) and the total specific amount of art.sal uptake (g/g), respectively, were calculated as a ratio of the individual amount of liquid absorbed by the tablet (g) and the weight of the individual tablet (g).

2.8. Mathematical model

For a detailed analysis of a disintegration behavior, a mathematical model based on the system ordinary differential equations (ODE) was used. This model describes two processes ongoing during tablet disintegration *i.e.* water uptake and disintegration. The tablet mass change rate can be described as a sum of the rate of sorption and disintegration:

$$\frac{dm}{dt} = \frac{dm_w}{dt} + \frac{dm_d}{dt} \quad , (7)$$

where $\frac{dm}{dt}$ is the mass change of the tablet per time, $\frac{dm_w}{dt}$ is the wetted mass change rate of the tablet and $\frac{dm_d}{dt}$ is the disintegrated mass change rate of the tablet. The change of the rates is shown in Fig. 2.

The different rate phases during disintegration can be described with the corresponding conditions:

Phase A: $\frac{dm_w}{dt} > \frac{dm_d}{dt}$, where the rate is constant and dominated by liquid sorption; Phase B: $\frac{dm_w}{dt} = \frac{dm_d}{dt}$, where the total rate $\frac{dm}{dt}$ is equal to 0; Phase C1: $\frac{dm_w}{dt} < \frac{dm_d}{dt}$, where the disintegration rate is dominant and this phase can be constant (solid line) or decreasing (dotted line) and Phase C2: $\frac{dm_w}{dt} < \frac{dm_d}{dt}$, where also disintegration rate is dominating and the phase can be constant (solid line) or increasing (dotted line).

The system of ODE (Eq. (8)) was numerically solved for m_w *(t)* and m_d *(t)* with Wolfram Mathematica 11.

Also the numerical fitting of the sum of m_w *(t)* and m_d *(t)* was fitted with Wolfram Mathematica 11. The fitted disintegration curve was differentiated to obtain the position of an inflection point (2nd derivative = 0). The tangent line was calculated for the fitted curve at the inflection point and solved for time at the intersection with the x-axis. The complete Mathematica workbook is available in Supplementary material.

The process of sorption and disintegration are described as follows under the assumption, that only wet solids can disintegrate:

$$\begin{cases} \frac{dm_w}{dt} = \lambda_1 \cdot m_w \left(1 - \frac{m_w}{h_m}\right) \\ \frac{dm_d}{dt} = \lambda_2 \cdot m_w + \lambda_3 \cdot m_d \end{cases} \quad (8)$$

where $\frac{dm_w}{dt}$ is the wetted mass change rate (g/s), λ_1 is the water sorption rate constant (s^{-1}), m_w is the wetted mass of the tablet (g), h_m the

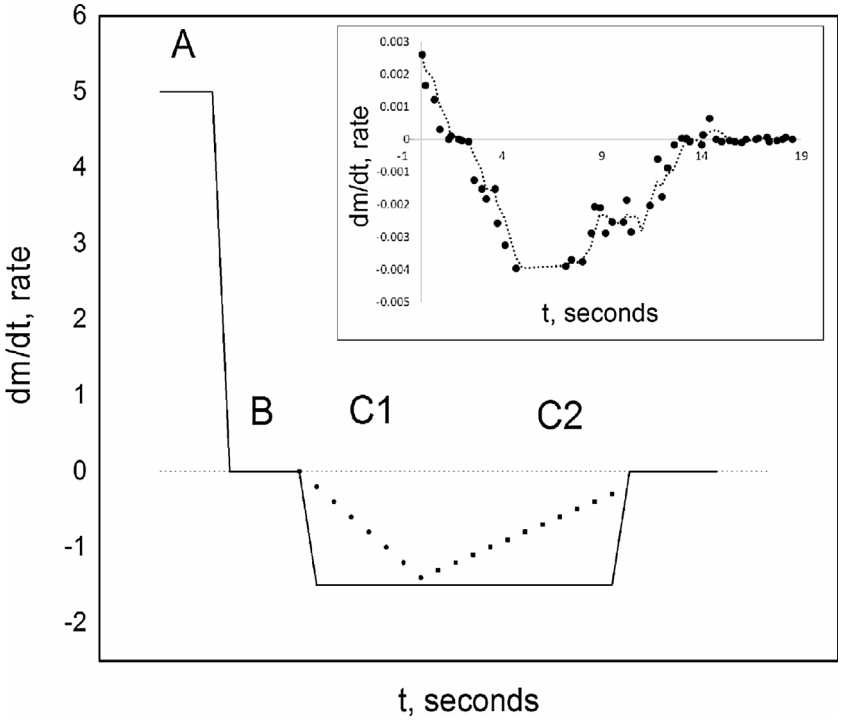

Fig. 2. Schematic representation of the different sections of tablet mass change during disintegration of an ODT, inset is an example of experimental data, approximated with smoothing function (thin dashed line).

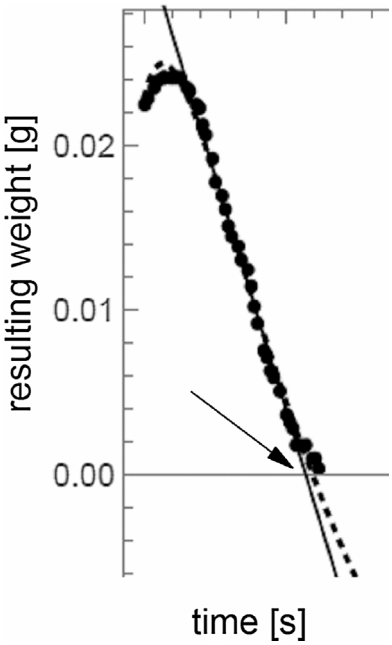

Fig. 3. Example of data measured by the tensiometer method and then fitted with the model, where the dots are the experimental data, the black line is the tangent and the dashed line is the modeled function. The arrow indicates the intersection of the tangent with the x-axis.

maximum possible amount of water that can be absorbed by the tablet (g). The value for h_m was determined with water uptake measurements of the tablet. The $\frac{dm_d}{dt}$ is the disintegration rate (g/s), λ_2 the disintegration rate constant (s^{-1}) and λ_3 is the additional disintegration rate constant (s^{-1}). The λ_2 describes how much mass is disintegrating depending on the wetted tablet mass. The λ_3 describes the case, where wetted mass does not immediately disintegrate; this slows down the process of disintegration. An example fitting to the experimental data is shown in Fig. 3.

From this numerical fitting the parameters λ_1, λ_2, λ_3 and the intersection point of the tangent with the x-axis were obtained. This intersection represents the disintegration time of the tablet (s).

2.9. In vivo disintegration time and mouthfeel assessment

In 20 healthy volunteers (age between 20 and 40), *in vivo* disintegration time of the 5 mm ODTF tablet was measured with a stopwatch. Mouthfeel was assessed using 10-step visual analog scale (VAS). On our VAS the answer 0 represented the most positive answer the volunteer could choose. This was underlined with icons showing happy, neutral and sad faces. It was also assessed whether the volunteer was fasting two hours prior to the study. Eight different questions concerning the mouthfeel and taste were asked (Q1–Q8). In Fig. 4 you see all the questions with the scale and the corresponding possibilities to answer.

- Do you have a feeling of mechanical roughness in your mouth (during disintegration)? (Q1)

  (0 → not at all rough; 10 → very rough)

- Do you have a feeling of mechanical roughness on your teeth (during disintegration)? (Q2)

  (0 → not at all rough; 10 → very rough)

- Do you have a pleasant feeling in your mouth (during disintegration)? (Q3)

  (0 → very pleasant; 10 → not at all pleasant)

- Does the tablet taste good (generally)? (Q4)

  (0 → very good; 10 → not at all good)

- Do you have a dry mouth (after disintegration)? (Q5)

  (0 → not at all dry; 10 → very dry)

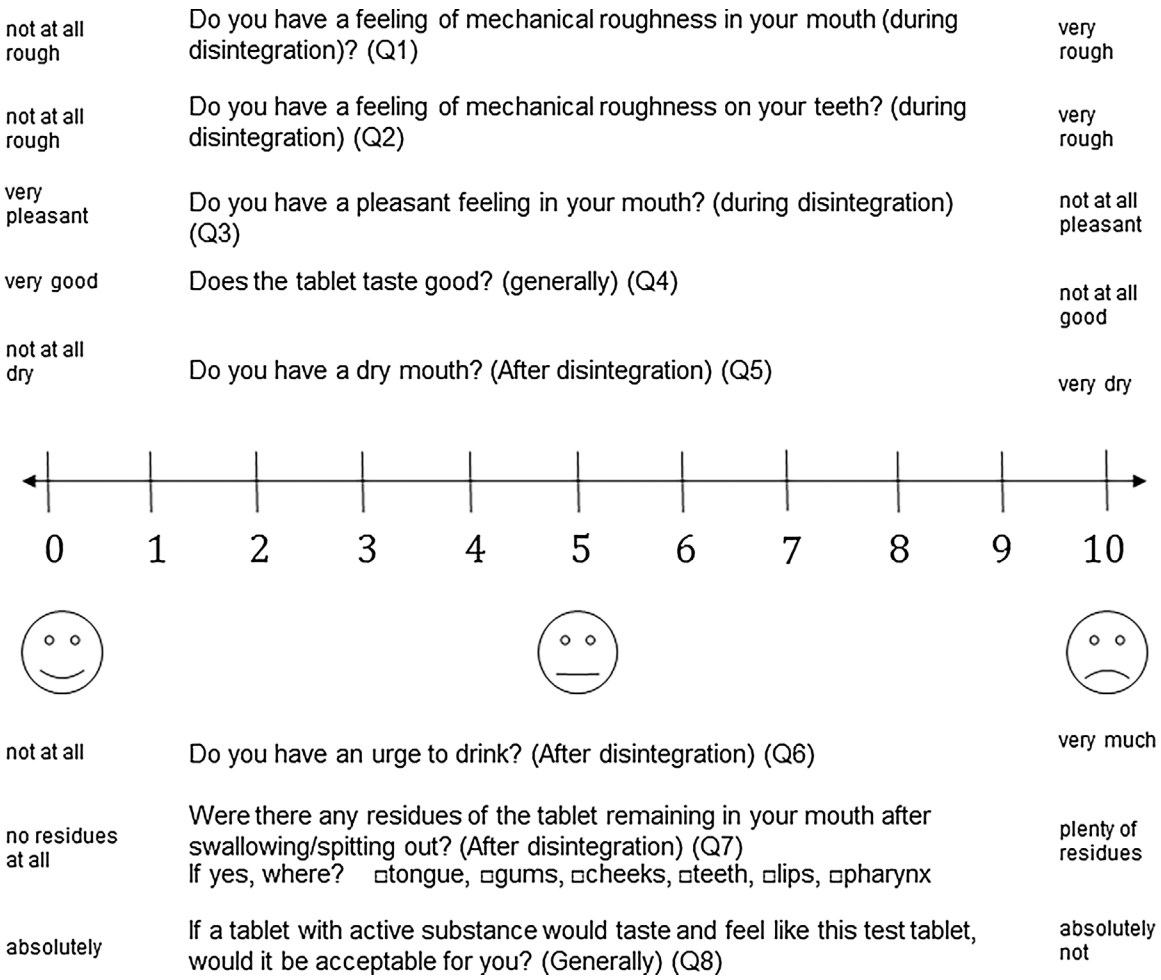

Fig. 4. Scale and possible answers of all the 8 questions in the mouthfeel study.

- Do you have an urge to drink (after disintegration)? (Q6)

  (0 → not at all; 10 → very much)

- Were there any residues of the tablet remaining in your mouth after swallowing/spitting out (after disintegration)? (Q7)

  (0 → no residues at all; 10 → plenty of residues)

- If yes where? (Q7a)

  (tongue, gums, cheeks, teeth, lips, pharynx)

- If a tablet with active substance would taste and feel like this test tablet, would it be acceptable for you? (Q8)

  (0 → absolutely; 10 → absolutely not)

After answering these eight questions the volunteers were invited, in a form of semi-structured interview, to give their comments about the sensations experienced while taking the tablets. Volunteers were free to describe their perceptions in own words. These comments were recorded in the corresponding section of the questionnaire.

The volunteer was free to choose whether he/she wanted to swallow the tablet or spit it out. Only volunteers fulfilling the following criteria were accepted to the study: Being non-smoker, not pregnant, do not take any antibiotic treatment, do not report a known hypercalcemia nor impaired renal function. Additionally, it was not allowed to participate if one wears braces or has any dental prosthesis. All volunteers had to be free of injuries in the oral cavity, not show any inflammation in the mouth or throat, not have a dysphagia nor have any impairment of the ability to smell and could not show a known allergy to any of the excipients used.

The protocol for this study was submitted to the local ethical committee Ethikkommission Nordwest-und Zentralschweiz (EKNZ Req-2016-00249).

2.10. Statistical data analysis

The data set was tested for normality using OriginPro2016. Pearson correlation coefficients with 2-tailed test of significance, were calculated for the entire dataset (Q8 was left out, because all volunteers answered with “0”). Additionally, mode, kurtosis and skewness were calculated. The gender was assigned to 0 for male and 1 for female, respectively. For the question about fasting within 2 h prior to the study 0 was assigned to fasting and 1 to non-fasting. Normality test was performed using Saphiro-Wilk approach with a decision level of 5%.

Analogous to a record of pain sensations, the 10-step VAS can be divided in 3 subsections depending on a value of the asked aspect (Scott and Huskisson, 1976): Rather positive sensation (VAS range 0–3.33), intermediate range (VAS range 3.33–6.66) and rather negative sensation (VAS range 6.66–10). The asked aspect is rated as favorable if the values for mode and median lie within a range of 0–3.33. The tablet is considered as “well accepted” if all the answers are within a favorable range, *i.e.* within 0–3.33.

Table 2
Compressibility and compactibility parameters for ReadyMix and ODTF granulates.

Parameters	ReadyMix	ODTF
Heckel analysis		
k (10^{-3} MPa^{-1}) ± SD[a]	2.75 ± 0.05	2.26 ± 0.03
A ± SD	0.435 ± 0.005	0.563 ± 0.004
σ_y (MPa)	363.70 ± 6.03	443.19 ± 6.36
R^2	0.976	0.975
Modified Heckel analysis		
C (10^{-3}MPa^{-1})	0.820 ± 0.040	0.725 ± 0.008
ρ_{rc} ± SD	0.226 ± 0.008	0.285 ± 0.001
R^2	0.998	0.997
Leuenberger analysis		
σ_{max} (MPa) ± SD	14.01 ± 0.63	13.49 ± 0.31
γ (10^{-3}MPa^{-1})	2.83 ± 0.1	2.09 ± 0.11
R^2	0.999	0.999

[a] SD denotes standard deviation.

3. Results

3.1. Results of the compactibility study

The results of the Heckel, modified Heckel and Leuenberger analysis showed comparable results for the ReadyMix and the ODTF, respectively. The standard deviations of the values are below 6% for all findings, which underlines consistency (see Table 2).

The Heckel plot showed linear behavior (R^2 = 0.975–0.976) for both formulations. This is a sign of plastic behavior (Ilkka and Paronen, 1993). The σ_y has been found to be comparable with literature with the value 363.7 MPa and 443.2 MPa for the ReadyMix and the ODTF, respectively. These values are lower than the ones found in literature for Calcium Carbonate 330 (σ_y = 513 MPa) (Stirnimann et al., 2014), which indicates plastic characteristics of the FCC. The σ_y for the ODTF was higher than the one for the ReadyMix, indicating that additional excipients in the formulation change the plastic deformation behavior of FCC under compressive stress.

Modified Heckel analysis shows values for the relative critical density that are higher than reported in literature 0.226 and 0.285 for ReadyMix and ODTF respectively, where literature reports 0.125 to 0.154 for pure FCC (Stirnimann et al., 2014). These findings show that a stable compact is formed at this density. The values for the relative critical density of pure powder FCC are slightly lower but still comparable, and indicates that compactibility was not reduced compared to pure FCC.

The results for σ_{max} (13.49–14.01 MPa) are suggesting plastic behavior, and the value for γ (2.09–2.83 × 10^{-3}MPa^{-1}) is indicating brittle behavior according to the suggestion in literature (Leuenberger and Rohera, 1986). Compared to the values from literature for σ_{max} of pure FCC (*i.e.* 8.55–13.92 MPa (Stirnimann et al., 2014)) and σ_{max} of cellulose (*i.e.* 12.40 MPa (Stirnimann et al., 2014)) our values show higher mechanical resistance (Stirnimann et al., 2014). The value for R^2 in Table 2 is referred to the fitting of the average curve shown in Fig. 5.

3.2. Results for tablet parameters and in vitro disintegration time measurements

The ReadyMix granule yielded a median particle size of 522.36 µm. The apparent true density of the ReadyMix was 2.67 g/cm3 and 2.49 g/cm3 for the ODTF, respectively.

For both formulations, the high porosity (approx. 35% (v/v)) is associated with high physical stability (tensile strength about 7 MPa).

The results of the liquid sorption, the absolute amount of liquid, the disintegration rate and the disintegration time are shown in Table 3.

The sorption rate constant was the highest (0.084 s^{-1}) for the 11.28 mm ODTF tablet absorbing water and the lowest (0.0078 s^{-1}) for the 5 mm ReadyMix tablet absorbing art.sal. The 11.28 mm tablets are larger, hence, the absolute amount of water is higher for both formulations. With the height difference of the tablets (*i.e.* 1.5 mm height for 5 mm diameter and 2.8 mm for 11.28 mm), the specific total liquid uptake is higher for 5 mm tablets than for 11.28 mm tablets. The 5 mm ODTF tablet disintegrates slightly slower in art. sal. than in water, where the ReadyMix 5 mm tablet is 8 s slower in art. sal. than in water. The constant λ_1 increases with tablet size, which is understandable as the tablet has a larger diameter and height, consequently, a higher mass. The constant λ_2 decreases with increasing tablet size.

3.3. Results of the data analysis from human panel test

With Pearson correlation test, 9 significant positive correlations were identified, where Pc is the Pearson correlation factor with corresponding *p*-value (confidence interval of 95%):

- The stronger the roughness was felt in the mouth, the stronger the roughness was felt on the teeth. (Pc = 0.53; p = 0.017)
- The stronger the roughness was felt in the mouth, the less pleasant was the feeling in the mouth (Pc = 0.64; p = 0.003)
- The stronger the roughness in the mouth was felt, the worse was the taste of the tablet (Pc = 0.72; p = 0.000)
- The stronger the roughness was felt in the mouth, the more an urge to drink was felt (Pc = 0.66; p = 0.002)
- The stronger the roughness on the teeth was felt, the more an urge to drink was felt (Pc = 0.47; p = 0.038)
- The stronger the roughness was felt on the teeth, the more residues remained in the mouth after swallowing (Pc = 0.48; p = 0.031)
- The better the taste of the tablet was, the more pleasant the feeling was in the mouth (Pc = 0.54; p = 0.015)
- The more the volunteer had a dry mouth, the more of an urge to drink was reported (Pc = 0.45; p = 0.045)

One significant negative correlation was found:

- The older the volunteer, the less of an urge to drink was experienced (Pc = −0.46; p = 0.041)

An interesting correlation was found that shorter disintegration

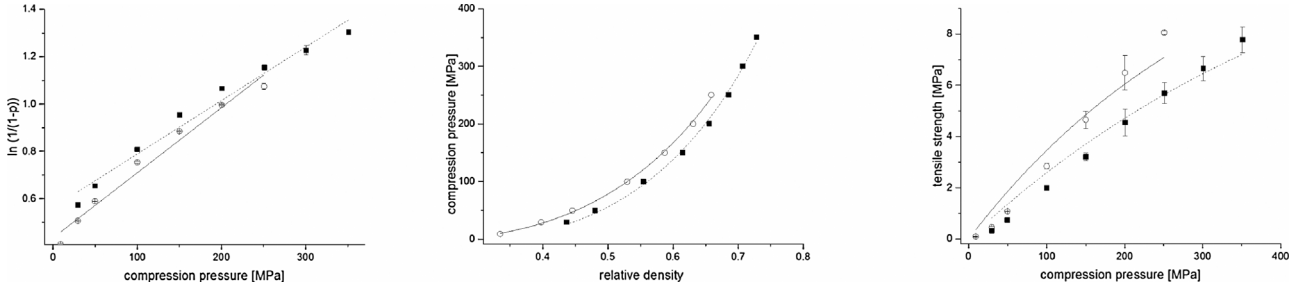

Fig. 5. The Heckel plot, modified Heckel plot and Leuenberger plot are shown for the ReadyMix (○) and the ODTF (■) with the corresponding fitting or the ReadyMix (solid line) and the ODTF respectively (dashed line). The standard deviation was not included for the modified Heckel plot as the values were < 1 MPa.

Table 3
The tablet parameters of the investigated formulations, sorption rate constants, absolute amount water/art. sal. uptake, *in vitro* disintegration time in water/art. sal. of the ReadyMix and the ODTF for 5 mm and 11.28 mm tablets. *In vivo* disintegration time for the ODTF is shown as well. The R^2 values for all the fitted curves were between 0.981 and 0.999.

	ReadyMix 5 mm	ODTF 5 mm	ReadyMix 11.28 mm	ODTF 11.28 mm
Height (mm) ± SD[a] (n = 12)	1.53 ± 0.05	1.55 ± 0.02	2.82 ± 0.01	2.93 ± 0.02
Diameter (mm) ± SD (n = 12)	5.04 ± 0.00	5.04 ± 0.00	11.36 ± 0.00	11.36 ± 0.01
Weight (mg) ± SD (n = 12)	52.3 ± 1.4	51.6 ± 0.7	502.2 ± 2.5	499.6 ± 2.4
Porosity (%) ± SD (n = 12)	35.58 ± 0.68	33.04 ± 0.54	34.16 ± 0.22	32.38 ± 0.40
Tensile strength (MPa) ± SD (n = 3)	8.00 ± 0.38	6.27 ± 0.46	8.05 ± 0.06	5.69 ± 1.41
Water sorption rate constant λ_1 (s^{-1}) ± SD (n = 3)	0.0134 ± 0.0045	0.0269 ± 0.0149	0.0580 ± 0.0103	0.084 ± 0.0201
Absolute water uptake (g) ± SD (n = 3)	0.26 ± 0.02 (after 70 s)	0.32 ± 0.02 (after 100 s)	1.40 ± 0.05 (after 80 s)	1.11 ± 0.08 (after 250 s)
Total specific amount of water uptake (g/g)	5.08 ± 0.36	6.14 ± 0.32	2.78 ± 0.1	2.22 ± 0.15
Disintegration rate constant λ_2 in water (s^{-1}) ± SD (n = 3)	0.4086 ± 0.1361	0.6054 ± 0.3504	0.1603 ± 0.0356	0.2543 ± 0.0130
Disintegration time in water (s) ± SD (n = 3)	10.23 ± 1.02	11.44 ± 0.90	26.11 ± 0.55	21.04 ± 1.96
Sorption rate constant λ_1 in art. sal (s^{-1}) ± SD (n = 3)	0.0078 ± 0.0017	0.0228 ± 0.0089	0.0468 ± 0.0110	0.0766 ± 0.0152
Absolute art. sal. uptake (g) ± SD (n = 3)	0.34 ± 0.02 (after 90 s)	0.28 ± 0.03 (after 60 s)	1.24 ± 0.06 (after 100 s)	0.99 ± 0.11 (after 250 s)
Total specific amount of art. sal. uptake (g/g)	6.52 ± 0.38	5.39 ± 0.54	2.46 ± 0.12	1.98 ± 0.22
Disintegration rate constant λ_2 in art. sal. (s^{-1}) ± SD (n = 3)	0.2457 ± 0.045	0.5190 ± 0.1867	0.1299 ± 0.0328	0.2207 ± 0.0043
Disintegration time in art. sal. (s) ± SD (n = 3)	18.92 ± 2.76	13.49 ± 0.7	24.15 ± 3.17	21.67 ± 0.74
In vivo disintegration time (s) ± SE[b] (n = 20)	–	22 ± 2	–	–

[a] SD denotes standard deviation.
[b] SE denotes standard error.

time yields stronger feeling of mechanical roughness in the mouth and on the teeth. Additionally, the shorter the disintegration time, the less pleasant the feeling in the mouth was and the less pleasant was the taste.

In Table 4 the mode, variance, kurtosis and skewness are shown for the age, *in vivo* disintegration time, fasting in the last 2 h, gender, and questions 1 to 8 (Q1–Q8).

For all eight questions, the values for the skewness are all positive, which indicates an overall positive trend for the acceptance of the tablets by the volunteers. The kurtosis of the different questions shows that Q1, Q3 and Q4 are sub-Gaussian distributed and Q2, Q5, Q6 and Q7 are super-Gaussian distributed. The values in the vicinity of 0 for the age and the disintegration time show that the data set is normally distributed. The mode is in Q1 at the value 1 and in all other questions at 0. This shows that the most frequent answer for Q1 was “1” and for Q2–Q8 it was “0”. The median and the mode of the answers for all the eight questions were lower than 3.33, which indicates a tendency of the answers to group in the range of “rather positive sensation”, *i.e.* VAS 0–3.33. The values of 1.25 and 1.00 for the median were observed for answers to Q1 and Q3. The answers in the vicinity to zero are associated with positive perception.

The mechanical roughness in the mouth (Q1) was reported by one volunteer as “rather negative sensation” (VAS = 7), by five volunteers the intermediate range (VAS 4–5.5) was reported, and fourteen volunteers rated the feeling in the mouth as rather pleasant (VAS 0–3).

The mechanical roughness on the teeth (Q2) was reported by one volunteer as rather negative sensation (VAS = 7), two reports are in the scale of intermediate range (VAS = 4) and seventeen volunteers gave rather pleasant sensation estimate (VAS 0–3).

The question whether the volunteers have a pleasant feeling in their mouth (Q3), by one volunteer was answered in the scale of intermediate range (VAS = 4) and nineteen volunteers gave rather positive sensation estimates (VAS 0–3).

The general taste assessment of the tablet (Q4) by all volunteers the rather positive sensation estimate was given (VAS 0–3).

The dry mouth sensation (Q5) was reported by two volunteers as intermediate (VAS 4–5) and eighteen volunteers gave it a rather positive sensation estimate (VAS 0–3).

The urge to drink (Q6), was reported as intermediate (VAS 5–6) by two volunteers and eighteen volunteers indicated a rather positive sensation (VAS 0–3).

The residues in a mouth (Q7) were rated as intermediate by one volunteer, nineteen volunteers rated the residues in a mouth as a rather positive sensation (VAS 0–3).

The last question (Q8) about the acceptability of the test tablet all of the 20 volunteers answered with “absolutely acceptable” estimate (VAS = 0). This underlines the enhanced mouthfeel and acceptable taste.

In Table 5 the results of the normality test are shown. For age and *in vivo* disintegration time, the normality cannot be rejected, whereas for questions Q1–Q7 normality is rejected at the decided level of 5%. Q8 was excluded from analysis (all values were equal to 0).

The age and the *in vivo* disintegration time in the cohort were distributed normally which shows a representative group of volunteers. These findings are supported by the values of kurtosis that are close to 0.

Table 4
The different statistical values of the assessed questions and the age, in vivo disintegration time, fasting within the last two and sex are shown with a confidence level of 95%.

	Mean	Standard Error	Median	Mode	Sample Variance	Kurtosis	Skewness	Confidence Level
Age	29.250	0.912	29.500	31.000	16.618	0.205	0.639	1.908
Disint.time	22.407	1.646	21.550	25.200	54.215	−0.020	0.377	3.446
Food in 2h	0.550	0.114	1.000	1.000	0.261	−2.183	−0.218	0.239
Gender	0.600	0.112	1.000	1.000	0.253	−2.018	−0.442	0.235
Q1	2.350	0.480	1.250	1.000	4.608	−0.664	0.779	1.005
Q2	0.975	0.436	0.000	0.000	3.802	4.031	2.124	0.913
Q3	1.225	0.273	1.000	0.000	1.486	−0.313	0.745	0.571
Q4	0.550	0.153	0.000	0.000	0.471	−0.240	0.887	0.321
Q5	0.800	0.321	0.000	0.000	2.063	3.682	2.046	0.672
Q6	0.950	0.394	0.000	0.000	3.103	3.582	2.074	0.824
Q7	0.875	0.261	0.500	0.000	1.365	1.508	1.435	0.547
Q8	0	0	0	0	0	–	–	0

Table 5
The results for a normality test with p-value and the decision at the level of 5%.

	Statistic of Normality test	p-value	Decision at level(5%)
Age	0.94519	0.29994	Can't reject normality
In vivo disint.time	0.97765	0.9003	Can't reject normality
Q1	0.87118	0.01232	Reject normality
Q2	0.58192	1.92E-06	Reject normality
Q3	0.86907	0.01132	Reject normality
Q4	0.73884	1.21E-04	Reject normality
Q5	0.63405	6.77E-06	Reject normality
Q6	0.61808	4.56E-06	Reject normality
Q7	0.76203	2.47E-04	Reject normality

In Fig. 6 the volunteers' answers to the 8 questions are shown. The results have a trend towards 0, which is underlined by the positive values for skewness. This indicates that the values for the answers are lower than the mean value. For Q7, ten volunteers answered that there were residues remaining after swallowing the tablet. Residues were reported in Q7a to be on the tongue (n = 4), on the teeth (n = 3), on the gums (n = 4) on the lips (n = 1) and in the cheeks (n = 1). One volunteer answered that there were residues, but did not indicate where they were located

The results of the semi-structured interview, where the volunteers were free to describe their perceptions in the mouth while taking the tablet, show that some of the volunteers described the feeling of the disintegrating tablet as nice, sparkly and tickly. There were no negative nor natively-tinted descriptions given by any of the volunteers.

4. Discussion

The results for Heckel analysis, modified Heckel analysis and Leuenberger analysis in Table 2 (*i.e.* σ_{max} and γ) indicate plastic and brittle behavior (Leuenberger and Rohera, 1986). Therefore, we show that the unique compaction properties of the FCC are preserved in formulations with other components. The addition of mouthfeel enhancing excipients had no significant impact on the mechanical properties of compacts. These findings are highly encouraging as they support a formation of stable tablets at rather low compaction pressures while keeping a high porosity to absorb liquid (Stirnimann et al., 2013, 2014).

From the results of the tablet properties, we see that tablets have high physical stability (tensile strengths are between 5.7 and 8.1 MPa) compared to pure FCC that shows a tensile strength of about 8 MPa at the same compaction pressure (Stirnimann et al., 2014).

The porosity of the four different tablets was between 32% (v/v) and 36% (v/v), which are higher values than reported in literature on ODTs produced with other substances (Schiermeier and Schmidt, 2002). This result is solely associated with FCC performance, which yields tablets with high porosity and high physical stability (Stirnimann et al., 2013). These material characteristics seem to be preserved in the ReadyMix granules and in the ODTF. For ODT production, the ReadyMix and the ODTF are better suitable due to lower bulk volumes and better flowability when compared to pure FCC powder.

The results in Table 3 show that ODTF tablets take up water faster and disintegrate quicker than the ReadyMix tablets. This is associated with citric acid and sodium bicarbonate reaction in presence of moisture.

The total specific liquid uptake is dependent on tablet volume. The results show, that the disintegration time is independent of the nature of the disintegration medium. In both media, the disintegration was within 30s.

The sorption rate constants and the disintegration rate constants (λ_1 and λ_2) depend on the tablet geometry and are invariant to formulation differences. Therefore, the mechanism of liquid sorption and disintegration is similar in water and art. sal., thanks to the governing role of the FCC.

The results show that large amounts of liquid are taken up by the tablets. This comes from the flow into the porous media combined with the swelling capacity of croscarmelose sodium (Zhao and Augsburger, 2005, 2006). Due to the swelling effect, a disintegrant component is enlarging the capillary volume and therefore, more water can be absorbed (Washburn, 1921). This observation can be underlined with the findings of (Stirnimann et al., 2013) for FCC-based ODTs. The measured sorption and disintegration rates, as well as specific liquid uptake are indispensable to develop efficient and palatable ODTs. Total liquid availability in a human mouth is an important factor and the amount of liquid needed to disintegrate an ODT must not exceed this value.

In Table 3, the results of liquid uptake experiments with art. sal. suggest that a necessary volume of 0.28 ml for 5 mm ODTF tablets is necessary to disintegrate these tablets. This volume is easily available in an adult human mouth. In literature, the unstimulated saliva flow rates are reported to be of 0.3 ml/min (Porter et al., 2004). In children and young adults (3–16 years) values of 0.4 to 0.51 ml/min are reported (O'Sullivan and Curzon, 2000). It has to be considered, that with sensations of taste, the salivary flow is stimulated, as well as while chewing or eating. Moreover, citric acid has been reported to generate the largest salivary flow production when used as a stimulant (Carpenter, 2013). The literature reports here a stimulated salivary flow of 4–5 ml/min (Porter et al., 2004) and for children and young adults (3–16 years) of 1.08 to 1.21 ml/min (O'Sullivan and Curzon, 2000). For patients suffering from xerostomia, the stimulated salivary flow is also sufficient to disintegrate the tablet completely (0.7 ml/min (Anabel et al., 2016)).

The results of the *in vivo* study show that disintegration time is measured to be 22.41 ± 1.65 s (SE), which is very reasonable for the patient. This value is not far from the *in vitro* data for the disintegration time (13.49 s).

In order to formulate ODTs that disintegrate in predictable time *in vivo*, the mechanism of disintegration has to be known. In this respect, a correlation between λ_2 obtained *in vitro* and *in vivo* needs to be established. We propose a correlation factor of 0.95 for 5 mm ODTF tablets. Application of this factor leads to prediction of *in vivo* disintegration time 10 s slower than *in vitro*. We expect this correlation factor to be smaller for 11.28 mm ODTF tablets (approx. 0.85). For larger

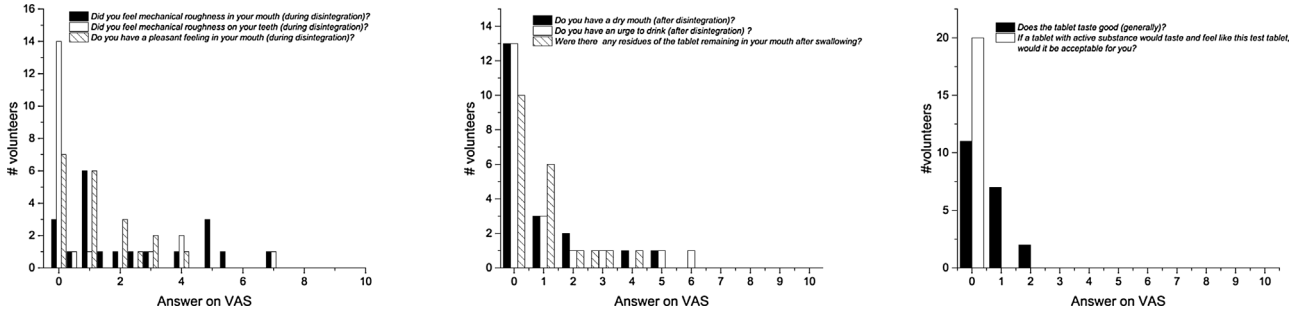

Fig. 6. Histograms with the answers given by 20 healthy volunteers to all eight questions.

geometries, the surface difference becomes important in a constrained environment such as a human mouth. For the ReadyMix tablets, where CO_2 formation does not take place, this correction factor remains equal to 0.95.

The answers to the eight questions are rated as pleasant since the median and the mode are in a lower range of VAS (≤ 3.33). Therefore, we can speak of a tablet as being well accepted by the volunteers. The answers to questions 1 show that the volunteers felt the particles, by reporting a rough sensation in the mouth (mode and median were 1 and 1.25, receptively), however it was not rated as an unpleasant sensation (Answers to Q3, mode and median were 0.00 and 1.00, respectively) This finding is not surprising as humans are able to detect particles sizes of about 5 μm (Guinard and Mazzucchelli, 1996).

The results of the correlation study show, that all positive correlations follow logical assumptions *e.g.* when the roughness in the mouth increases, the roughness on the teeth increases as well.

The good acceptability of the ODTF tablets root in the addition of sweetener and aroma as well as the citric acid in combination with sodium bicarbonate. The sodium saccharine and the sodium cyclamate have a high sweetening power therefore only little amounts are necessary to reach pleasant sweetness (Sodium saccharine is 300–600 times sweeter than sucrose (Rowe et al., 2009)). The orange aroma is reported to be well acceptable (Strickley et al., 2008), also used in pediatric formulations, and combining well together with the citric flavor of the citric acid. The combination of citric acid and sodium bicarbonate is used in effervescent tablets (Jacob et al., 2009). In our formulation, it created a tickly, fresh sensation that was positively experienced by the volunteers.

5. Conclusion

The results of our study show that FCC is a suitable material for proposed ODT formulations without any unpleasant sensation in the mouth. The proposed ODT formulations preserve high physical stability, thanks to good compactibility properties of FCC, and feature a fast disintegration time. With our proposed model for analysis of experimental data, we observed that the amount of saliva necessary to completely disintegrate a tablet is available in the mouth of adults. With the results of the palatability study, we show good acceptance of FCC-based ODT formulation in healthy volunteers. These findings make the proposed formulation strategy very appealing to be used in further development of age-appropriate ODTs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijpharm.2017.10.009.

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3.2 Stability investigation of FCC-based tablets for oral suspension with caffeine and oxantel pamoate as model drugs

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RESEARCH ARTICLE

Stability investigation of FCC-based tablets for oral suspension with caffeine and oxantel pamoate as model drugs

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ABSTRACT

Tablets for oral suspension (TOS) present a convenient alternative dosage form to conventional tablets. Dispersed in a glass of water or on a spoon, such tablets can be easily administered, which can become beneficial for pediatric or geriatric patients. The novel excipient functionalized calcium carbonate (FCC), consisting of calcium carbonate and calcium phosphate, has already shown to be suitable to produce orally disintegrating placebo tablets. In this study, the influence of formulation composition on disintegration time in water and artificial saliva was investigated using caffeine and oxantel pamoate as model drugs, reflecting BCS class 1 and BCS class 4, respectively. The optimized formulation for each model drug underwent a stress test. The results show that the drug content in DTs was not influenced by FCC under stressed conditions, however the disintegration and dissolution performance was affected by temperature and humidity. It can be concluded that it was possible to produce TOS characterized by rapid disintegration complemented by high physical stability of the tablets and chemical stability of the drug.

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Introduction

Excipients used in formulation development of solid dosage forms need to fulfill several characteristics to be used as such [1]. For solid dosage forms, these include chemical stability, good compactibility, good flowability and absence of any remarkable pharmacological effect. Differences from excipient to excipient are not solely material based but can also differ in particle size or surface morphology. Microcrystalline cellulose and cellulose nanofibers are basically the same from the chemical point of view, but differ strongly in terms of morphology [2]. For some applications, the particle surface morphology is essential as, e.g. for the delivery of the drug substance Pranlukast in dry powder inhalators using different types of lactose [3]. When the characteristic of the excipient is mainly based on its surface morphology, it is essential that this surface structure is not influenced by the drug substance itself [4]. Surface morphology can also reflect porosity of the material, therefore contribute to the facilitated ingress of water, which is essential for fast disintegrating formulations [5]. Excipients with high specific surface are often used in formulations requiring rapid liquid ingress, wherever the high contact surface should not become a promoter of drug degradation in the tablets [6].

An important advantage of tablets for oral suspension (TOS) is, that they can be dissolved or dispersed in water prior to administration to form either a suspension or a solution [7]. This makes TOS very convenient dosage forms which offer a possibility of high dose administration without having to swallow a monolithic dosage form [8] when dispersed in a glass or disintegrated on a spoon. This can be advantageous for special patient groups like pediatrics and geriatrics [9]. For TOS – the same is valid for orally disintegrating tablets (ODTs) – a rapid disintegration is crucial [10,11]. Moreover, applying manufacturing methods that are cost effective is a necessity [12]. Therefore, a deep understanding of the influence of different factors on disintegration time facilitates formulation work for TOSs [13]. It should be noted that taste is an essential factor for tablets for oral suspension to ensure patients' compliance. Previous research show that FCC based dispersible tablets are well accepted with taste enhancement components, such as artificial sweeteners and aromas [14]. To exclude any potential influence of taste enhancement excipients on model drug stability in presence of FCC, the formulations investigated in this study were simplified.

Functionalized calcium carbonate (FCC) is a novel pharmaceutical excipient that can be compacted into stable compacts at relatively low compressive pressures. It is highly porous, with lamellar surface structure [15] and can be used to produce orally disintegrating tablets [16] along with gastroretentive formulations [17] and colonic drug delivery formulations [18]. The lamellar structure of the FCC particles is very rigid, featuring high resilience to mechanical stress, such as compression or shear stress in hot melt extrusion process [19]. This lamellar structure of the FCC particles is responsible for high specific surface and porosity of the individual particles, thus accountable for higher contact surface between drug and excipient particles. Therefore, it is essential to investigate the potential influence of the drug on the stability of the TOS formulations with FCC.

In this work, the influence of drug, humidity, and temperature on FCC-based TOS characteristics was investigated. The results on drug content, hardness, and disintegration time in water and in artificial saliva (art.sal.) after accelerated stress test were obtained for hydrophilic model drug caffeine (BCS class 1) and the hydrophobic model drug oxantel pamoate (BCS class 4).

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Materials and methods

Materials

For tablet preparation, caffeine (Sandoz, Switzerland) and oxantel pamoate (Megafine, India) as well as FCC S02 (OM2501, Omya International AG, Switzerland) and the Croscarmellose Sodium (AcDiSol, FMC, USA) were used. For the analysis of disintegration time, demineralized water and artificial saliva was used. The artificial saliva was composed of calcium chloride dihydrate, sodium chloride, sodium phosphate dibasic heptahydrate, magnesium chloride hexahydrate, potassium carbonate sesquihydrate, sodium phosphate monobasic monohydrate, and porcine mucin. All used chemicals were of analytical grade purchased from Sigma-Aldrich (St. Louis, MO, USA)

For HPLC analysis of caffeine samples, acetonitrile (Carl Roth, Germany) was used. For samples containing oxantel pamoate N,N-dimethylformamid (Carl Roth, Germany), a 42:58 (v/v) mixture of acetonitrile and formate buffer was used. All samples were filtered through 0.45 µm PTFE filter (Wicom, Germany) prior to the analysis.

For the different conditions in stability test NaCl solution was prepared for the 73–78%RH and saturated LiBr solution for a relative humidity of 5–10%.

Dissolution tests were carried out in 1000 ml of simulated gastric fluid (0.1 N HCL, Carl Roth, Germany) for caffeine samples and in simulated gastric fluid with 1% (w/v) cetyltrimethylammonium bromide (CTAB) for oxantel pamoate tablets.

Methods

Preparation of the tablets and powder mixtures

The drug substances caffeine (Sandoz, Switzerland) and oxantel pamoate (Megafine, India) were sieved to obtain the size fractions below 500 µm. The tablet compositions are shown in Table 1 and follow the 3-factor, 2-level escribed central composite design (CCD) multiplied by trivial single-factor design (Stavex, AICOS, Switzerland) with mixture factors constraint. As factors for CCD the croscarmellose sodium concentration, drug load, and FCC concentrations were used. The CCD was multiplied by single-factor (drug type) design, where drug type was varying between caffeine and oxantel pamoate. The complete design is shown in Table 1, star points correspond to formulations 1, 2, 3, 4 and 5, 6, 7, 8 for caffeine and oxantel pamoate, respectively. Central points correspond to positions 9 and 10 for caffeine and oxantel pamoate respectively. Regression model used to create the response surface includes quadratic interactions. Response of disintegration time in artificial saliva has been transformed with y^{-2} function.

Prior to blending with drug powder, the FCC S02 (OM2501, Omya International AG, Switzerland) and the Croscarmellose Sodium (AcDiSol, FMC, USA) were dry granulated by roller compaction process (Figure 1).

In order to obtain placebo granules, the FCC and Croscarmellose Sodium powders were sieved <500 µm and blended together at the variable ratios (Table 1) for 10 min in a powder blender (TurbulaT2C, Basel, Switzerland) followed by roller compaction with Chilsonator IR220 (Fitzpatrick, Elmhurst, IL, USA). Rolls pressure was set to 10 bars, rolls gap was kept at 0.5 mm. The vertical and horizontal feed screws were operated at 150 rpm and 20 rpm, respectively. The resulting ribbons were milled at 300 rpm with the Fitz®Mill comminutor L1A (Fitzpatrick, Elmhurst, IL. USA) using hammer mill setup with 1.5 mm diameter screen. The granule size fraction between 180 µm and 710 µm (Retsch Vibro, Schieritz&Hauenstein AG, Arlesheim, Switzerland) was used in all further formulations [14].

Tablets for oral suspension were produced by tableting the powder blends of an active pharmaceutical ingredient (API) and the granulates at variable ratios according to Table 1.

According to the optimal formulations, powder mixes were prepared in order to see potential impact of roller compaction on the performance of the TOS.

Tablet preparation

Styl'One Classic compaction simulator (Medel'Pharm, France) equipped with Euro D 11.28 mm flat round tooling with upper punch immersion depth of 4 mm was used for compaction of all formulations in this study. The compaction cycle consisted of five sections: 1.5 s filling, 1.5 s upper punch approach, 3.0 s compression, 1.0 s relaxation, 5.0 s ejection. Variable compressive force

Table 1. Compositions of screening formulations, optimized formulations and the formulations undergoing stress test.

Screening	Drug type	Disintegrant concentration (%)	Drug load (%)	FCC concentration (%)
1	Caffeine	5.49	17.32	77.19
2	Caffeine	17.51	17.32	65.17
3	Caffeine	5.49	52.68	41.83
4	Caffeine	17.51	52.68	29.81
5	Oxantel pamoate	5.49	17.32	77.19
6	Oxantel pamoate	17.51	17.32	65.17
7	Oxantel pamoate	5.49	52.68	41.83
8	Oxantel pamoate	17.51	52.68	29.81
9	Caffeine	11.50	35.00	53.50
10	Oxantel pamoate	11.50	35.00	53.50
11	Caffeine	3.00	35.00	62.00
12	Caffeine	20.00	35.00	45.00
13	Caffeine	11.50	10.00	78.50
14	Caffeine	11.50	60.00	28.50
15	Oxantel pamoate	3.00	35.00	62.00
16	Oxantel pamoate	20.00	35.00	45.00
17	Oxantel pamoate	11.50	10.00	78.50
18	Oxantel pamoate	11.50	60.00	28.50
Optimal formulations	Caffeine	5.2	18.7	76.1
	Oxantel pamoate.	5.2	18.7	76.1
Formulations undergoing stress test[a,b]	Caffeine	5.2	18.6	75.7
	Oxantel pamoate	5.2	18.6	75.7

[a]All the formulations contained 0.5% magnesium stearate <500 µm.
[b]The same granule as in the formulation undergoing stress test was used as a placebo formulation.

from 6 kN to 10 kN was used to obtain a tablet hardness range within 90 to 120 N. The punches were manually lubricated with magnesium stearate (Sandoz, Switzerland) prior to compaction. Obtained tablets were stored in a desiccator under dry conditions prior to the analysis.

Hardness testing

Tablet hardness ($N = 3$) was tested using Dr. Schleuniger Tablet Tester 8 M (Pharmatron, Switzerland) immediately after tablet compaction.

Disintegration time measurement and analysis

In vitro disintegration time was analyzed from disintegrating tablet net force plot versus time registered with Tensiometer K100 (Krüss, Germany) equipped with a custom-made tablet holder. In details, the method is described in [14]. Tests were carried out in 35 ml of water or artificial saliva. The disintegration volume of 35 ml is required to accommodate the tablet holder grid used in the selected method for disintegration assessment [14,16]. This amount of liquid is not representative for the situation in a human oral cavity, however it provides sufficient, yet not excessive, amount of liquid to ensure disintegration and sufficient discrimination between studied formulations.

The composition of the artificial saliva was: 0.228 g L^{-1} calcium chloride dihydrate, 1.017 g L^{-1} sodium chloride, 0.204 g L^{-1} sodium phosphate dibasic heptahydrate, 0.061 g L^{-1} magnesium chloride hexahydrate, 0.676 g L^{-1} potassium carbonate sesquihydrate, 0.273 g L^{-1} sodium phosphate monobasic monohydrate, and 1 g L^{-1} porcine mucin. Net force was registered until the tablet was completely disintegrated. The obtained curves were used to numerically fit the system of linear ODE (ordinary differential equations) model (Equation (1)) and analyzed for the sorption rate constant (λ_1, s^{-1}), the disintegration rate constant (λ_2, s^{-1}), the additional disintegration rate constant (λ_3, s^{-1}), and the disintegration time [14].

$$\begin{cases} \frac{dm_w}{dt} = \lambda_1 \cdot m_w\left(1-\frac{m_w}{h_m}\right) \\ \frac{dm_d}{dt} = \lambda_2 \cdot m_w + \lambda_3 \cdot m_d \end{cases}, \quad (1)$$

where $\frac{dm_w}{dt}$ describes the wetted mass change rate (g s^{-1}), λ_1 represents the liquid sorption rate constant (s^{-1}), m_w is the wetted mass of the TOS (g), h_m is the maximum possible amount of test liquid that can be absorbed by the TOS (g). The $\frac{dm_d}{dt}$ is defined the disintegration rate (g s^{-1}), λ_2 is the disintegration rate constant (s^{-1}), and $\lambda_3$represents the additional disintegration rate constant (s^{-1}). The constant λ_2 illustrates how much mass is disintegrating depending on the wetted tablet mass. The constant λ_3 represents the case where wetted mass does not immediately leave the tablet surface; this slows down the process of disintegration by increasing a liquid sorption path length.

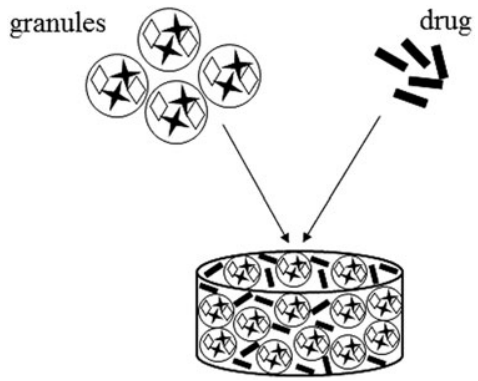

Figure 1. Schematic representation of a manufacturing process for the tablets for oral suspension.

Drug content analysis

The content of caffeine and oxantel pamoate was analyzed chromatographically with Shimadzu Nexera 2 uPLC system with software LabSolutions Lite Version 5.82. For analysis of caffeine samples, an adapted method of Ph.Eur. 7.6 was used [20]. The tablet and powder samples were prepared by dispersing in 100 ml and 50 ml, respectively, of 50:50 (v/v) mixture of acetonitrile (Carl Roth, Germany) and water. Aliquots of 750 µl and 500 µl of dispersion for tablet and powder samples, respectively were diluted with 10 ml of 50:50 (v/v) mix of acetonitrile and water. All samples were filtered through 0.45 µm PTFE filter (Wicom, Germany) prior to the analysis. An amount of 20 volumes of tetrahydrofuran (Merck, Germany), 25 volumes of acetonitrile and 955 volumes of a solution containing 0.82 g L^{-1} of sodium acetate (Carl Roth, Germany) adjusted to pH4.5 with glacial acetic acid (Hänseler, Switzerland) were mixed and used as mobile phase. The flow rate was set to 1 ml min^{-1}. As a stationary phase the Symmetry® C18, 3.5 µm, 4.6 mm × 100 mm (Waters, US) column was used. The column oven was set to 30 °C and the injection volume was 10 µl. The detector was set to 275 nm. Caffeine elution time was at 4.5 min. The total acquisition time was set to 10 min.

Oxantel pamoate samples were prepared by dispersing either tablet or powder mix or the pure powder in 50 ml of N,N-dimethylformamid (Carl Roth, Germany). After sonication (approx. 4 min), the sample solutions were topped up to 100 ml with a 42:58 (v/v) mixture of acetonitrile and formate buffer at pH 2.9. The 25 mM formate buffer was prepared by adding 1.02 g of formic acid (Merck, Germany) to 0.19 g of ammonium formate (Sigma Aldrich, Germany) in 1 L of water. All the samples were filtered through a 0.45 µm PTFE filter (Wicom, Germany) prior to the analysis. As a mobile phase, the 25 mM formate buffer was used together with acetonitrile in a binary gradient pump at a flow rate of 2.5 ml min^{-1}. The binary solvent composition was kept at 30% acetonitrile till 4.00 min, followed by a change to 55% acetonitrile until 5.00 min. Between 5.00 and 8.00 min, the concentration of acetonitrile was kept constant at 55%, followed by a change from 55% acetonitrile at 8.00 min to 30% acetonitrile at 10.00 min. As a stationary phase the column µBondapak® C18 10 µm 125 Å, 4.6 m1 × 50 mm (Waters, US) was used. The acquisition time was set to 10 min; the wavelength of the detector was set to 298 nm. Oxantel pamoate elution time was within 5.5–6.2 min.

Dissolution tests

In order to investigate the changes in drug dissolution rate after stress test without influence of FCC, which is water insoluble mineral salt, the dissolution studies were carried out in 1000 ml simulated gastric fluid (0.1 N HCl, pH 1.1) for caffeine tablets and in 1000 ml of simulated gastric fluid (pH 1.1) with 1% (w/v) of CTAB for oxantel tablets. For reference purposes the pH neutral media (distilled water) was used for caffeine formulations and with 1% (w/v) CTAB for oxantel pamoate tablets. For the experiment the SOTAX AT7 Smart dissolution apparatus (Sotax, Aesch, Switzerland) was used. The components of the FCC (calcium

carbonate and hydroxyapatite) are soluble in 0.1 N solutions of HCl, forming solutions of calcium chloride and calcium hydrophosphate, therefore, the influence of the insoluble FCC on the drug particles will be minimized. Paddle speed was set to 100 RPM, samples were collected with piston pump every minute and analyzed spectrophotometrically (Ultospec 3100 pro, Amersham Bioscience, UK) in the flow-through 1 mm quartz cuvettes at 273 nm and 376 nm for caffeine and oxantel pamoate samples, respectively. For dissolution trials, the samples before and after stress test (80 °C, 80RH, 7 days) were used.

Scanning electron microscopy

For scanning electron microscopy, the samples were sputtered with a 20 nm gold layer using Leica EM ACE600 (Germany). The images were obtained using FEI Nova Nano SEM 230 at the Nano Imaging Lab (Biozentrum, University of Basel, Switzerland).

Stress test conditions and sample collection

The stress test design follows the 3-factor, 2-level full factorial design multiplied by trivial single-factor design. As factors for full factorial design the temperature, humidity, and time were used. Temperature was varied from room temperature to 80 °C (2 levels). The higher level of temperature was chosen to maximize possible degradation of the model substances within 7 days period. Under assumption of Arrhenius type of degradation kinetics, the chosen conditions are comparable to 3 months under ICH guidelines recommended conditions for accelerated stability test (40 °C, 75% RH). Relative humidity (RH) was varied from 5–10% and 73–78%RH (2 levels). Samples were taken after 3 and 7 days, respectively. The resulting full-factorial design was multiplied by single-factor (drug type) design, where drug type was varying between caffeine, oxantel pamoate and placebo. Regression model used to create the response surface is linear, without quadratic or cubic interactions.

Samples were tested according to schema shown in Figure 2. A total of 24 runs were investigated for disintegration time in water and art.sal., hardness and drug content of caffeine and oxantel pamoate, respectively (see Figure 2). Additionally, the formulations were investigated immediately after preparation (i.e. under non-stressed conditions) for reference purposes. All measurements were carried out in triplicates.

To obtain the set relative humidity atmospheres, four desiccators were filled with saturated salt solutions: Saturated NaCl solution was prepared for the 73–78%RH and saturated LiBr solution was prepared for a relative humidity of 5–10% [21]. To reach the 80 °C an oven Heraeus UT 6200 (Hanau, Germany) was used.

The powder mixtures and pure drug substances were investigated for content only, the placebo tablets were investigated for disintegration time (water and art.sal.) and hardness as shown in Figure 2. The verum tablets were investigated for disintegration time (in water and art.sal.), hardness, and drug content. A regression analysis was carried out with the software MODDE version 9.0.0.0 (Umetrics AB, Sweden).

The tablets undergoing the stress test showed an average weight of 498.9 ± 5.5 mg. The placebo tablets had a volume of 0.377 ± 0.003 cm^3. The tablets containing caffeine had an average volume of 0.387 ± 0.002 cm^3 and the tablets containing oxantel pamoate had an average volume of 0.415 ± 0.003 cm^3.

Results

Formulations prepared according to Table 1 were analyzed to obtain the disintegration time response surface shown in Figure 3. The optimum formulation was found at the minimum of disintegration time for all drugs and media. The optimized formulations are given in Table 1 and marked with an arrow in Figure 3, respectively.

From the regression analysis, several factors are significant ($p \leq 0.05$) for the minimization of disintegration time. For the response disintegration time in water (goodness of fit: $R^2 = 0.90$), the disintegrant concentration and the FCC concentrations are significant. Disintegrant concentration has a positive impact, whereas FCC concentration has a negative influence on disintegration time in water (i.e. the more disintegrant, the longer the disintegration time, and the higher the FCC concentration the shorter the disintegration time). For the disintegration time in art.sal. (goodness of fit: $R^2 = 0.9168$), the drug influence becomes significant. Oxantel pamoate has a negative impact on disintegration time, whereas caffeine increases the disintegration time in art.sal. (i.e. tablets with oxantel disintegrate faster and tablets containing caffeine disintegrate slower).

Stress test results

In Table 2, all the investigated parameters measured immediately after preparation (i.e. no stress conditions) are shown.

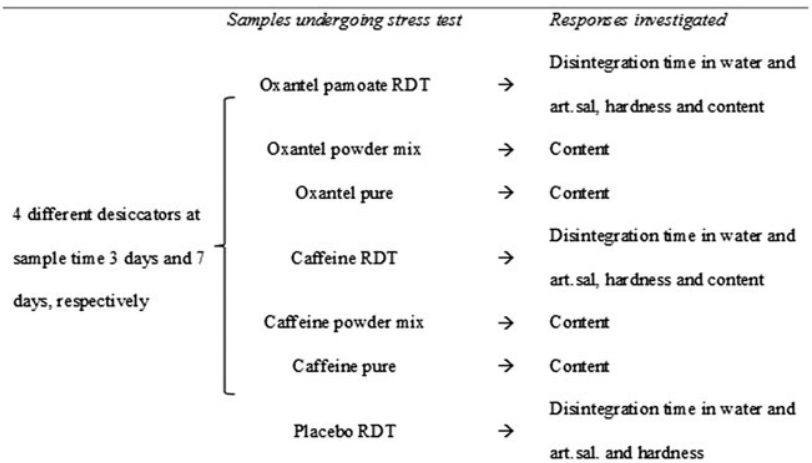

Figure 2. Overview of the conditions, samples, and response variables investigated during the stress test.

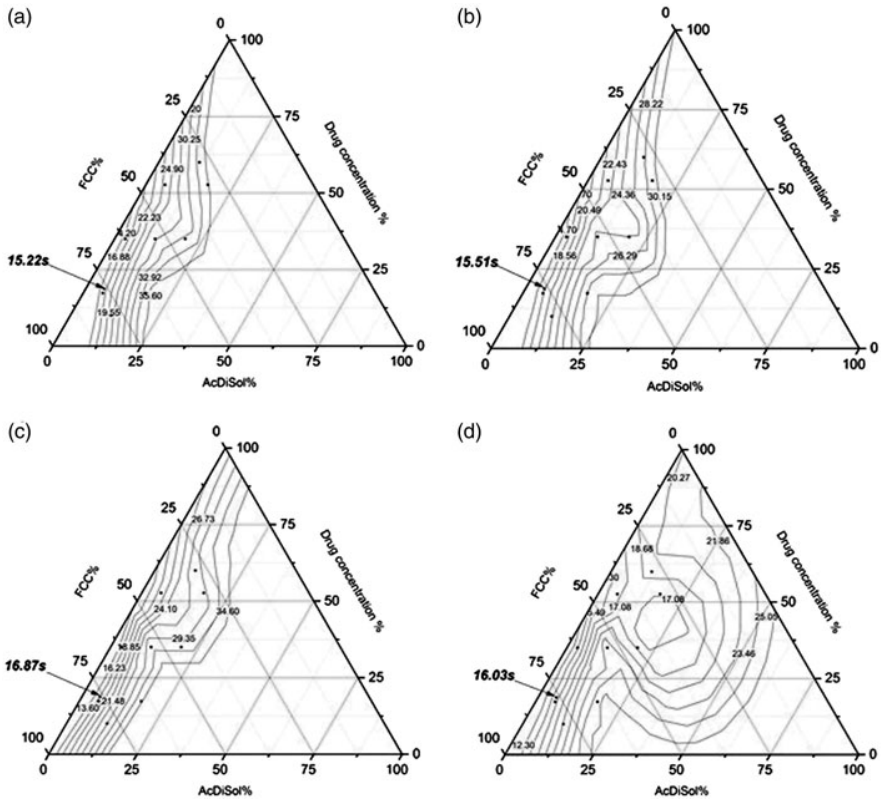

Figure 3. The contour plots of the two drugs and the disintegration time in the two test liquids, where (a) shows the disintegration time of caffeine tablets in water, (b) shows the disintegration time of caffeine tablets in art. sal., (c) shows the disintegration time of oxantel pamoate tablets in water, and (d) shows the disintegration time of oxantel pamoate tablets in art.sal. The arrow shows the disintegration time of the optimized formulation.

Table 2. Results of disintegration time in water and art.sal., hardness and drug content of the tablets, powder mixtures, and pure substances prior to stress test (average ± standard deviation).

Parameter	Caffeine	Oxantel pamoate	Placebo
λ_1 water (s^{-1})	0.062 ± 0.254	0.096 ± 0.016	0.118 ± 0.024
λ_2 water (s^{-1})	0.276 ± 0.081	0.472 ± 0.068	0.455 ± 0.153
λ_3 water (s^{-1})	0.256 ± 0.099	0.476 ± 0.07	0.458 ± 0.168
Disintegration time in water (s)	20.2 ± 0.5	18 ± 2	17.1 ± 2
λ_1 art.sal. (s^{-1})	0.089 ± 0.037	0.185 ± 0.044	0.119 ± 0.032
λ_2 art.sal. (s^{-1})	0.363 ± 0.192	0.573 ± 0.151	0.412 ± 0.092
λ_3 art.sal. (s^{-1})	0.362 ± 0.22	0.617 ± 0.175	0.418 ± 0.102
Disintegration time in art.sal. (s)	19.2 ± 1.7	15.1 ± 1.8	18.4 ± 3.4
Hardness (N)	91 ± 2	75 ± 2	96 ± 1
Drug content RDT (%)	99.57 ± 5.11	91.73 ± 8.11	–
Drug content powder mix (%)	102.15 ± 1.19	94.08 ± 8.94	–
Drug content pure substance[a] (%)	93.32 ± 3.58	98.70 ± 3.79	–

[a]Measurements taken for reference purposes.

Figure 4 shows the significant factors for the responses (and goodness of fit, R^2) of disintegration time and the constants λ_1–λ_3 in water ($R^2 = 0.844$, 0.851, 0.840, 0.836, respectively) and art.sal. ($R^2 = 0.898$, 0.88, 0.918, 0.917, respectively) as well as the hardness ($R^2 = 0.993$) and drug content ($R^2 = 0.917$) of the tablets, powder mixes ($R^2 = 0.845$) and pure substances ($R^2 = 0.815$) after stress test. Placebo tablets that were stored at 80 °C and high humidity after 3 days for both disintegration time in water and art.sal. were excluded because they did not disintegrate. Additionally, placebo and caffeine tablets that were stored at 80 °C and high humidity after 7 days were excluded for disintegration time in water and art.sal. due to incomplete disintegration.

As shown in Figure 4, the hardness was influenced by several factors. The significant factors ($p < 0.05$) were found to be temperature, humidity, and type of drug (i.e. caffeine, oxantel pamoate, and placebo). The temperature had a positive coefficient which shows that a higher temperature leads to increased hardness. The influence of humidity is negative, suggesting that the lower the humidity, the harder are the tablets. For the factor drug type, caffeine and oxantel pamoate are reversely proportional to hardness. This shows that the presence of drug leads to lower values measured for hardness. This is directly supported by the results of placebo tablets, showing higher hardness values than verum tablets. The drug containing tablets show higher hardness values if stored under higher humidity conditions. For the placebo tablets, high humidity conditions resulted in weaker tablets.

The factors influencing the disintegration rate parameters and, therefore, the disintegration time in water were: Temperature for λ_1, for λ_2 and λ_3, temperature as main effect and interaction between temperature and drug type: caffeine. Disintegration time

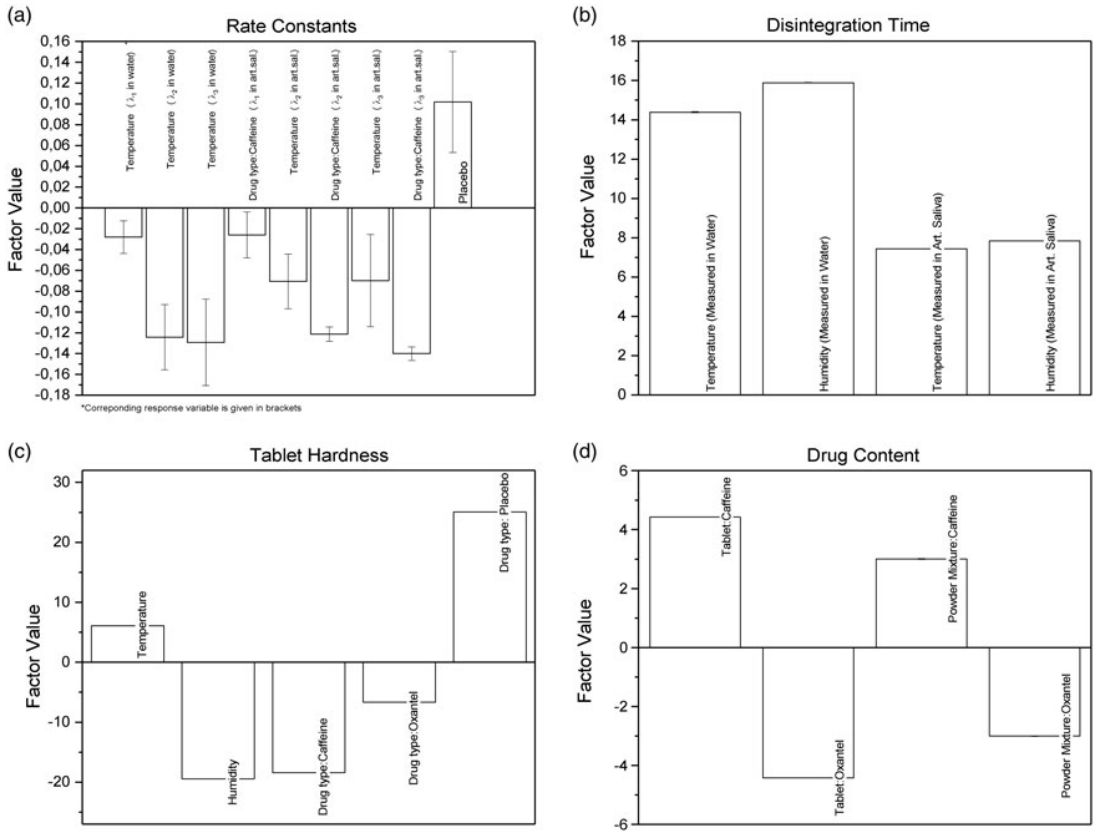

Figure 4. Significant factors of the full factorial design for the stress test. In plot (a), the factor influences on the tablets' rate constants (λ_1, λ_2, and λ_3) measured in water and art. sal. are shown. An effect of placebo on disintegration rate constant 3 is shown for measurements carried out in art.sal. In plot (b), the influence of humidity and temperature on the tablet disintegration time in water and art. sal. is shown. Plot (c) shows the influence of temperature, humidity and drug types on the tablet hardness. In plot (d), the drug content influences on the drug types for tablets and powder mixtures after stability tests are shown. *p* values are indicated as error bars; in plots (b–d) the values are too small to be visible. Only significant factors are shown.

in water is influenced by temperature and humidity. All the factors influencing the sorption and disintegration rate constants had a negative impact (e.g. the higher the temperature, the smaller the value for the rate constants). Humidity and temperature had proportional effect on disintegration time (i.e. the higher the humidity and temperature, the longer the disintegration time).

For the rate constants of disintegration time in art.sal., several factors were significant (see Figure 4). The factors temperature and caffeine are negatively influencing all the constants as well as the disintegration time in art.sal. Disintegration time in art.sal. was influenced significantly by temperature and humidity. The influences were all negative for λ_1 (i.e. the higher the factor, the smaller the constant λ_1). For λ_2 and λ_3, the same is valid.

Drug content of the tablets and the powder mixtures were only influenced by the type of drug. Content of the pure substance is not influenced by any factors in a statistically significant way.

Dissolution trials

The results of the dissolution experiments are shown in Figure 5 for both model drug substances before and after stress test; as well as reference release profiles for both model formulations in water and water/surfactant media. The rate of drug release for caffeine samples in SGF did not significantly change after stress test, both samples release more than 80% (w/w) of the drug within first 5 min for SGF media and $<$10 min for reference water medium. For the caffeine formulations, the release studies (in SGF) do not reveal remarkable changes in the release rate after application of the stress conditions. However, this is not the case for the oxantel pamoate formulations. During the dissolution experiments (in SGF), the formulations after stress conditions were producing small floating agglomerates, which were present in the dissolution vessels for a longer time periods compared to unstressed oxantel pamoate formulations. This behavior can be well reflected by the release curves, where the rate of drug dissolution of the stressed tablets is less compared to the reference formulation; however, is still significantly faster than the latter acquired in water-surfactant dissolution medium. Both oxantel pamoate samples release more than 90%(w/w) drug after 15 min of dissolution. After the dissolution, experiments were completed (after 25 min for caffeine and 120 min for oxantel pamoate) the tablets were dissolved completely, without leaving any visible residuals in the dissolution vessels.

SEM pictures

In Figure 6, SEM pictures of the tablet surfaces are shown for not stressed as well as after storage under humid and hot conditions. Before the stress test, the surface of the tablet containing caffeine was smooth and even. The same is valid for oxantel pamoate tablets. After storage at high RH and higher temperature, the tablets with caffeine show cracks and ruptures which is not observed for oxantel pamoate formulation.

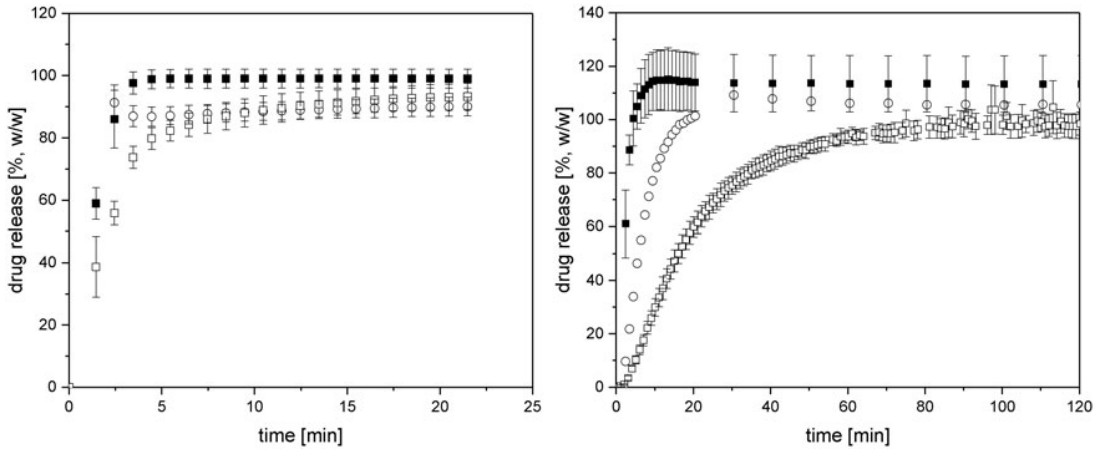

Figure 5. Dissolution profiles of caffeine (left, $N = 6$) and oxantel pamoate (right, $N = 5$) tablets, before (■) and after (○) stress test (80 °C, 80RH, 7 days). The reference curves obtained from pH neutral media are marked with (□) for caffeine (left) and oxantel pamoate (right) charts. The error bars represent standard deviations.

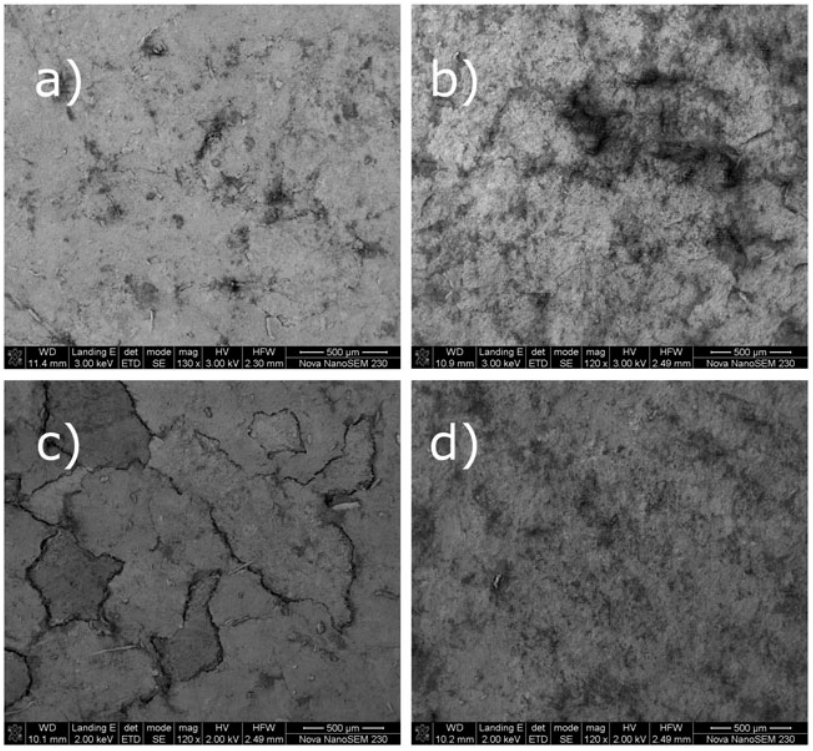

Figure 6. SEM surface images of caffeine (a and c) and oxantel pamoate (b and d) tablets. Images (a) and (b) correspond to tablet before stress test, the images (c) and (d) show tablets' surfaces after stress test under 80 °C and high relative humidity.

Discussion

It was confirmed that the presence of a disintegrant in the FCC mixtures are significantly influencing the disintegration time [16]. The increased concentration of AcDiSol leads to slower disintegration due to its tendency to swell and therefore, at higher concentrations, no longer acting as a disintegrant but a hydrophilic matrix component that prevents liquid penetration. In addition, the elevated local pH values at the site of croscarmellose sodium contact points to the FCC particles lead to formation of hydrolyzed by-products with increased water solubility, which leads to swelling front formation [22]. At higher amounts of FCC in a tablet, the disintegration time decreases due to liquid uptake facilitation by porous structure of FCC which is, therefore, essential for fast disintegration.

There was absence of non-linear effects observed and the extrapolation performance of the model is sufficient for the formulations optimization task. Therefore, it was possible to validate the monotonous polynomial model for disintegration time with the optimal formulation from the central-composite design (see Figure 3). This is an important side finding for formulations based on FCC and its derivative products.

The compressive force of 6.8 kN was used to compress the optimal formulations, which corresponds to compressive stress of approx. 68 MPa. This low compressive stress is resulting in sufficiently high hardness values of 75 N, 91 N, and 95 N for oxantel

pamoate, caffeine and placebo tablets respectively. This confirms the previous finding made for placebo and paracetamol FCC formulations [15] and now extends to caffeine and oxantel pamoate model drugs. The values for hardness are in the upper range for a dispersible dosage form, this allows standard packaging and ensures tablet integrity during transport.

Before the stress test (time 0), all the tablets showed rapid disintegration comparable to the results from optimized formulation. Caffeine tablets disintegrated by approx. 4 s slower, which is potentially influenced by lubrication with magnesium stearate. This addition does not have an impact on the disintegration time of oxantel pamoate tablets, as this API shares the same hydrophobic nature as magnesium stearate.

The tablets that were excluded from the regression analyses did not show complete disintegration. This result can be explained by drug recrystallisation or irreversible swelling of the disintegrant under higher humidity. In the latter case, the disintegration capacity of croscarmellose sodium was no longer sufficient to ensure complete disintegration. This effect of reduced performance of AcDiSol is already known in the literature in context of wet-granulation [23]. The tablets containing oxantel pamoate did disintegrate completely which suggests that the hydrophobic nature of the drug, distributed around the granules shielded them from this effect. Apparently, this effect is stronger in the inner part of the tablets, leading to partial tablet disintegration with solid non-disintegrating core.

The sorption rate constant λ_1 is inversely proportional to temperatures, suggesting slower liquid sorption resultant of storage at higher temperature. Under elevated storage temperatures, the FCC particles are consolidating, making interparticulate voids tighter. This leads to a slight inhibition of the water uptake by the tablets. This tightening was also shown by the increase of hardness at increasing temperatures. The higher the humidity and temperature, the slower the tablets were disintegrating. The same is valid for disintegration time in art.sal. Moreover, the drug type caffeine influences all three constants of disintegration in art.sal.

The hardness was shown to be significantly influenced by temperature, humidity and presence of drug. High storage temperatures lead to harder tablets, whereas humidity leads to softer tablets. This can be explained by the behavior of AcDiSol in the formulation. Under heat, the tablets are temperature cured, which leads to strong bonds between the granules due to drug recrystallisation, especially for drugs with tendency to sublimation-recrystallization, such as caffeine. Humidity, on the other hand, leads to pre-swelling of AcDiSol, which reduces tablet stability. The presence of drug as well as any other substances reduces tablet hardness; as the FCC granules alone have a higher surface available for interlocking compared to the tablets containing drug, any admixture which reduces the contact surface of the FCC particles will depress the mechanical stability of the compacts. The SEM pictures revealed that the recrystallizing of the caffeine under high temperatures led to the formation of cracks, which causes the caffeine tablets to be weaker than the oxantel pamaote and placebo formulations. After the stress test, the drug content did not change, which is indicating that there was no degradation of API in presence of FCC.

The results of the dissolution test show a certain impact of stress conditions (80 °C and 80%RH) on the release pattern of the model drug substances. This impact is negligible for caffeine tablets, however can be seen as release rate reduction for oxantel pamoate tablets. One of the possible explanations for this effect is a secondary agglomeration, i.e. curing, of drug particles into larger aggregates which dissolve slower as primary drug crystalls. This is supported by the visual observations during the dissolution tests, where the floating particles were seen for a longer time for stressed samples. In general, the changes to the release profiles of the tested FCC-based formulations can be considered as minimal, the 80% release of both drugs before and after stress conditions happens within first 20 min of dissolution, which is can be classified as fast, unmodified release formulation. Although, the comparative results were obtained from acidic media, where the influence of undissolved calcium carbonate and calcium phosphate on the drug particles dissolution is minimized, the reference profiles obtained in water and water-surfactant media allow to assume a similar tendency for dissolutions in pH-neutral buffers. The significant reduction in dissolution rates for both model substances observed in the reference profiles is explained by partial obscuration of a solid-liquid interface of drug crystals by insoluble and inert FCC. This is well supported by a high specific surface area of the FCC particles, reaching up 60 m^2 g^{-1}. The effect of release rate inhibition due to geometric features of the filler material is very well seen for oxantel pamoate formulations (Figure 5, right), where untreated tablets dissolve completely in acidic buffer within 5 min, whereas the same tablets tested in pH neutral medium show significantly slower release pattern.

Conclusion

It can be concluded that the two model drugs in the studied FCC-based tablets for oral suspension do not show any chemical degradation. The content was not influenced by humidity, temperature nor storage time. Humidity and temperature did influence dissolution rate, disintegration, and hardness of the tablets. We can conclude that the FCC-based formulation platform can be used to manufacture physically stable, fast disintegrating, unmodified release tablets when stored at the normal conditions (i.e. room temperature, dry condition). The formulations can withstand the stress conditions keeping the drug substances stable for longer periods of time.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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3.3 Study of Drug Particle Distributions within Direct-Compressible Mini-tablets Using Synchrotron X-ray Microtomography and Superpixel Image Clustering

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Drafted manuscript

Study of Drug Particle Distributions within Direct-Compressible Mini-tablets Using Synchrotron X-ray Microtomography and Superpixel Image Clustering

Abstract

Drug distribution in fast disintegrating tablets is of high importance, especially when used to treat local infections in the gastrointestinal tract, such as helminths. In this work, the drug particle distribution in mini-tablets was studied with synchrotron phase contrast X-ray microtomography, using a simple linear iterative clustering (SLIC) superpixel method for segmentation analysis. The compositional results from the X-ray microtomography were compared to and found to be in good agreement with chromatographic measurements. The presented method can be used for the quantitative analysis of drug content and drug distribution within pharmaceutical tablets and for optimization of fast disintegrating formulations, such as those used for local treatment of parasitic infections. The results of the content uniformity analysis suggest the safe concentration region to prepare direct-compressible robust formulations for anti-infective drugs, such as moxidectin.

Keywords: synchrotron X-ray microtomography, functionalized calcium carbonate, moxidectin, distribution analysis, superpixel clustering, percolation theory.

Introduction

According to major pharmacopoeias, the drug content uniformity (CU) is one of the major quality attributes associated with medicinal products. In case of solid preparations such as tablets and capsules, the CU is a measure of a dose distribution within a limited-size sample set, i.e. 10-20 tablets or capsules. However, the CU, as a formulation characteristic, is not providing any information about spatial distribution of a drug substance within an individual dosage form (1). Such information is of high importance for fast dispersible delivery platforms, such as orally disintegrating or rapidly disintegrating tablets. The therapeutic advantage of such formulations is due to efficient and fast distribution of the drug particles near the site of action, e.g., for local treatment of gastro-intestinal infections (2). Failure to evenly distribute the drug in a single tablet leads to formations of drug agglomerates and therefore poor therapeutic outcomes despite a good dose distribution between tablets from the same batch.

The tablet formulations for local treatment in the gastrointestinal tract (GIT), specifically anthelmintic therapies, require methods to assess the drug particle spatial distribution in an individual dosage unit. This is especially important for anthelmintic low-dose moxidectin preparations, for example. Moxidectin is an anti-parasitic drug used in the veterinary field (3,4), mostly for livestock treatment, such as sheep (3), horse (4) or goat (5). In the last few years, moxidectin has been used in humans in clinical trials carried out in Côte d'Ivoire and Tanzania, in order to investigate its anthelmintic therapeutic efficacy (6,7). The mode of action of moxidectin bases on the selective paralyzing of the parasite by increasing muscle Cl^- permeability (8). Moxidectin shares this mode of action with the other avermectins (ivermectin, abamectin, doramectin and milbemycin D). To guarantee an effective local action in the intestinal tract, the drug needs to be precisely dosed and the dosage form must allow high dispersibility. The required dose regimens are comprising 8mg (6,7), which is relatively low considering the average bodyweight of 39.4 kg in the study with adolescents and 54 kg for adults, respectively (6,7). The yielding dose is therefore between 0.15 mg and 0.2 mg per kilogram of bodyweight. A dosage form is required to provide accurate dosing with excellent drug dispersibility in the intestinal lumen and good patient compliance. Helminth infections are mostly prevalent in low and

middle income countries (9,10), therefore it is important to avoid high production-cost formulations, maintaining high quality standards (11).

To fulfill the aforementioned requirements, the low dose fast dispersible small size or mini-tablets produced by direct compaction can be a strategy of choice. Mini-tablets (size of 2-3mm) are a solid dosage form that is accepted by trained children between the age of 6 months and 6 years (12). Functionalized Calcium Carbonate (FCC) based fast disintegrating formulations were previously investigated in palatability studies, reporting excellent compliance benchmarks (13). A rapidly disintegrating version of a mini-tablet – orally disintegrating mini-tablets (ODMT) – are proposed to be even more convenient for the use in the pediatric population (14). In general, ODMTs have good compliance in all age groups (15), are not difficult to swallow (16) and, if rapid disintegration is provided, can allow the intake without water (17). The dose can be quantized per mini-tablet and can be easily adjusted according to specific needs by varying the number of mini-tablets administered (18). Moreover, if the mini-tablets are made with FCC-based fast disintegrating granules, an optimal local treatment in the intestinal lumen can be expected (2). On the other hand, the agile disintegration of the FCC-based granules does not guarantee a uniform drug distribution in the lumen of GIT due to possible agglomerates formation during blending and tableting processes. Therefore, it is necessary to investigate and understand the distribution of a drug within such tablets. In the current study, mini-tablets composed of moxidectin and functionalized calcium carbonate (FCC) were used as model drug delivery systems to study the drug particle distribution with X-ray microtomography as a function of drug load.

X-ray microtomography is an established non-destructive technique used in research fields as diverse as paleontology, materials science, biomedical research, earth sciences and in many others, as well as in industrial R&D and quality assurance processes, capable of determining the internal three-dimensional structure of samples with submicron resolution. In contrast to laboratory-based computed tomography systems running on X-ray tubes, the high brilliance and nearly parallel beams provided by synchrotron beamlines allow for a higher resolution and much faster scans, while the partially

coherent beams enable the use of phase information to boost the contrast between materials with very similar X-ray absorption coefficients and atomic densities, such as many organic materials (19).

The aim of this work is to measure the 3D spatially resolved drug particles' and clusters' positions in mini-tablets and to quantitatively determine the corresponding drug distribution. We apply synchrotron X-ray microtomography with phase retrieval filtering to obtain the volumetric scans of the tablets with high phase specificity of the constituting ingredients. The SLIC superpixel clustering analysis is used to generate discrete scalar fields of tablet components from gray-scale values. The conventional method (i.e. chromatography) to determine the content uniformity of the tablets was compared to the results from the tomographic investigations.

Material and Methods

Production of rapidly disintegrating granulate and mini-tablets

The granulate used to produce the mini-tablets was manufactured by roller compaction followed by a milling step. The granulate described in this publication is equal to the Omyapharm FCC granulate used in another work by Wagner-Hattler et al. (13). It contains 97% Omyapharm FCC (Omya International AG, Switzerland) and 3% crosscarmelose- sodium (AcDiSol FMC, US).

Four different formulations were prepared. First, the Omyapharm FCC granules fraction 180-710 µm and moxidectin USP37 (Livzon New North River Pharmaceutical Co, Ltd., China), sieved <500 µm were blended in a Turbula powder blender T2C (W.A. Bachofen, Switzerland) for 10 min at 34 rpm. To avoid sticking of the compacted mini-tablets to the punches and die walls, the granules were blended with 2% (w/w) magnesium stearate for lubrication. The compositions of the formulations are shown in Table I.

Table I: Composition of the four formulations and their nomenclature

Nomenclature	Moxidectin (%, w/w)	Granule (%, w/w)
DL 2.5	2.5	95.5
DL 5.0	5	93
DL 9.0	8.88	89.12
DL 20.0	20	78

All formulations contained 2% (w/w) magnesium stearate, sieved <500 µm.

The mini-tablets from four formulations (Table 1) were produced with a Styl'One Classic compaction simulator (Medel'Pharm, France), equipped with 12 mini punches of 2 mm diameter and a cap curvature radius of 1.4 mm (Notter, Germany). The mini-tablets were compacted with 80 MPa compressive pressure. The filling height was adjusted to obtain a tablet weight of approximately 10 mg (weighed with Kern balance ABT 120-5DM, Kern+Sohn GmbH, Germany). After compaction, the diameter and height of 10 individual mini-tablets were measured with a digital caliper. All tablets had a height of 2.74±0.1 mm and a diameter of 2.01±0.01 mm.

X-ray microtomography

Synchrotron X-ray microtomography measurements of the tablets were performed at the TOMCAT X02DA beamline of the Swiss Light Source at the Paul Scherrer Institute (Villigen, Switzerland) (20). The X-ray beam produced by the superconducting bending magnet source was monochromatized to a beam energy of 19.9 keV using a large bandwidth ($\Delta E/E \sim 2\%$) Ru/C multilayer monochromator. Samples were placed in the essentially parallel X-ray beam about 25 meters from the source. The radiographic projections of the sample were converted to visible light by a 20 µm thick LuAG:Ce scintillator coupled to an optical light microscope with a 10-fold magnification (Optique Peter, France), placed 12 mm downstream of the sample to obtain some degree of edge enhancement for phase contrast reconstructions. The magnified image was recorded using a pco.Edge 5.5 sCMOS camera with 2560 x 2160 pixels (h x v) of 6.5 µm in size, resulting in an effective pixel size of 0.65 µm and a field of view (FOV) of 1.66 mm x 1.40 mm (h x v).

In order to fit the entire tablet diameter into the reconstructed volume from one scan at this resolution, we used an extended FOV scanning protocol, rotating the sample through 360 degrees while placing the rotation axis near one side of the detector frame (21). This results in almost a doubling of the horizontal FOV (a small bit of projection overlap is required). A total of 3601 projections with an exposure time of 250 ms were recorded per scan, resulting in a scan time of approximately 15 minutes. In the vertical direction, it was necessary to acquire two slightly overlapping stacked scans to fit the total height of the tablet. Hence, the total measurement time per tablet was around 30 minutes, and the overall FOV covered about 3.31 mm x 2.78 mm (h x v).

Tomographic reconstructions were computed after applying a single distance propagation-based phase contrast filter (22), using a δ/β ratio of 50, with the gridrec reconstruction algorithm employing a standard ramp filter (23).This resulted in a sufficiently strong contrast between the Omyapharm FCC and moxidectin phases. The volume data was cropped down to 3701 x 3701 pixels in the axial cutting plane during the reconstruction since this was sufficient to fit the entire tablet diameter, thus limiting the horizontal extent of the reconstruction to about 2.4 mm.

Data analysis

The analysis of the reconstructed data was performed in Image J 1.51j8 (National Institutes of Health, USA) by first binning by factor 4 in all dimensions using an averaging function to reduce the memory footprint necessary for effective computation, followed by a SLIC clustering analysis for the segmentation of mini-tablet components (24). To increase the discriminative efficiency of the segmentation algorithm, a circular mask was applied to the reconstructed images to discard the air volume around the tablet. After clustering, the volumetric percentage of each component was calculated as the ratio between the number of voxels assigned to each phase and the total number of voxels in the tablet, including pores. To obtain the mass of the component from the microtomography scans, the number of voxels corresponding to that component was multiplied by its density. Since all mini-tablets have a bi-convex geometry, the analysis was carried out for the cylindrical part of the tablet only to ensure accurate clustering results. Clustering and analysis were performed separately on both vertically stacked scan volumes and the final metrics were calculated as the average of those two data sets. The result of the clustering algorithm is a three-dimensional array of byte-sized scalars, which is referred to a voxel of 0.275 μm^3 in volume. Each of the voxels was assigned to a type corresponding to a cluster intensity.

The resulting number of components found by the segmentation algorithm was variable, however mostly yielding three main components of the studied formulations. The first component is the drug moxidectin, the second component is the FCC granules and third component has been classified as a mix of moxidectin and FCC intensities. Porosity was not detected by the clustering algorithm, neither cracks nor other types of air pockets. The apparent true density of moxidectin used to convert between volumetric and mass percentages was 1.23 g/cm^3.

The final drug content calculations from clustered microtomographic images have been corrected for sodium croscarmellose content in those cases where the X-ray absorption coefficients of drug particles and croscarmellose fibers were indistinguishable for the SLIC clustering algorithm. Furthermore, due to a very low contrast to other formulation components, the 2% (w/w) of the magnesium stearate

phase could not be reliably detected by the SLIC algorithm; and thus, are not separately assessed in this study.

To obtain the density of the compacted FCC-granule, the weight of a mini-tablet containing no drug was divided by the volume of the same tablet. The volume was calculated according to equation 1.

$$V = 2 \cdot \left(\frac{\pi}{3} \cdot {h_c}^2 \cdot (3r_c - h_c)\right) + {r_t}^2 \cdot \pi \cdot h \qquad \text{eq.1}$$

Where V is the volume of the tablet in cm^3, h_c is the height of the cap, r_c is the curvature radius of the cap, r_t it the radius of the tablet, and h is the height of the cylindrical part of the tablet, i.e., $2 \cdot h_c$ subtracted from the total height of the tablet. The value h_c was calculated by subtracting $\sqrt{r_c^2 - r^2}$ from r_c. All lengths are measured in units of centimeters.

To obtain a measure for the spatial drug distribution, the three-dimensional images of reconstructed tablets were subdivided into several equal volume cylindrical annular regions. The start and end radii of the annuli were calculated as follows: $r(i,n)_{start} = \sqrt{\frac{i}{n} r_t^2}$, and $r(i,n)_{end} = \sqrt{\frac{i+1}{n} r_t^2}$, where i is the index of an annulus from the total number of annuli n. The radius r_t is the tablet radius. For each annulus the sum of voxels associated with drug substance was calculated. The low annulus numbers are corresponding to the volumetric regions at the center of the tablet and higher numbers are towards the tablet walls. Total number of subdivisions n has been set to 30. In Figure 1 an example distribution histogram is shown for a uniform drug particle distribution in the cylindrical part of the tablet. Calculations were made with Wolfram Mathematica 11.0 (Wolfram Research, Inc., Version 11.0, Champaign, IL, USA).

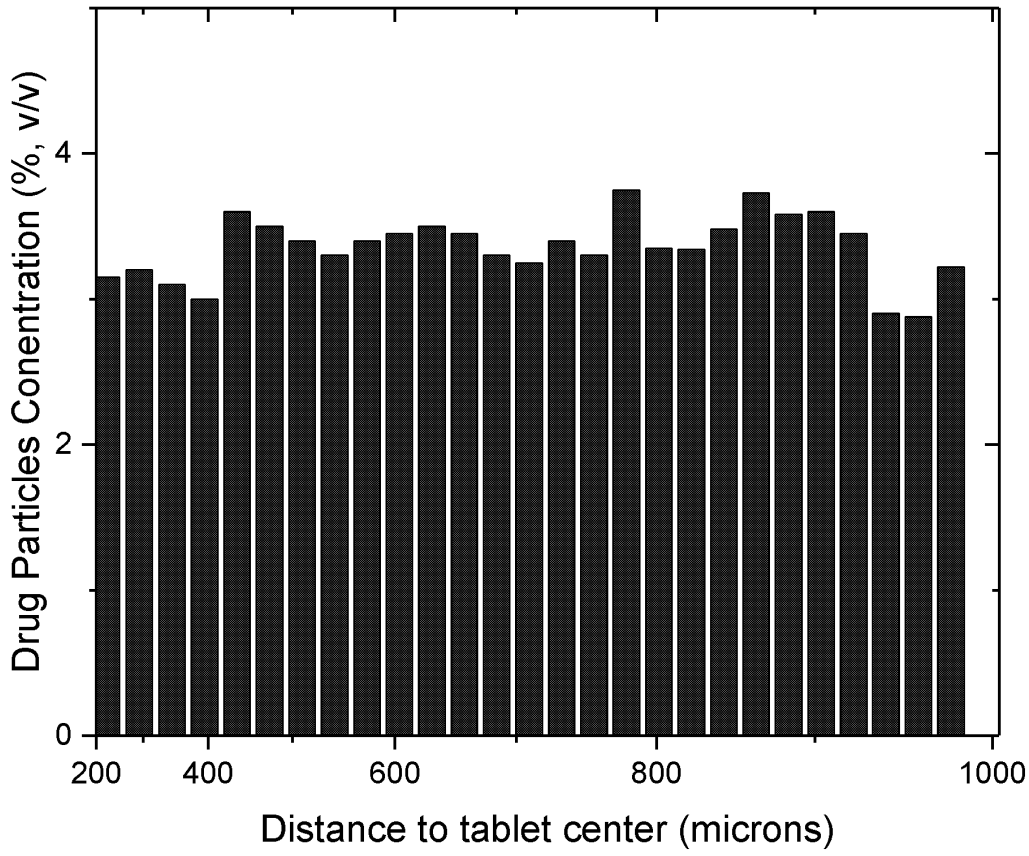

Figure 1. An example histogram of a uniform drug voxels distribution in a cylindrical volume subdivided by 30 equally-sized annular volumes. On the abscissa to the distances of the annulus from tablet center are given.

Chromatographic Analysis of Drug Content

The tablet content was analyzed using a Shimadzu Nexera 2 UPLC System. To detect moxidectin, the Ph.Eur. method for moxidectin was applied (25). The tablet was dissolved in 5 ml acetonitrile (Carl Roth, Germany) and crushed with a glass rod. After 10 min of sonication, the suspension was filtered using a 0.45 µm PTFE filter. For UPLC analysis, a mobile phase of 40% (v/v) ammonium acetate buffer 0.25M and 60% acetonitrile (v/v) at a flow rate of 2.5 ml/min was used. The ammonium acetate buffer contained 7.7 g ammonium acetate (Carl Roth, Germany) in 400 ml of water. The pH was adjusted to 4.8 with glacial acetic acid (Hänseler AG, Switzerland). For chromatographic separation (15 min acquisition time, in triplicates), a column Resolve™ C18, 5 µm, 90 Å, with a diameter of 3.9 mm and a length of 150 mm was used (Waters, USA), the column temperature was set to 50ºC, the detector wavelength was set to 242 nm, and the injection volume was 10µl.

Results

The production of mini-tablets from the powder blends according to Table 1 did not reveal any complications, i.e., there were no signs of capping, lamination, picking or sticking behavior. The tablets were stable and uniform in weight and geometrical dimensions. The results of the measured parameters of the mini-tablets such as the weight (N=10) and effective dose (N=10) are shown in Table II. The measured contents of the individual mini-tablets were scattered in a fairly wide range (i.e. >20% for DL2.5), except for DL9.0, which showed a considerably lower variation of about 5% RSD.

Table II: Target dose, measured content and the acceptance value of the four formulations

Formulation	Tablet weight (mg)	Target dose (mg/tablet)	Effective dose (mg/tablet)±CI (95%)	Effective dose to target dose ratio (%)±SD	% RSD
DL 2.5	9.87±0.34	0.25	0.3±0.03	121.38±20.65	17.01
DL 5.0	9.72±0.51	0.49	0.44±0.05	90.88±16.71	18.39
DL 9.0	9.39±0.37	0.83	0.89±0.03	106.22±5.19	4.89
DL 20.0	9.71±0.55	1.94	2.12±0.15	109.21±12.32	11.28

The measured content in percent of the target dose ranged from 93.2% -152.0% for DL2.5, from 62.8% -122.1% for DL5.0, from 93.9%-112.9% for DL9.0 and from 86.8%-128.5% for DL20.0.

As shown in Figure 2, it is possible to visually differentiate the four main formulation components in the reconstructed image, i.e., drug, calcium carbonate/hydroxyapatite granules (FCC), croscarmellose-sodium, and air. The FCC material appears in light gray values due to its higher absorption of the x-ray photons. The dense crystals of calcium carbonate appear as almost white spots on the FCC material. Drug substance and the croscarmellose appear in similar grey levels due to similar qualitative chemical compositions. A qualitative distinction between these two materials is only possible by shape and location of the croscarmellose fibers entrapped in the FCC granules.

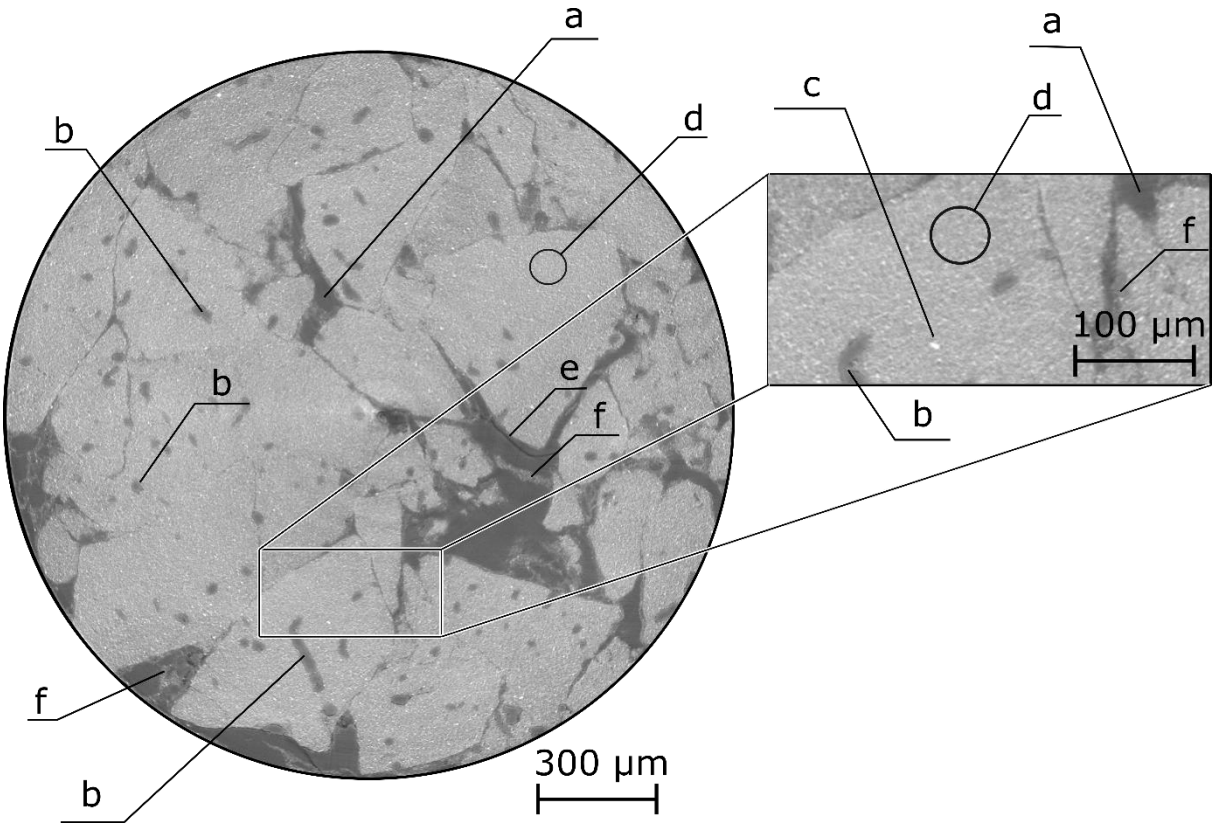

Figure 2: The six different components of the formulations visually differentiated for a non-clustered image: a) moxidectin, b) croscarmellose-sodium, c) dense calcium carbonate crystals surrounded by calcium phosphate (light gray), d) compressed FCC particles, e) pores, f) mixture material of moxidectin and FCC

Inspecting the second magnification in Figure 2 (upper right corner) closely, the different intensities for calcium carbonate and calcium phosphate are evident. In some parts of Figure 2, the edges of the single grains are visible as well. The single granules look intact and do not show any cracks or disruptions. The same can even be seen at the edges of the tablets, where the FCC granules were in direct contact to the die walls during compression. Visual inspection of the reconstructed mini-tablet images did not show a significant number of air pockets, there were no laminations nor cracks detected. The tablets look non-porous, the porosity of the tablets is solely associated with the porosity of the FCC granules, and constitutes of ~40% (v/v) (26). Particular attention should be payed to the

mixture material, which appears as an intermediate gray between FCC and moxidectin. The mixture material (MM) is mostly located at the contact surface between drug and FCC granules.

The reconstruction results with simple absorption contrast did not produce sufficient differentiation for the cluster analysis between formulation components. An application of the Paganin phase retrieval filter was necessary to obtain a sufficient contrast to allow for a reliable segmentation. The cluster analysis was therefore only carried out for phase contrast reconstruction images (see Figure 3).

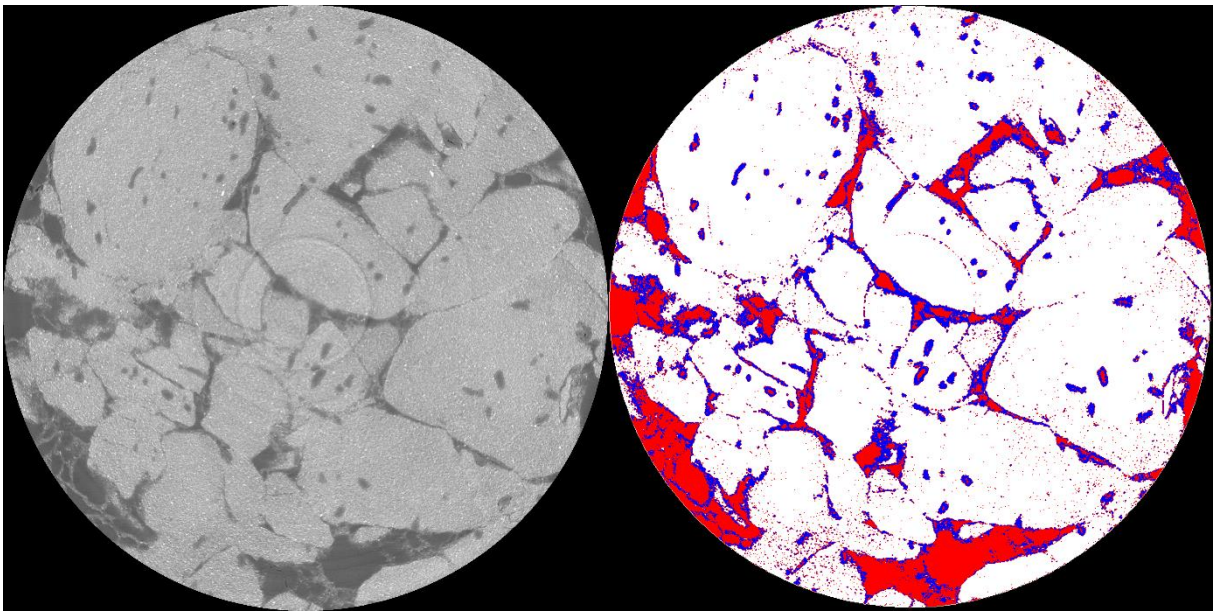

Figure 3: A cross-sectional axial slice through the phase contrast reconstructed volume data set of a mini-tablet (left) together with the corresponding results of the SLIC clustering (right). The clustering algorithm allows a reliable and discriminative breakdown of gray scale values to differentiate the three main tablet components: FCC (white), Moxidectin (red), and Croscarmellose Sodium and mixture material (MM) (blue).

The clustering algorithm recognizes this mixture material (MM) on all cross-sections for all formulations. On the right side of Figure 3 and in Figure 2, this mixture material structure can be seen in blue or light gray, respectively. It consists of lamellar calcium phosphate, denser crystals of calcium carbonate and drug, which leads to averaged X-ray opacity. The quantitative composition of the mixture material cannot be obtained from these images.

The reconstructed grey level values of the fibrous component (i.e. croscarmellose-sodium) were not sufficiently different to discriminate them from the mixture material; therefore, the clustering algorithm recognizes these fibrous structures as mixture material and drug. Nevertheless, the distribution of the fibrous component in the FCC granules can be visually inspected.

Table III: Results of the SLIC-clustering analysis of moxidectin content in the four formulations (n=2)

	Drug Concentration, %, w/w	Percentage of the expected dose, %, w/w	Average percentage of the dose for the whole cylindrical part of a tablet, %, w/w
DL2.5, tablet 1, lower part	3.2	128.4	176.3
DL2.5, tablet 1, upper part	5.6	224.2	
DL2.5, tablet 2, lower part	1.6	63.0	72.0
DL2.5, tablet 2, upper part	2.0	81.0	
DL5.0, tablet 1, lower part	5.8	116.1	116.3
DL5.0, tablet 1, upper part	5.8	116.5	
DL5.0, tablet 2, lower part	5.4	108.5	112.3
DL5.0, tablet 2, upper part	5.8	116.2	
DL9.0, tablet 1, lower part	8.7	96.8	98.5
DL9.0, tablet 1, upper part	9.0	100.1	
DL9.0, tablet 2, lower part	8.8	97.7	98.4
DL9.0, tablet 2, upper part	8.9	99.2	
DL20.0, tablet 1, lower part	21.9	109.6	122.5
DL20.0, tablet 1, upper part	27.1	135.5	
DL20.0, tablet 2, lower part	23.6	118.0	158.3
DL20.0, tablet 2, upper part	39.7	198.5	

In Figure 4, the composition analysis results from the clustering analysis as shown in Table III are compared to the drug content in mini-tablets obtained from liquid chromatography measurements (Table II). Only the results of drug content determination from the clustering analysis for formulation DL9.0 are close to the expected range. With an increased number of microtomographic measurements per formulation, the accuracy and precision of this quantification method is expected to improve. As an additional factor contributing to the deviation between expected and obtained drug concentration from image analysis, is the mixture material with unknown composition. The segmentation algorithm has been applied on the binned (factor 4) images, thus introducing 64-fold averaging. This and an exclusion of the minitablets' cups regions from the analysis leads to an introduction of additional error to the results.

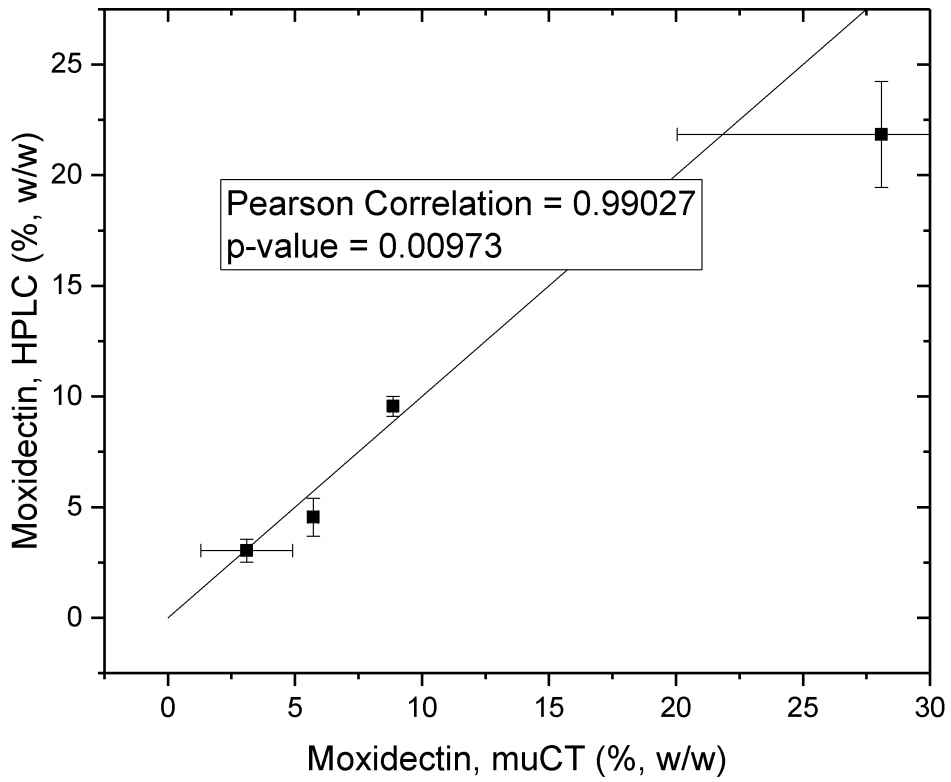

Figure 4: Correlation plot of average moxidectin concentration measured with chromatographic method vs. calculated from microtomography data.

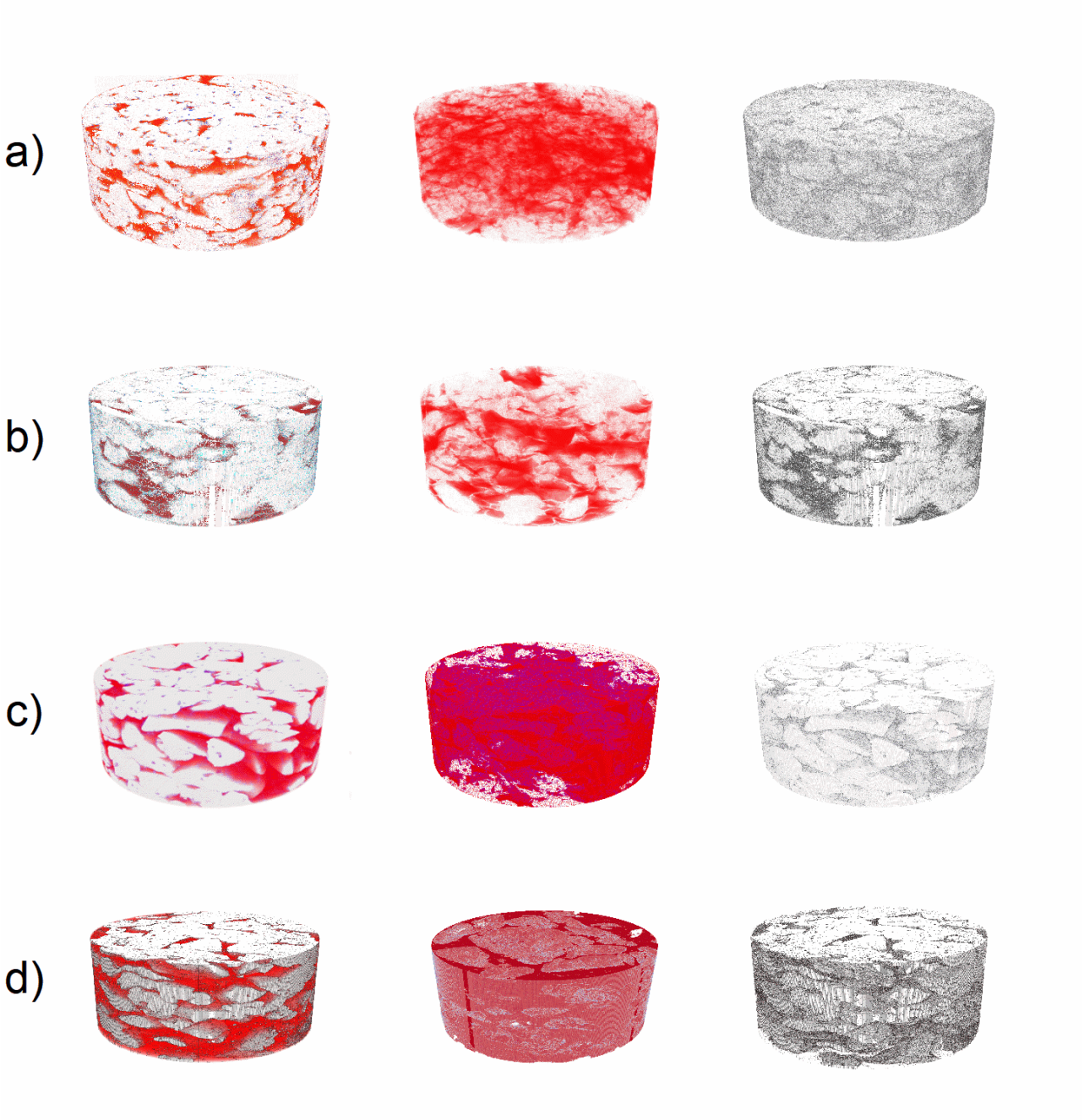

Figure 5: Results of the clustering analysis. In the left column, the phase contrast reconstructed and clustered volume data is shown for all four tablet formulations; The middle and right columns show the three-dimensional rendering of the volume comprised of only the drug and FCC component, respectively. All other phases are not visible as they have been made fully transparent in the rendering.

In Figure 5, the middle and right columns show a rendering of the drug and FCC volume surfaces extracted from the reconstructed and clustered images in three dimensions. To statistically analyze the drug component distributions within different formulations, the results of the drug voxels occurrences versus distance to the tablet center are shown in Figure 6. A uniform distribution (Figure 1) of the drug

particles in a tablet results in equal values for all annual volumes. As shown in Figure 6, the studied formulations do not feature an ideal uniform distribution of the drug within a tablet. The effect of drug material migration from the tablet center towards tablet walls is increasing with increased drug load.

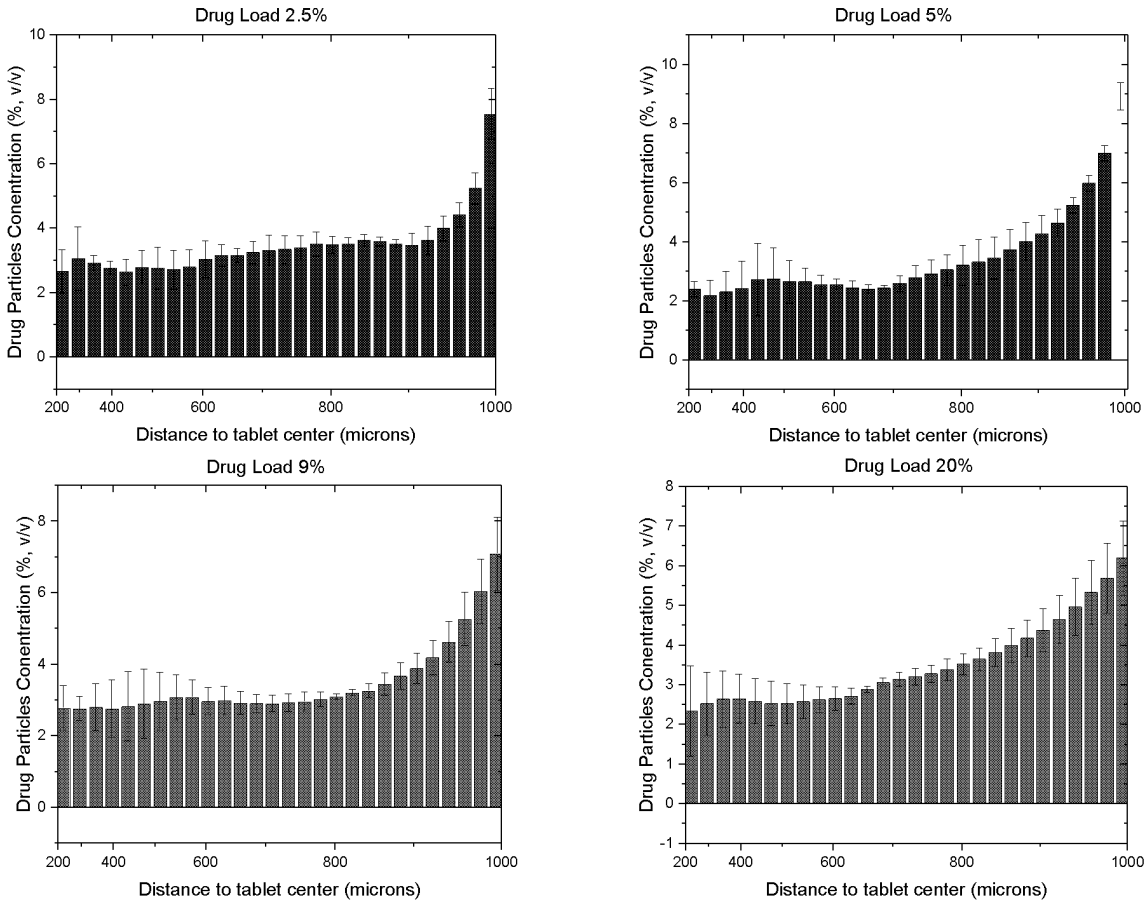

Figure 6: Histograms of the of the drug particle distribution with respect to radial position in the tablet for the four different formulations DL 2.5, DL5.0, DL9.0, DL20.0. Standard deviations are shown as error bars.

Discussion

Among all the tested tablets, the DL9.0 formulation shows the best content uniformity measured by liquid chromatography. This finding is consistent with the microtomography results, although, due to the small number of samples measured with tomography, the latter result is lacking statistical relevance. The deviation of content between microtomography and chromatography results for DL2.5 and DL5.0 formulations is significantly less than the deviation found for DL20.0 tablets as seen in Figure 4. Interestingly, this finding supports the concept of the percolation theory (27), which is stating the presence of a fixed critical concentration, i.e. a percolation threshold, in the vicinity of 16 % (v/v) (28). If the effective drug load is expressed in the volumetric concentrations, assuming the moxidectin apparent crystalline density equal to 1.23 cm^3/g, the resulting percentages are 3.3%, 4.8%, 9.8% and 23.3% for DL2.5, DL5.0, DL9.0 and DL20.0, respectively. This shows that the critical value of 16% (v/v) must be located between DL9.0 and DL20.0 formulations. It means that all formulations with moxidectin content below 16% are qualitatively different to DL20.0. In this respect, the formulations with drug content greater than the percolation threshold show stronger drug cohesion interaction rather than drug-FCC interaction during powder blending, thus inducing segregation and therefore higher deviation in the content.

The results of the distribution analysis reveal that the drug particles are fairly uniformly distributed for all studied formulations, with slight increase in drug content towards the outer rim of the tablets. The effect of the drug substance accumulation near the tablet walls is slightly higher with increase in drug load. It can be hypothesized that this nonuniformity in distribution is induced by a preferential radial migration of the drug particles during compressive deformation (29,30). However, this effect is not strongly pronounced. Based on (29), this migration of the material to the die walls during tablet compaction is not surprising, however, this effect can be expected for lubricant components only, such as magnesium stearate. Nevertheless, the observed difference in the drug distribution for 20% drug loading does not directly explain the deviation in the content. As it is seen in Figure 5, the FCC granules are no longer forming a spanning cluster throughout the tablet geometry, in contrast to the moxidectin component. The FCC granules are almost suspended and isolated from each other in the percolating drug. Therefore, the higher amounts of the drug induce a secondary agglomeration of the

drug particles as the net cohesive forces dominate the adhesion of the drug to the FCC surfaces. This finding corroborates the hypothesis suggesting an increased risk of segregation during powder blending and also content uniformity issues. The presence of the secondary agglomeration also suggests a potential reduction in drug dispersibility in the gastro-intestinal tract after administration. Non-uniform distribution and lumps appearance should be avoided in the formulation of drugs for local treatment, such as anthelmintic preparations.

The important outcome of the visual and the correlation analysis suggest that fast disintegrating FCC granules are suitable for low (i.e., below 15% w/w) drug load (i.e., below percolation threshold concentrations) direct compression formulation development, which therefore allows for significant simplification of the medicine production process.

Another important result from the visual analysis is that the granules remain integral during tablet compaction, i.e., granular crushing does not take place, even at those sites where such destructive deformation is normally expected, for example in close proximity to the die walls. This effect can only be explained by the properties of the FCC-based granules used as bulking and fast-disintegrating component. FCC particles are featuring a significantly high specific surface area (approx. 70 m^2/g), due to developed lamellar structures on the surface of the individual FCC particles. These lamellae interlock under mild compressive stress, allowing for strong Van der Waals interactions due to high contact surface, which leads to formation of hard yet very porous compacts. However, at the interfaces between drug and FCC granules such interaction is less evident; therefore, the formation of a mixture material can be clearly seen on the microtomographic images. The nature and origin of this material is not clearly revealed by the data. The specific features of FCC particles, i.e. denser carbonate cores, can be detected in the mixed layers, and we can assume that the drug particles are present in this mixture as well. Whether this material was formed by attrition and detachment of the individual FCC particles during the blending process or *in situ* during compaction requires further investigation; however, the appearance of this mixture may support a hypothesis that the rough granular surfaces may assist uniform drug layering during powder blending. Further investigation of this phenomenon may suggest

different recommendations of the blending times during powder mixing than those which are conventionally recommended.

The results of this work have shown that the Paganin filters for material information retrieval during the tomographic reconstruction of the pharmaceutical formulations is an enabling step to quantities analysis of pharmaceutical tablet formulations. The combination of this method with segmentation algorithms allows quantitative and special analyses of the drug distribution in the tablets.

Conclusion

We have successfully applied a combined method to investigate and quantify the moxidectin drug particle distribution in mini-tablet formulations with Omyapharm FCC as a main excipient.

The proposed combined analysis of the content and drug particles distributions confirms the applicability of the direct compaction method to produce tablets with required content uniformity and fast dispersibility of the drug in the human GI tract. The identified issue with content uniformity for drug loads greater than 9% can be explained with the concept of a critical concentration for three-dimensional geometries with randomly distributed components. The concentrations below 16% (v/v) can be considered as low risk with respect to segregation. As suggested from the percolation theory the formulations in the direct vicinity to the percolation threshold are prone to stochastic behavior; thus, the robust direct-compressible formulations with Omyapharm FCC granules can be achieved at drug concentrations less or equal to10% (v/v).

The investigated formulations with 2.5-9% (w/w) drug load can serve as a starting point for formulating low-dose anthelmintic formulations with moxidectin, or other avermectins, where low dose and fast and effective drug distribution is required.

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3.4 Characterization of new Functionalized Calcium Carbonate-Polycaprolactone Composite Material for Application in Geometry-constrained Drug Release Formulation Development

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RESEARCH ARTICLE

Characterization of new functionalized calcium carbonate-polycaprolactone composite material for application in geometry-constrained drug release formulation development

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ABSTRACT

A new mineral–polymer composite (FCC-PCL) performance was assessed to produce complex geometries to aid in development of controlled release tablet formulations. The mechanical characteristics of a developed material such as compactibility, compressibility and elastoplastic deformation were measured. The results and comparative analysis versus other common excipients suggest efficient formation of a complex, stable and impermeable geometries for constrained drug release modifications under compression. The performance of the proposed composite material has been tested by compacting it into a geometrically altered tablet (Tablet-In-Cup, TIC) and the drug release was compared to commercially available product. The TIC device exhibited a uniform surface, showed high physical stability, and showed absence of friability. FCC-PCL composite had good binding properties and good compactibility. It was possible to reveal an enhanced plasticity characteristic of a new material which was not present in the individual components. The presented FCC-PCL composite mixture has the potential to become a successful tool to formulate controlled-release dosage solid forms.

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Mineral-polymer composite; elastoplastic deformation; geometrically modified release; tablet formulation; TIC device; dry-coated tablet; functionalized calcium carbonate; polycaprolactone

Introduction

Controlled release dosage forms present a possibility to prolong drug release over several hours [1,2]. Considerable techniques, such as hydroxypropylmethylcellulose (HPMC) [3] or hydroxypropylcellulose (HPC) [4] in a matrix and using semipermeable membranes in osmotic-controlled release oral delivery system (OROS) [5,6] are known. Well established methods to control the drug release, e.g. hydrophilic HPMC matrix, often result in low drug loads due to a higher demand of a matrix components in a formulation. Therefore, a geometric alteration, such as a release surface constraint, is appealing to employ in combination with release sustaining excipients. To control the drug-release profile by geometric alteration there are number of successful examples. Geomatrix® [7], Smartrix [8], donut-shaped tablets [9], one-step dry-coated tablets (OSDRC) [10] or Dome Matrix® [11] are controlled-release products which take advantage of this approach. Release-rate modification by geometric alteration is desirable, however, difficult due to lack of suitable materials. Physical stability, compactibility [12], manufacturing [13], scale-up [13] and risk of dose dumping [14] are known issues associated with these formulations. Because individual materials suitable for pharmaceutical manufacturing lack these mentioned properties, polymer-mineral composites are of particular interest. Functionalized calcium carbonate (FCC) has already shown good performance to enhance disintegration, compressibility and compactibility while being admixed with other excipients [15–17]. FCC is easily compactable and has particles with an array of randomly oriented lamellae that form a porous meshwork. FCC tablets yield high tensile strength at low compressive pressures [16]. Calcium carbonate is in general inert to a large majority of active substances [18,19]. The second component of FCC, calcium phosphate, is as well commonly used as a diluent for capsules and tablets [19].

Production of a polymer-mineral mixtures through a hot-melt extrusion process is a common practice in material engineering to produce structure with improved mechanical properties [20–22].

For industrial pharmacy, a hot-melt extrusion process is of interest for product quality enhancement (i.e. less process variability [23] and easy scale up by time extension [24]) during large-scale manufacturing.

To summarize all above mentioned, it is important to identify and test material for industrial manufacturing of more complex geometries than a simple tablet. There were a number of projects presented in the past to facilitate the accomplishment of similar task [7,8,25]. While many of those materials intent to solve individual problems, almost none are covering the entire required spectrum.

The aim of the current study is to characterize the FCC-PCL composite material for its physical stability, mechanical properties under compressive deformation, and its suitability for geometry-constrained sustained release formulation development.

For better scale-up it is quite important for a material of choice to exhibit high flowability under compressive stress to be able to fill the gaps or voids of a complex geometry.

The success is in combining different methods i.e. geometric alteration, low excipients concentration and ease in production. The novel tablet-in-cup (TIC) device is presented as an example tool to formulate efficiently controlled release dosage forms with the new composite material to improve the patient compliance,

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especially in children or patients with swallowing problems by reducing the volume of a final tablet. The TIC performance was compared to that of the marketed product Kombiglyze®XR.

Materials and methods

The core tablet consisted of 96% (m/m) metformin HCl (Harman Finochem Limited, Mumbai, India), 2% (m/m) polyvinyl alcohol (PVA) (Nippon Goshei, Osaka, Japan), and 2% (m/m) Carbopol 980 NF (Lubrizol, Advanced Materials, Brussels, Belgium). The FCC-PCL composite consists of a 1:1 (m/m) mix of Omyapharm FCC (VP-220976 S03) and polycaprolactone (Capa 6506, Perstorp UK Limited). Magnesium stearate (Sandoz, Basel, Switzerland) was used for lubrication. Kombiglyze®XR 5 mg/500 mg (Astra Zeneca, London, UK) was taken as a reference.

Compaction of core tablet

All excipients were sieved (<500 μm) and blended using a Turbula blender (T2C, W.A. Bachofer, Muttenz, Switzerland) at 32 rpm for 10 min. This core formulation was compacted on a Styl'One compaction simulator (Medel'pharm, Beynost, France) with a 10 mm Euro B flat punch. Compaction cycle was defined with the following speed sections: Filling 2.0 s, upper punch approach 1.5 s, compaction 70 ms, relaxation 1.0 s, ejection 5.0 s, and tablet selection 700 ms. An amount of 520 mg core formulation was compacted at a force set at 17 kN.

Hot-melt granulation

To produce the FCC-PCL composite, hot-melt granulation was carried out on a twin screw hot-melt extruder with perforated die (Three-Tec, ZE9 20602, Seon, Switzerland). The 5 heat cells were adjusted to the following temperatures: cell 1: 10 °C, cell 2: 50 °C, and cell 3, 4, 5 to 80 °C. Feed rate was set between 3.1 and 4.5 g/min. Twin screws were set at 100 rpm. The extruded product was cryo-milled with an IKA A11 (IKA, Staufen, Germany) single-speed hand-mill with cut tooling. The milled product was sieved through a 500 μm sieve. To analyze the FCC-PCL composite, a deformation profile was performed with 11.28 mm flat Euro D punch using compaction pressures from 45 to 295 MPa, time for compaction was set to 1.5 s.

Compaction of the TIC

The final compaction of the TIC was carried out with a 13 mm Euro B beveled punch. The cycle was defined with the following speed sections: Filling 2.0 s, upper punch approach 10.0 s, compaction 70 ms, relaxation 0.14 s, ejection 70 ms, and tablet selection 700 ms. Compaction force was set at 20 kN. Filling height was set at 9.2 mm, the core was centered on the lower punch, and FCC-PCL composite (<500 μm) was filled in the die manually (see Figure 1).

In this project, the core tablet was manually placed on the punch in order to compact it to a TIC device. This process can be transferred to a standard dry coating production line. This is due to the fact that the TIC device is produced the same way, only leaving out the top layer [26]. Centering the core in a dry coated tablet is a challenge, as we used a beveled punch, this centering is facilitated which is also possible on a standard production line.

The empty cups for hardness testing were produced in the same way as the TIC device but instead of a core tablet, a metal

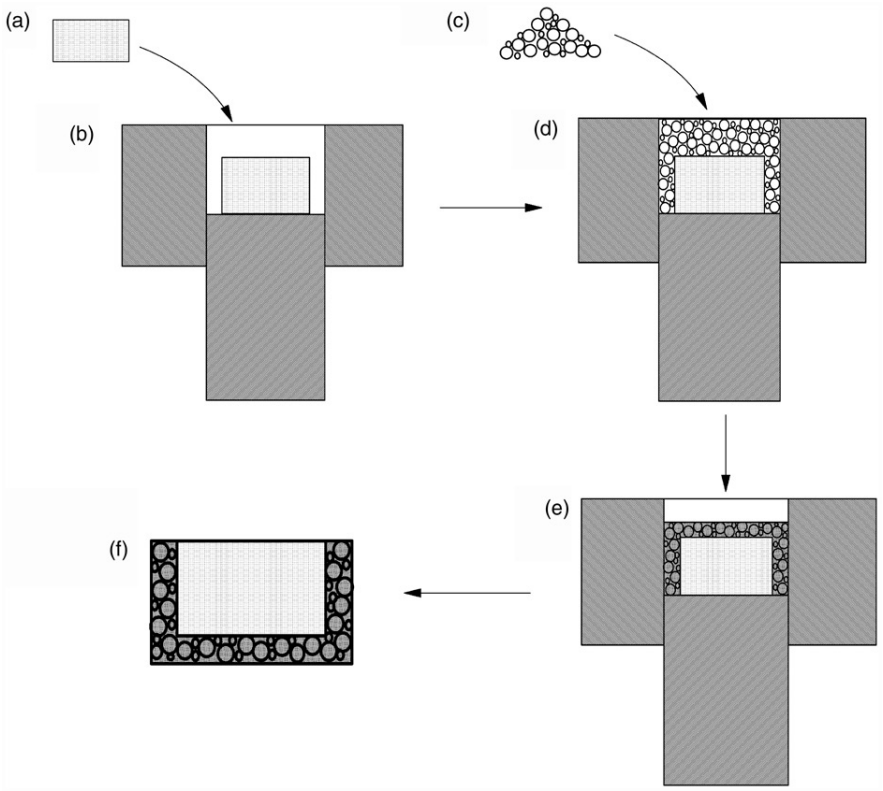

Figure 1. Schematic representation of the TIC manufacturing process. The previously compacted core (a) is centered on the lowered punch into the empty die (white, b). The tooling is represented in dark gray. The random white circles represent the FCC-PCL composite material (c) that is filled over the core (d). The dark gray circles represent the compacted FCC-PCL composite material (e). After ejection the TIC (f) is manufactured.

tablet was used as a template. After compaction, the metal tablet was removed.

Scanning electron microscopy

Scanning electron microscopy (SEM) pictures were made with a FEI Nova Nano SEM 230. The samples were sputtered with a 20–40 nm gold layer by a LEICA EM ACE600 double sputter coater.

Compactibility and compressibility

Compressibility of the FCC-PCL composite was investigated using the Heckel equation (Equation 1) [27]:

$$\ln\left(\frac{1}{1-\rho}\right) = k \cdot \sigma + A, \tag{1}$$

where k is the Heckel parameter (MPa^{-1}), σ is the compressive pressure (MPa), ρ is the density of the tablet (g/cm^3), and A is a constant. Compressive stress was varied between 45 MPa and 295 MPa. Density of the tablet was calculated according to Equation 2 [28]:

$$\rho = \frac{\left(\frac{m}{\pi \cdot r^2 h}\right)}{\rho_{true}}, \tag{2}$$

where m is the mass of the tablet (g), r is the radius of the tablet (cm), h is the tablet height and ρ_{true} is the true density of the material (g/cm^3).The yield pressure was calculated by taking the reciprocal of the Heckel slope [28] ($\sigma_y = \frac{1}{k}$)

In order to investigate compaction susceptibility of the material, the modified Heckel equation was used [29]:

$$\sigma = \frac{1}{C}\left[\rho_{rc} - \rho - (1-\rho_{rc}) \cdot ln\left(\frac{1-\rho}{1-\rho_{rc}}\right)\right], \tag{3}$$

where σ is the compressive pressure (MPa), C is a constant (MPa^{-1}), ρ_{rc} is the critical density (g/cm^3) and ρ is the relative tablet density (g/cm^3).

Powder compactibility was investigated by plotting tensile strength as a function of compressive pressures [12]. Tensile strengths were calculated according to Equation 4.

$$\sigma_t = \frac{2 \cdot F}{\pi \cdot d \cdot h}, \tag{4}$$

where σ_t is the tensile strength (MPa), F is the crushing force (N), d is the diameter (mm) of the round tablets and h the height of the round tablet (mm).

Information about the deformation of the material under stress and bonding properties of the material was obtained by calculating the factors compactibility and compression susceptibility using Leuenberger equation [12] (Equation 5):

$$\sigma_t = \sigma_{(tmax)} \cdot (1 - e^{(-\gamma \cdot \sigma \cdot \rho)}), \tag{5}$$

where σ_t is the tensile strength, $\sigma_{t\ max}$ is the tensile strength when compressive pressure (σ) $\rightarrow\infty$ and relative density (ρ)$\rightarrow$ 1, γ is the compression susceptibility, and σ is the applied compressive pressure. Data obtained at 45–295 MPa were included in the calculation.

Permeability assessment of compacted material

Porosity, median pore diameter, permeability and tortuosity of the compacted FCC-PCL material has been obtained through mercury porosimetry with Auto Pore IV9500 mercury porosimeter (Micromeritics Instrument, Norcross, GA, USA). Low-pressure mercury intrusion ranged from 3.59 to 206.64 kPa and during the high-pressure mercury intrusion the pressure ranged from 206.64 to 206.78 MPa.

Pressure difference required to establish a flow through a porous structure of FCC-PCL material is calculated with Hagen–Poiseuille equation [30]

$$\Delta p = \frac{v \cdot 32\mu l}{d^2} \tag{6}$$

Where, v is the liquid velocity on a porous media (m/s), μ is the dynamic viscosity of liquid (Pa*s), l is a length of a membrane (m), and d is a median pore diameter (m).

Stress-strain curve of the mineral-polymer composite

To obtain the stress–strain curve, an additional experiment was carried out. The molten composite was compressed in a 11 mm die manually to yield a uniform flat disk and to remove all entrapped air from the material. After cooling to the room temperature, the disk was subjected for a compressive deformation stress. For this purpose, the StylOne tablet press was equipped with 13 mm beveled lower punch and a 9 mm upper punch; a deformation within 10 s was carried out. The resulting force and punch displacements were recorded and used with Equations 7 and 8 to obtain mean engineering stress (p) and relative strain (ε) [31].

The stress–strain curve of FCC-PCL composite was obtained with plotting p vs ε (see Equations 7 and 8).

$$p = \frac{P \cdot h}{\pi \cdot R^2 \cdot H}, \tag{7}$$

$$\varepsilon = -ln \cdot \frac{h}{H}, \tag{8}$$

Where p is the mean stress (Pa), P is the value of the load (N), h is the gap between upper and lower punch (m), R is the radius of the upper punch, H is the original height of the sample (m) and ε is the relative strain.

The Young's modulus is the slope of the fitting of the linear section of the stress-strain curve.

Drug dissolution from TIC device

Dissolution testing (TIC: $n = 6$; Kombiglyze®XR: $n = 3$, cores: $n = 6$) was carried out on SOTAX AT7 Smart (Sotax, Switzerland) connected to a UV-spectrometer (Amersham Biosciences, Ultraspec 3100 pro, UK) with a Sotax CY 7–50 pump (Sotax, Switzerland). The dissolution profile was measured in water (37 °C), USP apparatus 2, 50 rpm over 24 h for TIC and Kombiglyze®XR and 3 h for the cores, respectively.

The spectrometer was set to 250 nm, and concentrations were calculated according the following equation: $y = 0.0015x + 0.0102$, $R^2 = 0.9998$.

F2 criterion was calculated according to FDA [32]: $f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\}$, where Rt is drug release in % (m/m) at time t of the reference sample and Tt is drug release in % (m/m) at time t of the test sample, $n = 145$.

Hardness and friability testing

Hardness testing (TIC $n = 6$; core $n = 6$, cup without core $n = 3$, Kombiglyze®XR: $n = 3$) was carried out with Dr. Schleuniger Tablet Tester 8 M (Switzerland). Friability ($n = 10$) was assessed using

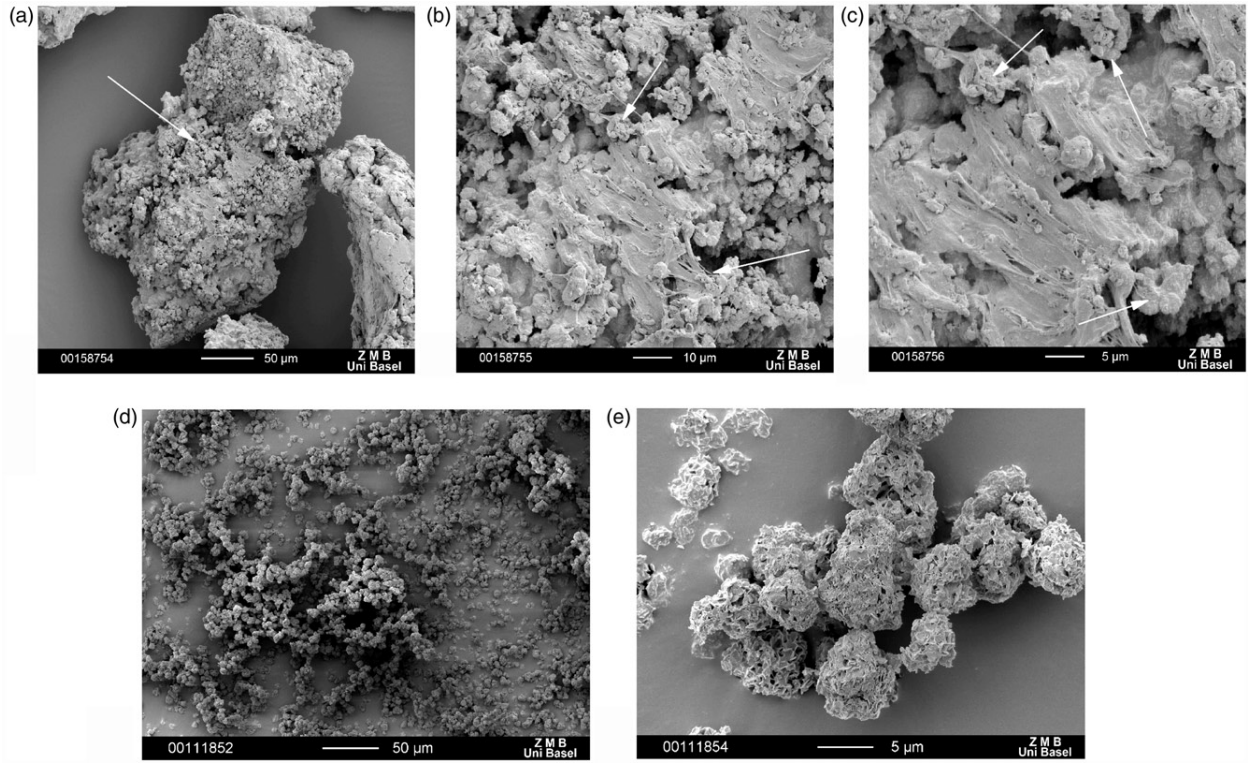

Figure 2. SEM picture of the FCC-PCL composite granule (a). Individual components are shown with corresponding arrows (a, b, c). FCC particles remain their shape and structures which is shown with the comparison pictures of pure FCC [17] (d, e).

Erweka TA200 (Erweka, Germany). Tensile strength was calculated according to Equation 4 for round tablets and according to Equation 9 for shaped tablets [33]:

$$\sigma_t = \frac{2}{3}\left[\frac{10 \cdot F}{\pi D^2 \cdot \left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)}\right], \quad (9)$$

where σ_t is the tensile strength (MPa) and F is the crushing force (N). For shaped tablet, D is the tablet width, t is the tablet height, and W is the shaft height (mm).

Results

To produce the FCC-PCL composite, first FCC and PCL were mixed, followed by hot-melt granulation. During hot-melt granulation, torque remained constant at 3.21 ± 0.04 Nm. Temperatures of cell 3, cell 4, and cell 5 were 80.12 ± 0.66 °C, 80.02 ± 2.31 °C, and 80.20 ± 3.01 °C, respectively. Only the temperatures of cell 3 to 5 were taken into consideration as polymer melting occurred in these cells. Production of the FCC-PCL composite used to form the cup did not pose any problems.

After granulation, the product was frozen, milled, and sieved. Figure 2 shows a SEM picture of the granules with the lamellar structure of FCC embedded in PCL. Only the granules sized <500 µm were used. The results of Heckel, modified Heckel, and Leuenberger analysis are shown in Table 1. Figure 3 shows the Heckel plot, modified Heckel plot, and Leuenberger plot.

The stress-strain curve of the FCC-PCL composite is shown in Figure 4. The Young's Modulus, which is represented by a slope of a linear section $0.02 < \varepsilon < 0.08$, is 0.462 GPa. ($R^2 = 0.987$).

The stress–strain curve is characterized by a clear upper yield point followed by a lower yield point.

Table 1. Compressibility and compactibility parameters for the FCC-PCL composite

Parameters	Values for FCC-PCL composite
Heckel analysis	
k (10^{-3} MPa^{-1}) ± SD	2.65 ± 0.22
A ± SD	2.09 ± 0.04
σ_y (MPa)	377.36
Adj R^2	0.873
Modified Heckel analysis	
C (10^{-3} MPa^{-1})	0.20 ± 0.14
ρ_{rc} ± SD	0.847 ± 0.04
Adj. R^2	0.940
Leuenberger analysis	
σ_{max} (MPa) ± SD	3.44 ± 0.07
γ (10^{-3}MPa^{-1})	19.43 ± 1.11
Adj R^2	0.870

The core tablets and cup material were compacted to form the TIC device with the geometrics as shown in Table 2. Resulting parameters of the TIC device (i.e., core compacted in the cup), are shown in Table 2 along with measured parameters of the reference product (Kombiglyze®XR). During hardness testing of the TIC, core and cup were not falling apart. Separately, the hardness of the cup was also assessed without core tablet and yielded 90.50 ± 4.68 N.

Despite the mediocre flowability of the cup material, the flow of the material under compaction can be characterized as good for both the slow (10 s) and fast (70 ms) compaction cycles. In both cases (i.e. fast and slow compaction speeds) the cup material distribution shows homogeneity (forming equally-sized cup walls, without cracks, ruptures or gaps). An example of compacted cup material is shown in Figure 5. The results obtained from porosimetry indicate median pore size diameter of the compacted cup material 8.9 ± 0.4 nm. According to Hagen–Poiseuille equation for a

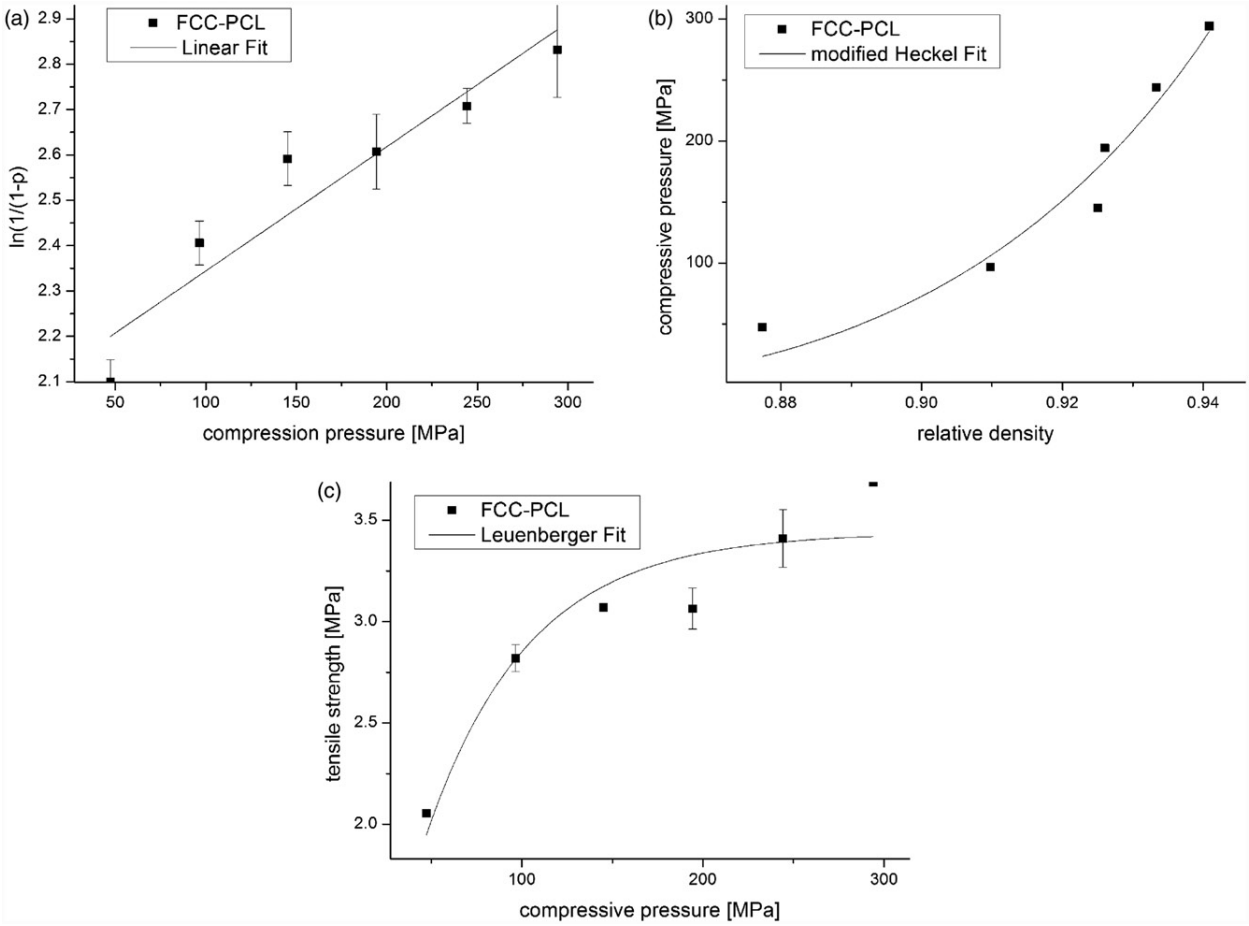

Figure 3. Heckel plot (a), modified Heckel plot (b), and Leuenberger plot (c) of the FCC-PCL composite. In the plot of modified Heckel no standard deviation is shown as the values were below 1%. The goodness of fit (adj. R^2) is 0.873, 0.94 and 0.97 for the all plots, respectively.

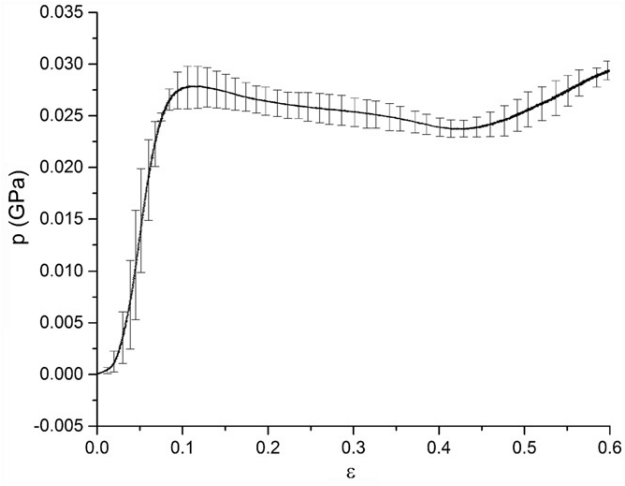

Figure 4. The stress-strain curve of the FCC-PCL composite material with the upper yield point near $\varepsilon = 0.1$.

flow through porous membrane [30] the pressure difference to obtain a liquid velocity of 1 mm/hour will require a positive pressure difference between outer surface of the cup and internal volume of approx. 2 mPa.

Figure 6 shows the release profile of TIC and Kombiglyze®XR 5 mg/500 mg. The release profile of the TIC was slightly slower than the profile of Kombiglyze®XR, showing a linear section between 200 and 800 min. Standard deviations did not exceed 1.33% (m/m) in the case of Kombiglyze®XR and 2.58% in the case of the TIC. The f2 test yielded a value of 78.60, hence the dissolution profiles were considered identical.

Discussion

The properties of a novel calcium carbonate-polymer composite (FCC-PCL) prepared in a hot-melt granulation process were studied.

The results of compactibility and compressibility assays of FCC-PCL yielded a set of unique properties. From Heckel analysis, the value for σ_y yielded 377.36 MPa, which is comparable with that obtained in a previous study where FCC S03 alone had a yield pressure of $\sigma_y = 294$ MPa [16]. The obtained values were higher than those reported in other studies where plastically deforming materials showed a yield pressure of 40–135 MPa [34]. The reason for this is the larger range of compressive pressure used in this study [16]. The relative critical density for FCC-PCL obtained with modified Heckel analysis ($\rho_{rc} = 0.847$) is indicating higher compressive stress requirement to form a stable compact compared to pure FCC particles [29]. From Leuenberger analysis, the value for σ_{tmax} yielded 3.44 MPa, which suggests plastic behavior of the material. For γ, a value of 19.43×10^{-3} MPa^{-1} was found. This value is high compared to that of FCC S03 investigated in the previous study and is significantly greater than the value for MCC (7.56×10^{-3} MPa^{-1}) [16]. Such a value might indicate additional

Table 2. Parameters of the core, TIC, and kombiglyze® XR.

Average	Core	TIC	Kombiglyze®XR
Weight (mg)	517.46 ± 2.32	994.53 ± 5.67	1197.90 ± 9.87
Diameter (mm)	10.03 ± 0.00	13.06 ± 0.00	9.78 ± 0.02[a] 19.60 ± 0.02[b]
Height (mm)	5.36 ± 0.03	5.70 ± 0.03	7.20 ± 0.02
Hardness (N)	127.00 ± 8.63	261.33 ± 15.19	297.33 ± 45.83
Tensile strength (MPa)	1.50 ± 0.11	2.24 ± 0.12	2.22 ± 0.33
Volume (mm^3)	423.49 ± 2.16	755.05 ± 4.01	985.7
Friability (%)	—	0.00[c]	—
Drug load (%) (m/m)	96.63	50.27	41.73

[a]Width of oblong tablet.
[b]Length of oblong tablet.
[c]No mass change was detected.

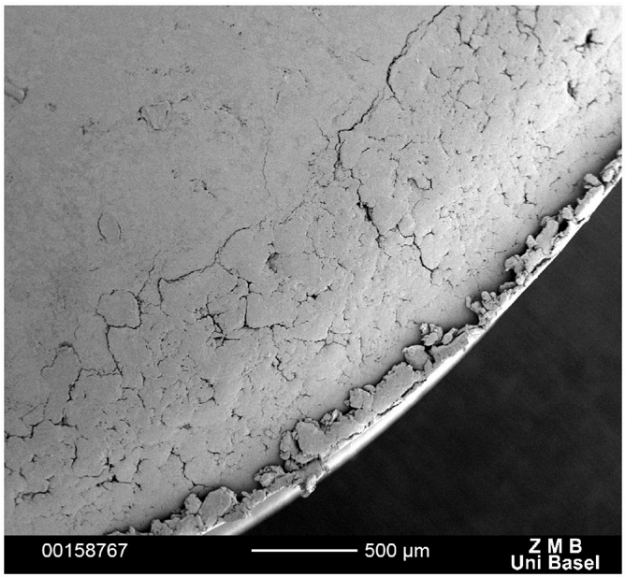

Figure 5. SEM picture of FCC-PCL composite material after compaction into TIC. Observable cracks with mean pore diameter of 8.9 nm do not allow liquid to penetrate intopenetrate TIC in significant amounts.

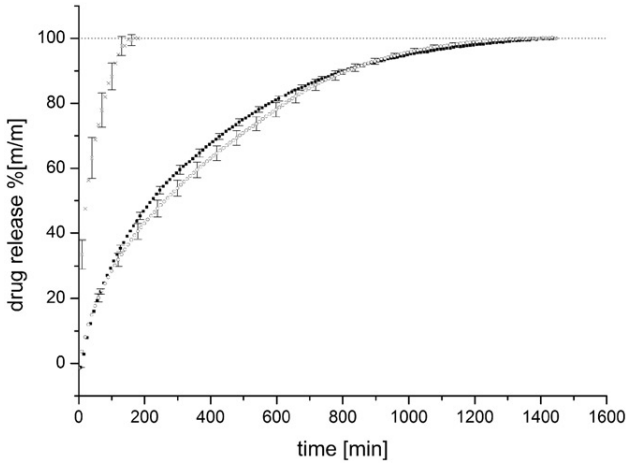

Figure 6. Dissolution profile of TIC 500 mg metformin HCl (O), Kombiglyze®XR 5 mg/500 mg (■) and the metformin core tablets (×). The error bars represent standard deviation, f2 criterion between TIC-metformin HCl and Kombiglyze®XR was 78.60.

bonding action of PCL polymer on FCC lamellae. High values of γ indicate plastic behavior and that the maximal tensile strength can be reached at low compressive pressures [12]. Both values, γ and σ_{tmax}, show the good bonding properties of the material [12].

The observed flow properties of the composite particles were excellent under compaction pressure. During the solidification, no cracking, rupture, nor gaps formation were observed even at fast compaction cycles. Such properties suggest a high inner structure mobility of the FCC-PCL material under a load, which is advantageous for upscaling the production of TIC geometries. Our study suggest that it is possible to compact this material at speeds comparable to those reached on conventional rotary presses and produce complex geometries such as TIC compacts.

It should be kept in mind that compaction of a pure PCL polymer without a thermoforming is limited because of a relative low value of a pure PCL Young's modulus. The Young's modulus of FCC-PCL composite material yielded a 2-fold increase compared to a pure PCL polymer (0.199 GPa), suggesting a fast onset of a plastic deformation phase. The value of 0.462 GPa is in agreement with literature data [35], where the PCL has been combined with different amounts of hydroxyapatite (HA), which results in an increase of a Young's modulus up to 0.48 GPa after 20% HA addition. Further increase of HA admixtures has increased the Young's modulus up to 0.75 GPa at 40% HA. This trend supports our finding that with the increase of mineral component concentration in a polymer causes composite material plastic behavior under stress to be reached much faster. The plastic behavior under a stress is a substantial requirement for compaction of a pharmaceutical tablet. With the FCC-PCL composite such requirement can be easily satisfied.

A second important property of a stress–strain diagram of the FCC-PCL composite is a presence of a lower yield point, which is often explained as presence of a Cottrel atmospheres in case of a homogeneous materials such as steels [36]. For the material proposed in this study we can assume an ordering of FCC microparticles in a PCL matrix under applied loads, supporting high plasticity of the material. At values around $\varepsilon = 0.45$ the stress increases for a second time (see Figure 4) until a suspected rupture. In pure PCL the lower yield point cannot be identified.

The results of the TIC compaction support a sufficient ductility of the composite material to form stable and robust cup under compressive stress without damaging the core tablet. These results were obtained for compaction dwell time of 70 ms, which correspond to 35,000 tablets per hour production scale on rotary tablet presses.

This new material has demonstrated a feasibility to manufacture a geometry-controlled sustained-release formulation taking metformin HCl as a model substance. Good compressibility and compactibility properties of FCC-PCL composite material allowed to prepare a sustained-release formulation with significantly reduced concentrations of matrix-forming components. As shown in Figure 2, the lamellae of the FCC were still present and were not damaged or clotted by PCL, indicating that the properties of the FCC were preserved. The lamellae interlocked with each other, which resulted in stable compacts [16]. The granules were not brittle, that is why freezing before milling was necessary. Another reason for freezing was the fact that energy generated by the milling process would have melted the PCL forming lumps.

The concentrations of PVA and Carbopol are around 2% of the total mass. This amount can be considered to be low. In other formulations using e.g. HPMC between 20% and 50% of polymer were used to achieve sustained release [3].

In order to investigate a mechanical stability and water barrier properties of the proposed composite material the TIC-metformin formulation was compared with the commercial product Kombiglyze®XR 5 mg/500 mg. TIC proved to be 203 mg lighter than Kombiglyze®XR. Hence, drug load of TIC was 8.5% higher than that of Kombiglyze®XR. The TIC device was less voluminous (754.27 ± 3.82 mm^3) compared to Kombiglyze®XR (985.7 mm^3),

which makes it easier to swallow. The amount of excipient to control the release was 20 mg; this is 2% (m/m) of the total mass of the TIC. Due to the fact that only one surface is accessible for the medium, only a small amount of excipient to control the release is necessary. This can help in formulation development. During friability test no mass change was detected. The TIC devices were stable and showed no breakage or deformation, hence a coating will not be required. The cup without core tablet was stable with a hardness of 90.50 N, which is not surprising due to the values γ and σ_{tmax} indicating good bonding at low compressive stress. As shown in Figure 5, the connection between core and cup was tight and hence, no dose dumping is expected. The studied material show a dense structure with pore sizes lying within 10 nm region. This is not a tight barrier for liquids and a certain liquid permittivity should always be considered. On the other hand, an assessment of pressure difference required for a minimal liquid velocity of 1 mm/hour (according to Equation 6 needs a positive value of 2mPa. This mass transfer does not include any concentration-driven diffusion for given geometry with one side open. The cup has good mechanical stability which is supported by undetectable friability. This shows high stability and density of the FCC-PCL material and its ability to stabilize the core.

The polymer PCL is biodegradable [37] but even if the cup of the TIC- device would stay intact it would be excreted in the feces. On the Swiss market there is a tablet available in a comparable size, where it is also described that the indigestible matrix will be excreted [38]. Because in this project a beveled punch was used, there are also no sharp edges that could harm the intestines. Irritations or damages to the intestinal tissues are not expected.

Conclusions

Our results suggest that FCC-PCL mixtures have the potential to become a useful material for successful dosage formulation at an early stage of drug development. Moreover, the FCC-PCL composite material can be considered as safe. PCL was previously shown to be biodegradable [37], and FCC was shown to be safe [39].

Sufficient stress resistance and good compressibility of the FCC-PCL composite were confirmed by Leuenberger and Heckel analysis. These characteristics make it possible to use this material at higher production speeds of 35000 tablets per hour or higher if necessary. It was important to demonstrate that production of TIC-device can be made in a single step—excluding core compaction—with standard equipment. Although industrial-scale production was not tried with this material, there is no indication of potential performance hindrance as other geometrically altered formulations have been proven to be industrially producible [10]. A significant effect on sustaining the release rate due to geometric constraints, as demonstrated in this study involving metformin HCl in a TIC device. This may allow simplification of the formulation work, reduction of matrix components and other excipient concentrations, and reduction of size and mass of the tablets. The advantageous mechanical properties of the studied material are attributed to the unique properties of FCC due to its high specific surface and highly developed lamellar structure. In general, this material and the proposed formulation strategy can find its application in other types of geometries and can be instrumental to develop more complex and specialized delivery devices.

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Disclosure statement

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4 Discussion

For the heterogeneous population of pediatrics, it is of necessity to provide dosage forms that are flexible, age-appropriate and cost effective. Novel strategies to formulate such dosage forms are of interest. The research described in this work shows new formulation platforms fulfilling the need to serve as a tool to formulate oral dosage forms for children. There is a need for new excipients that fulfill several functions at once as the currently available substances are not sufficient. FCC is advantageous as it is a co-processed material of two already well known excipients. With the co-processing, new properties were created by modifying the surface structure. This underlines the importance of the microstructure of excipients. The fact, that the functionality of FCC is based on its microstructure is beneficial for the use in the pediatric population as it is already known to be safe.

4.1 The microstructure as a key characteristic

The microstructure of the FCC particle is the key characteristic for the presented work and the use in pediatric formulations. During tablet compaction, the lamellae interlock with each other forming stable bonds. When used as ready-to-use granules, it was shown that the disintegrant is distributed within the granule and the granule particles do not break under pressure (see Figure 2) [128]. Also, this stability roots in the strong bondage between the FCC particles. When processed with hot melt granulation, the particles experienced high shear forces and were embedded in the polymer. As shown in Figure 5b on the SEM picture, the lamellar structure stays intact, suggesting a high degree of flexibility [129].

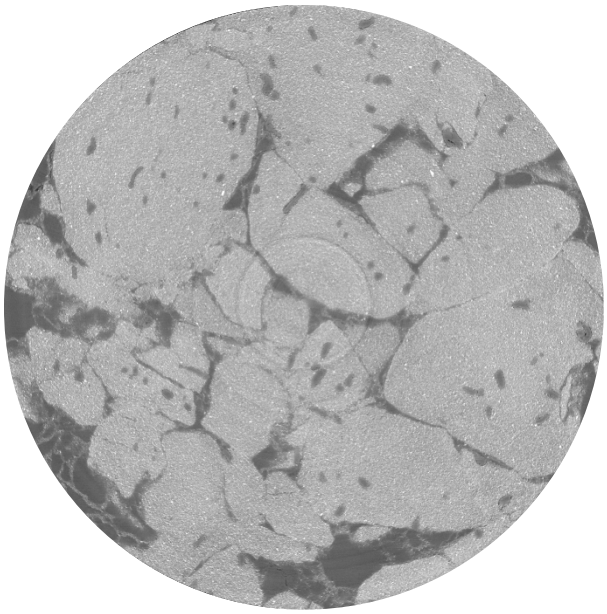


Figure 2: The 3D reconstructed X-ray micro tomography data with application of phase retrieval filter algorithm of a 9.0% (m/m) moxidectin mini-tablet with a diameter of 2mm [128]**. The dark grey substance is the drug moxidectin, the light grey shows the granules and the embedded dark grey particles in the light grey phase are disintegrant.**

4.2 FCC-based ODTs as age-appropriate formulations

When keeping the developmental physical differences in mind, an ODT is a suitable dosage form for children. It fulfills the requirements of an age-appropriate formulation (see section 1.5.1). The ODT does not need to be swallowed as a whole due to rapid disintegration upon contact with the saliva. The FCC consists of calcium carbonate and calcium phosphate which both are excipients that can be considered safe for children [130]. Taste masking and mouthfeel-enhancement was possible. In the presented work, artificial sweetener was used in combination with citric acid reacting with sodium bicarbonate, creating a tickly feeling in the mouth. The dose can be adapted when used in different sub-groups of the pediatric population. The ODTs can be compacted to large tablets or to mini-tablets. Like this, a dosing per kilogram of bodyweight is possible without additional formulation work.

The administration is easy, the ODT can be put on the tongue or in the buccal pouch, this way it is also possible to administer the tablet to infants. Also, the administration is not complicated (compared to an inhaling device) or in any way culturally inacceptable (compared to suppositories). With an ODT, compliance can be enhanced. The child is more likely to be willing to take such a formulation, so the risk of administering the medication the wrong way or not at all can be lowered.

The presented ODT (5mm diameter, 50mg weight) formulation does not need more liquid to disintegrate completely than there is present in the mouth of a child [131]. The mentioned 5mm ODT need 0.28ml of saliva for complete disintegration. Literature reports 1.21ml/min stimulated salivary flow rate and 0.51ml/min unstimulated salivary flow rate in children of age 3-16 years [132]. Considering that citric acid [133] is a stimulant, the stimulated salivary flow rate is more appropriate as a comparison.

The FCC was dry granulated and used for the preparation of ODTs and TOS (see section 4.3). Dry granulation did not show reduced compactibility properties after roller compaction [134]. When roller compacting FCC with a disintegrant (i.e AcDiSol), the values for Heckel analysis, modified Heckel analysis and Leuenberger analysis were comparable to the values proposed in literature [122,131]. Therefore, the unique properties are preserved yielding to a ready-to-use granule (ReadyMix) that can be further used [135]. The addition of more excipients needed for taste-masking did not change the unique compaction behavior of FCC either [131]. There is no evidence that the techniques of taste masking are limited to the option chosen in this work. The ReadyMix can also be blended with coated taste masked granules or particles prepared through hot melt extrusion.

4.3 FCC-based TOS as age-appropriate formulation

Rapidly disintegrating tablets based on FCC disintegrate in the same manner as ODTs. An advantage of TOS is the possibility do deliver larger doses than with a formulation that is directly placed in the mouth. By using a spoon to disintegrate the TOS in a liquid, a suspension can easily be prepared. This *in situ* prepared suspension can be administered the same ways as conventional suspensions known on the market. This can improve the acceptance of a novel stable formulation for the population in countries that are used to liquid preparations. The FCC based TOS can be dispersed in water on a spoon or in a glass. Due to the fact that the disintegration of the proposed formulation is based on a water insoluble swelling disintegrant (AcDiSol) and not containing large amounts of sodium, the danger of clinically relevant intakes of sodium is eliminated [3]. Disintegrated TOS on a spoon are desired as the volume of liquid to be taken by a child can be reduced. Moreover, infants and elderly patients can be treated with TOS. Influences on disintegration time of the TOS in water were found to

be independent of the drug load but affected by the disintegrant concentration and FCC concentration [136]. Under stressed conditions, it was shown that the disintegration time in water and art.sal. were influenced by temperature and humidity [136]. This underlines the importance of storage conditions. The content of the investigated TOS was not affected by the stressed conditions. With the used model drugs, degradation was not detected in the presence of FCC [136].

4.4 *In vitro* disintegration time analysis

To estimate if the saliva in a child's mouth is sufficient to ensure complete disintegration of the ODT, the developed model provides parameters to understand disintegration kinetics [131]. This approach allows to draw meaningful conclusions about the processes taking place in the oral cavity. This method to investigate the disintegration time has additional benefits as various disintegration media can be used. For example, TOS' time to disperse in water on a spoon or in a glass can be analyzed. For an ODT, artificial saliva can be used to approximate the situation in the mouth. Moreover, for even more sophisticated dosage forms used e.g. in a device like the nipple shield delivery system (NSDS) a human or bovine milk can be used [137]. The kinetic of the disintegration is governed by two processes: the liquid absorption and the disintegration of the wetted mass. These two processes are taking place simultaneously. It differs from a kinetic where the tablet first absorbs the liquid and subsequently disintegrates [123]. This has the advantage, that the tablet does not swell to the same extent and that the liquid can be reused once the particles have been disintegrated. All this information cannot be obtained with the conventional method given by the Ph.Eur. It is also not possible to accurately measure disintegration time with the conventional method, if it takes only a few seconds [123].

High dispersibility of the particles provided by TOS and ODTs can be beneficial for the treatment of local infections in the gastrointestinal tract because the drug can be evenly distributed [126].

4.5 Palatability testing

In a human panel test, the ODTs based on FCC granules were rated as pleasant by healthy adults. This data is necessary to collect before the formulation can be investigated for palatability in a panel test involving children. In the presented work the adults were asked for acceptability, therefore preference

was not assessed. To ask the questions, a VAS combined with a hedonic scale was used (see Figure 3). In addition the extremes of the scales were labeled with the best and the worst answer possible to ensure that all volunteers understand the questionnaire [131].

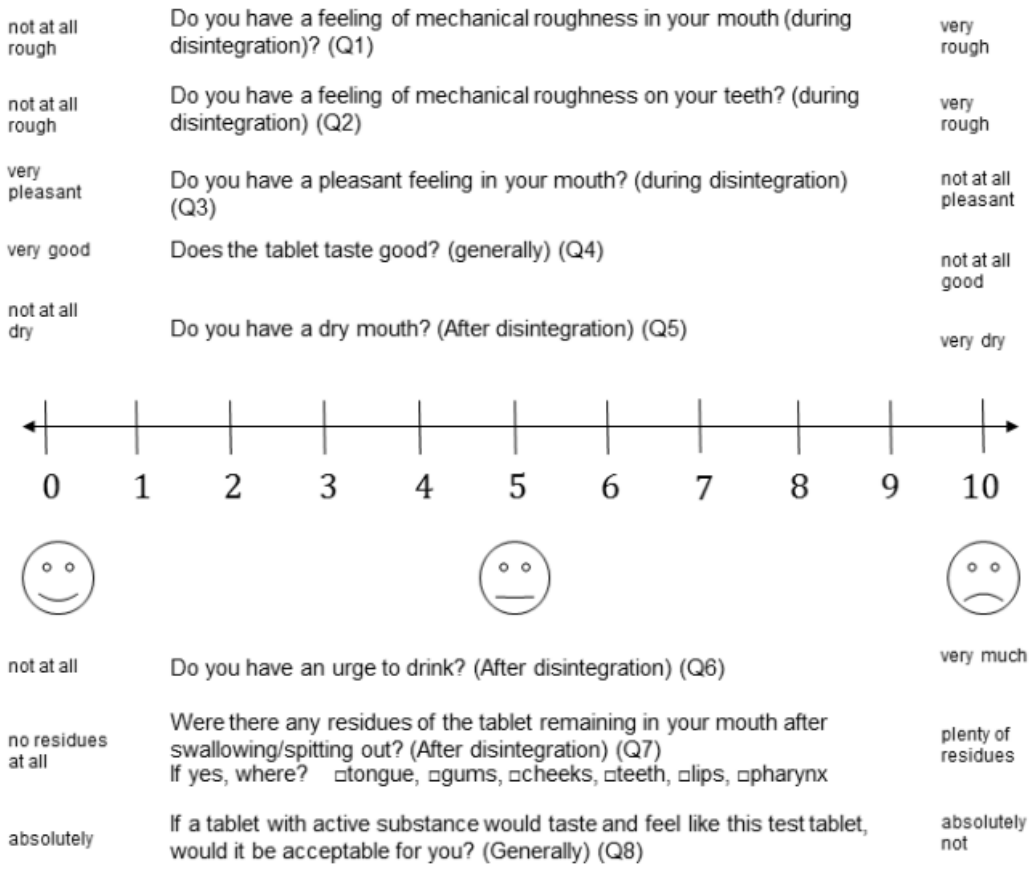


Figure 3: VAS combined with hedonic scale and possible answers [131]**.**

The statistical analysis showed that only *in vivo* disintegration time and the age of the volunteers was normally distributed. The answers to the questions were shifted toward the best possible answers. The volunteers reported to some extent a feeling of roughness in the mouth. This is not surprising as the FCC granules do not dissolve in the oral cavity and literature shows that humans can feel roughness of particles from the size >244µm [138]. Interestingly, in our study the volunteers reported to have a pleasant feeling in the mouth. This leads to the conclusion that rough sensation does not particularly lead to unpleasant feeling in the mouth [131].

4.6 Drug distribution in mini-tablets

Tablets based on the ready-to-use granule are shown to be characterized by fast disintegration times. This leads to high dispersibility of the particles that can be beneficial for local treatment of helminthiasis. In order to ensure equal drug distribution in the gastrointestinal tract, drug distribution in the tablet is essential. Therefore, a novel method was applied to investigate drug dislocation within FCC-based mini-tablets. It was shown, that it is possible to use synchrotron X-ray micro tomography with subsequent analysis to describe the location of the drug voxels inside of the mini-tablets. From our four proposed formulations the 9.0% moxidectin formulation showed the best content uniformity. This was shown with HPLC analysis as well as with microtomography results. The mini-tablet is a suitable dosage form to treat helminthiasis, as low doses are needed. With the mini-tablet, dosing is flexible and adjustable for individual patients.

4.7 Compliance enhanced formulation

The ODT platform is one among many options to enhance compliance. Another strategy is to simply adapt a concept used for adults. The Tablet-In-Cup (TIC) device showed to have sustained release comparable to a market product while having less volume and a higher drug load (see Figure 4).

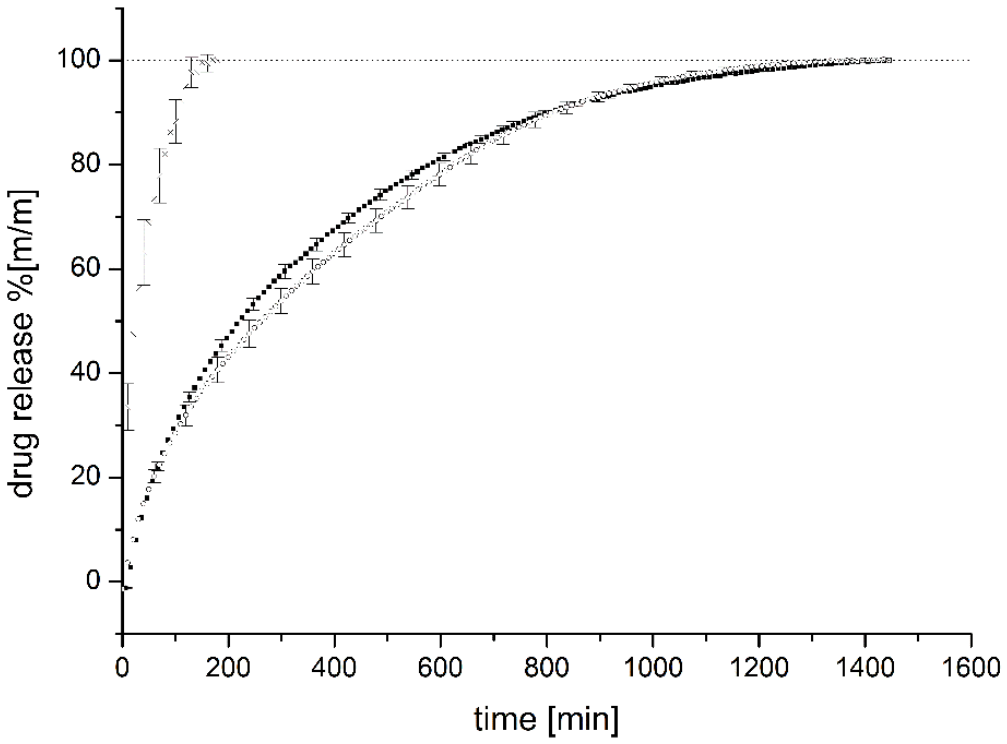
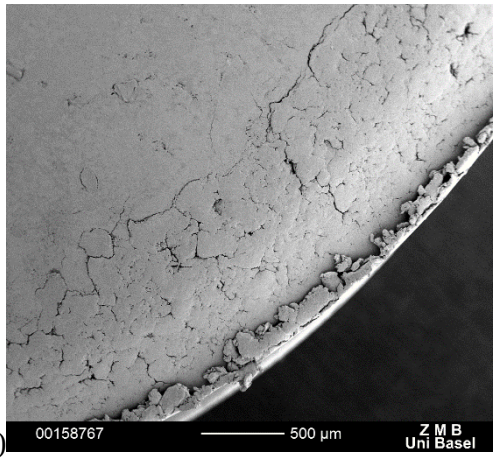


Figure 4: Dissolution profile of TIC 500mg metformin HCl (○), Kombiglyze® XR 5mg/500mg (■) and the metformin core tablets (Í). The error bars represent standard deviation [129]**.**

This approach can be used to adapt a formulation to the need of a pediatric formulation. By decreasing the size of the TIC, it is also possible to be swallowed by children [3]. No matter which dose needs to be delivered, the concept of the TIC stays the same. By using the FCC-PCL composite material, the surfaces of the core tablet can be successfully sealed (see Figure 5a) [129]. The FCC-PCL composite material shows good compactibility and compressibility and flows very well under pressure. This mainly roots in the embedding of the FCC in the polymer. The lamellae are highly flexible, even after hot melt granulation they are still intact (see Figure 5b). Therefore, they can still interlock yielding a stable TIC.

This feature also opens options for other dosage forms like abuse deterrent formulations (ADF). Moreover, the composite material shows plastic deformation under pressure, which is advantageous for formulating ADF. In case of ADFs, polymers are used to prevent manipulation of any kind [139].

Another application could be the use in sustained release formulations [140]. This makes the FCC-PCL composite material a unique multifunctional excipient.

a) 

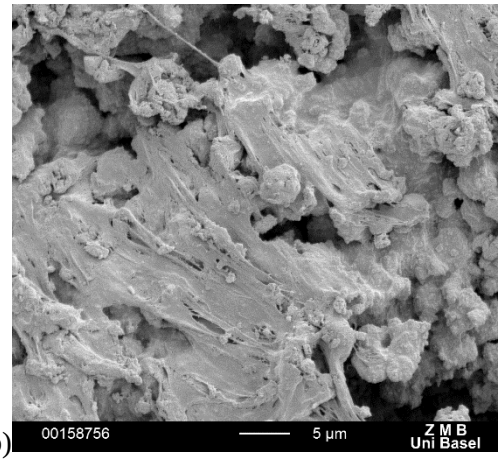
b) 

Figure 5: a) SEM picture of FCC-PCL composite material after compaction into TIC. Observable cracks do not allow liquid to penetrate into TIC in significant amounts; b) granules with visible lamellar structure of the FCC embedded in PCL [129]**.**

4.8 Simplicity of manufacturing

With the FCC-based granules, ODTs and TOS can be produced. The process was identical for both dosage forms. This makes the FCC a versatile multifunctional excipient. The granule can be blended with additional excipient or API without any further granulation or loading steps (see Figure 6). This is very advantageous, as the blending step is simpler compared to wet-granulation or loading. All the tablets show high physical stability and fast disintegration times. The additional excipients to enhance mouthfeel and mask a bad taste, did not change the unique characteristics during compaction of the granules. The process chosen to manufacture the granule was roller compaction, it is a continuous manufacturing process that is easier to scale up than a batch based process. To get a final formulation from the ready-to-use mix, the excipients simply need to be blended together. Blending is an easy step that allows fast and efficient formulation development.

With this knowledge, also other APIs can be admixed to the ready-to-use mix. It was possible to produce mini-tablets that had sufficient physical stability and no occurrences of sticking, picking or capping during the compaction process.

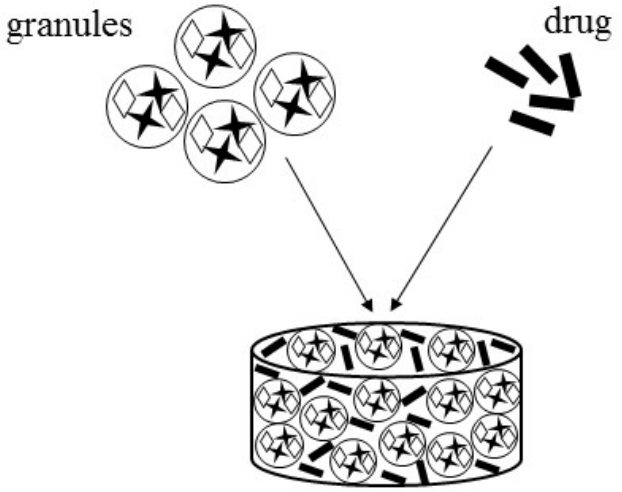


Figure 6: Blending step of the ready-to-use granule with e.g. drug [136]**.**

4.9 Regulatory aspects

The excipient FCC consists of two already very well-known excipients[130]. Hence the difference to calcium carbonate and calcium phosphate, respectively is based on the lamellar structure on its surface. This makes the safety assessment much easier than when a completely novel substance is introduced to the market. The ready-to-use granules can be used in TOS or ODTs. This way, they can serve as standard platforms to fulfill requirements in a PIP. FCC is on the market in powder form under the name Omyapharm and the ready-to-use granule is available under the name Omyapharm ODG [141].The Critical Path Initiative (CPI) is a project by the FDA that has its goal to drive innovation in drug development [142]. Therefore, it is of need to make the development process itself efficient and effective [143]. Our presented formulation platforms are fulfilling these requests, moreover, by choosing robust processes, the requirements for the concept quality by design (QbD) are met, too [144].

4.10 Application of the developed platform in low and middle income countries (LMIC)

The lack of pediatric formulations is present all over the world, but access and availability are more of an issue in LMIC than e.g. in Europe. Therefore, a suitable formulation platform needs to fulfill climatic and economical requirements in LMIC. Moreover, it would be ideal to provide a strategy where a technology transfer to the country in need can be carried out. The FCC-based ODT platform can serve as such. The granules (available on the market [141]) can be blended and tableted using basic technological equipment (e.g. conventional blenders and tablet presses). The high physical stability of the ODTs does not require any special packaging such as those required for freeze dried products [145]. Simple packaging (i.e. blisters or tablets bottles) that keeps the product dry is sufficient. Moreover, refrigeration is not required as the ODTs are stable at room temperature.

5 Conclusion and Outlook

We can conclude that FCC is suitable to produce granules for the use in ODT, TOS, as well as in mini-tablet formulation development. The processes involved in the production of these granules are straight-forward and cost-effective. We showed that the microstructure of the FCC is the key characteristic for ODT/TOS formulation and is important as a composite-material in geometry constrained sustained release formulations. The ODT and TOS formulations fulfill the requirements of age-appropriate formulations. Also, the use of the TIC device seems to be a promising tool to enhance compliance in the pediatric population. The lamellar structure on the surface of the FCC is the key characteristic for both aforementioned formulation platforms. During roller compaction the particles are interlocking with each other without losing the good compactibility behavior which is important for the subsequent tableting process. The taste masking and the mouthfeel enhancement of the FCC-based ODT were successful and no unpleasant sensations were detected. The tablets were well accepted by the volunteers. The ODTs were rapidly disintegrating while preserving high physical stability. The results of the *in vitro* analysis showed, that the liquid in the human mouth is sufficient for complete ODT disintegration.

No chemical degradation was detected in the studied FCC-based TOS with the two model drugs caffeine and oxantel pamoate. There was no influence of humidity, temperature or storage time on drug content. However, humidity and temperature influenced disintegration time and hardness. The FCC-based TOS platform can be used to manufacture physically stable, fast disintegrating tablets when stored in normal conditions (i.e. room temperature, dry condition).

Drug dislocation in FCC-based mini-tablets was described by using synchrotron X-ray tomography followed by Superpixel Image Clustering. This method is a promising tool to describe segregation processes in solid oral dosage forms.

It was shown that the FCC in a FCC-PCL composite material can be used in a TIC device. The use of the TIC allowed for reduction of the amount of excipient to use for sustaining the release as well as the reduction of size and mass compared to a marketed product.

An important next step is the assessment of the acceptability of the FCC-based ODT in children. Therefore, the nature of questioning the children needs to be adapted to age and developmental capabilities. This is challenging for children at the age of 2-5 years. In this group, using a hedonic scale or VAS might not be the optimal method. Therefore, the ease of administration and the spontaneous verbal judgement might serve as a better tool. It is important that the assessor is trained, able to concentrate as well as to able isolate external factors from the details linked to the assessment of the taste [85]. Facts like spitting out the tablet, crying or demanding another one are important indices to evaluate acceptability of the FCC-ODT. This includes an interview with the care giver or parent in order to classify situations in correlation with everyday life (e.g. a child that does not like orange, will not like the ODT, as it includes orange aroma). After successful evaluation of acceptability, formulation development for pediatric use can be started. Drugs that are administered in low doses can be incorporated in ODTs, whereas e.g. antibiotics can be developed as a TOS. As a next step, the formulation has to be tested in vivo in a comparative pharmacokinetic study. The influence of physiological differences during childhood can potentially affect bioavailability when the formulation is based on FCC (e.g. difference of pH in stomach).

For the future, both formulations platforms have high potential. These technologies can form the basis of the change of the medication dosing in children worldwide. The availability of the FCC on the market promotes the application and research in the future. New formulations can be developed, for example: Antibiotic drugs can be developed as a TOS using a SnapTab ® shape. This is beneficial as the dose could then be accurately divided by hand [146]. Considering that Co-Amoxicillin is widely used, the amoxicillin and the clavulanic acid can be formulated in two separate tablets, thereby the dose and even the ratio of the two drugs are adjustable in field.

Corticosteroids that need to have adjustable dose regimens to meet the requirements of individual therapies can be formulated in ODTs. Possible formulations can be betamethasone 0.5mg or prednisolone 5mg. Moreover, an ODT that contains drugs against travel sickness could be developed, having the advantage that the medication does not need to be swallowed.

Based on the FCC-PCL composite material, formulation development can be done for ADF. This is beneficial for dosage forms containing opioids or narcotic actives, as abuse-related manipulation of such dosage forms should be prevented. Additionally, the FCC-PCL can yield sustained drug release which can be favorable in the treatment of pain.

The use of FCC-based formulations is not limited to the mentioned field of pediatric age-appropriate and compliance enhanced formulations. The knowledge of this work can be adapted for the geriatric population as well as patients suffering from conditions that lead to dysphagia. Of course the presented platforms can be applied as a replacement for conventional tablet if the API allows it.

The application of FCC is certainly not confined to the human pharmaceutical field. The use in areas like the food industry, water cleaning, fishkeeping, veterinary pharmacy as well as cleaning agents can be explored.

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