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Development of a child-appropriate drug formulation for poorly soluble protease inhibitors for HIV treatment in children

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I hear and I forget. I see and I remember. I do and I understand.

-Confucius

Für meine geliebte Familie

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List of abbreviations

ADE	Adverse drug effect
ALPS	Amorphous liquid phase separation
API	Active pharmaceutical ingredient
ASD	Amorphous solid dispersion
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BiPHa+	Biphasic Dissolution Assay
CPE	Co-processed excipient
CQA	Critical quality attribute
CYP	Cytochrome P
DC	Direct compression
DCS	Developability Classification System
DF	Dosage form
EMA	European Medicines Agency
EU	European Union
EuPFI	European Paediatric Formulation Initiative
FaSSGF	Fasted State Simulated Gastric Fluid
FaSSIF	Fasted State Simulated Intestinal Fluid
FDA	Food and Drug Administration of the United States
FDC	Fixed dose combination
FeSSIF	Fed State Simulated Intestinal Fluid
GIT	Gastrointestinal tract
HIV	Human immunodeficiency virus
IVIVC	In-vitro-in-vivo correlation

HME	Hot-melt extrusion
HPMC	Hypromellose, Hydroxypropyl methylcellulose
HPMCAS	Hydroxypropyl methylcellulose acetate succinate
LBF	Lipid based formulation
L-HPC	Low substituted hydroxypropyl cellulose
LPV	Lopinavir
MCC	Microcrystalline cellulose
MP	Medicinal product
Min	Minutes
ODT	Orodispersible tablet
ODMT	Orodispersible mini-tablet
PAMPA	Parallel Artificial Membrane Permeation Assay
pBCS	Paediatric Biopharmaceutical Classification System
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PSP	Paediatric Study Plan
PUMA	Paediatric use market authorisation
PVP	Povidone, Polyvinylpyrrolidone
PVPVA	Polyvinylpyrrolidone vinylacetate co-polymer
QbD	Quality by Design
RTV	Ritonavir
SD	Spray drying
SDDS	Supersaturating drug delivery systems
TIM	TNO Gastro-Intestinal Model
T_g	Glass transition temperature
US	United States

USP	United States Pharmacopeia
WHO	World Health Organization

Chapter I - Introduction

1 Introduction

1.1 Child-appropriate dosage forms

1.1.1 Challenges in the development of child-appropriate drug development

Child-appropriate formulations are a prerequisite for a safe and efficient pharmacotherapy. On the current pharmaceutical market, there is an immense lack of approved and safe medicines for children, in particular in the treatment of severe diseases [1-3]. Consequently, medicines are often used outside their approved authorised conditions or age groups (off-label), or in an altered form in the context of an individual therapy regime (unlicensed-use). Exemplarily, tablets are crushed and dispersed in a liquid, capsules are opened and mixed with food or smaller doses are intended in order to achieve suitable therapeutic regimes for children. These procedures are manifold and were found to a great extent in practical application [4,5]. A study conducted by Conroy et al. [6] highlighted the widespread use in five different hospitals in Europe. According to this, 67 % of the paediatric patients received at least one drug outside the market authorisation. In many cases extemporaneous manipulation is unavoidable, but often linked with considerable risks for the patients in terms of safety and efficacy of the therapy [4,7].

To counteract the problematic situation, in 2007 a new European Union (EU) regulation on medicinal products (MP) (Regulation EC No 1901/2006) for paediatric use came into force [8]. The overall aim was to improve the availability and quality of MPs for children. On the one hand, the industry is requested to develop a Paediatric Investigation Plan (PIP) for each new product to be authorised. The PIP should ensure sufficient collection of data and must be implemented in the drug development at the end of clinical phase 1 to ensure safety, quality, and efficacy of the product. On the other hand, companies were encouraged to develop appropriate dosage forms (DF) based on drug products which previously have been authorised for adults. For a successful development the companies may benefit from a paediatric use marketing authorisation (PUMA) receiving a 10-year market exclusivity. In the United States (US), the Food and Drug Administration (FDA) also introduced a mandatory submission of a Paediatric Study Plan (PSP), at the end of clinical phase 2 [9]. To date, there is still only one official regulatory document “Guideline on Pharmaceutical Development for Medicines for Paediatric Use” published by the EMA in 2013 which provides an overview of compulsory criteria for child-appropriate drug formulations [10].

The development of child-appropriate medicines compared to that of adults is characterised by numerous challenges which include physiological, pharmacological, ethical and regulatory

aspects [3]. The rapid development of the paediatric body within the first years of life requires a continuous adaption and individual adjustment of the medication. For this reason, high demands on the DF and the composition of the MP are required and need to be designed age-appropriate, ensuring the highest possible bioavailability (BA) while a high safety and quality is guaranteed [3,11]. According to Breitkreutz and Boos and other publications the following key aspects should be considered for child appropriate drug formulations [1,2,12].

- Sufficient bioavailability
- Toxicological safety of the active pharmaceutical ingredients (API) and excipients
- Palatability and acceptability
- Adequate dosing possibility
- Easy and safe administration
- Socio-cultural acceptability
- Precise and clear product information (child appropriate packaging)

The oral drug administration can be regarded as the most preferred route. Over the years, it was hypothesised that oral liquid formulations would fit best for children since dose flexibility is given, and the issue of swallowability of solid drug carriers could be overcome [13]. However, there are numerous concerns that arise when liquid DFs are administered such as poor taste, toxicologically critical excipients (e.g. preservatives), drug stability issues and the need for a suitable dosing device [12]. In recent years, new oral solid DFs with promising key attributes such as mini-tablets, dispersible tablets, orordispersible tablets (ODTs) and orodispersible mini-tablets (ODMTs) as well as orodispersible films provided new opportunities and already showed their superiority either in clinical or non-clinical approaches [14-17]. Experts from the World Health Organization (WHO) considered these modern formulations as the DFs of choice and are calling for a shift of paradigm from liquid DFs to novel oral solid DFs [18,19]. In the scope of this work ODTs were selected as DF of interest and will be intensively reviewed in *chapter II* for their overall potential in the field of paediatric drug development.

1.1.2 Poorly water solube drugs: classification

When focusing on the aspect of BA for orally administered drugs, the aqueous solubility of the API plays a major role, as it is a prerequisite for drug absorption in the small intestine [20,21]. For orally administered drugs, the molecules must dissolve in the gastrointestinal fluids, pass through the intestinal membrane, and reach the blood circulation in sufficiently high quantity to finally show a systemic therapeutic effect [22]. Low aqueous solubility may therefore contribute to an increased risk for uncontrolled pharmacokinetics. This could be expressed by factors like inter-and intra-subject variability of BA, a higher risk for food effects and difficulties in dose finding [23,24]. It has been stated that 40 % of the drugs currently on the market can be classified as poorly water soluble [25]. Regarding the recent development pipeline of the pharmaceutical industry this fact is even more pronounced, providing approximately 90 % of drug substances as poorly soluble according to the Biopharmaceutics Classification System (BCS) [25]. With bearing this in mind the research on suitable techniques for solubility enhancement is a subject of continuous work for the pharmaceutical industry.

Generally, it is possible to classify poorly soluble compounds broadly into two categories. “Grease balls” are highly lipophilic molecules with high LogP values with low melting points, and “brick dusts”, representing molecules with high melting points due to their high crystal lattice energies [26,27]. Focusing on the biopharmaceutical aspects rather than considering only physicochemical properties of the APIs a classification approach was published by Amidon et al. [20] introducing the BCS which classifies new drug substances according to their solubility and permeability in four different categories. The four BCS classes are schematically depicted in Figure 1. The respective APIs could be defined as highly soluble when the highest labelled single dose is soluble in a physiological pH range from 1 to 6.8 in a maximum volume of 250 ml or less of aqueous media at 37 ± 1 °C. A drug is considered as highly permeable when the BA or the extent of absorption of the highest administered dose is at least 85 % [28].

Butler and Dressman [29] have expanded the BCS and introduced modifications to reflect more on the drug product developability aspect than focusing only on the API itself and implemented the Developability Classification System (DCS). Besides the use of biorelevant media to achieve a more reliable assessment of in-vivo solubility, the authors further subdivided BCS class 2 into subcategories distinguishing between a dissolution-or a solubility-limited behaviour (DCS class 2 a resp. 2 b).

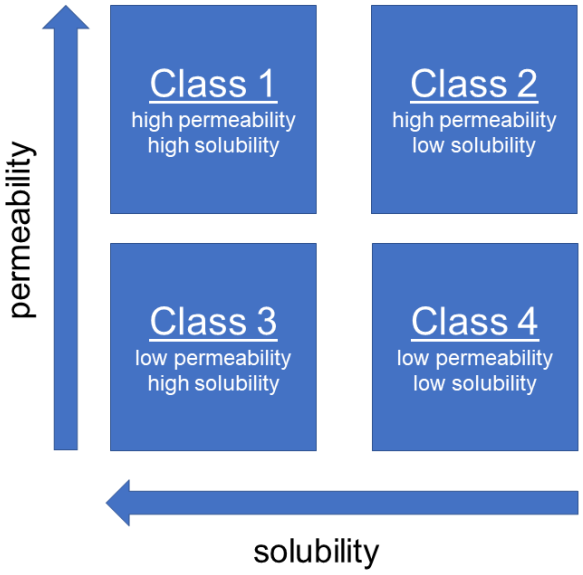

Figure 1 Biopharmaceutics Classification System according to Amidon et al. [20]

Usually, either the BCS or the DCS is taken as the starting point of rational drug product development [23]. However, considering the paediatric patient group, the applicability is highly questionable [24,30]. The general classification of drug substances based on solubility and permeability could result in a class change when applying to paediatric patients since there is a huge variability in the highest considered dose, as well as differences in gastrointestinal volumes and transit times between adults and children throughout the different developmental stages [23,30,31]. It should be kept in mind, that both the highest dose strength, as well as the considered volumes of 250 ml is only valid and proved for adults [20,32]. In order to illustrate the difficulty, the study conducted by Del Moral Sanchez et al. [33] can be taken into consideration. The authors created a provisional paediatric biopharmaceutical classification system (pBCS) and included several orally administered drug substances from the Essential Medicines List for children by the WHO. As a result of the study, several APIs finally showed a change in solubility and/or in permeability in the pBCS compared to BCS and therefore had to be assigned to a different classification group. Consequently, the previously satisfactory in-vivo performance assessed by solubility and permeability in adults cannot necessarily be extrapolated for children [33]. For many years researchers aimed for the implementation of a reliable pBCS to improve the paediatric drug development, but this approach could not be successfully implemented yet [24,30,32]. The great challenge here lies in the heterogeneity of the patient groups [23]. A meaningful pBCS would have to be additionally subdivided into several age groups, by far not only considering the solubility but also highly variable factors like intestinal permeability, gastrointestinal transit time and luminal contents [24,30].

1.1.3 Formulation development for poorly soluble drugs: considerations and approaches

A variety of pharmaceutical formulation technologies are used to enhance the poor aqueous solubility of APIs. Well-known attempts to counteract the poor solubility include salt formation, formation of co-crystals, complexation, solubilization and API micronization [34-36]. In recent years, however, so called *supersaturating drug delivery systems (SDDS)* have gained increased attention and yielded new possibilities especially for drugs more limited by the low equilibrium solubility rather than by the dissolution rate. Free drug concentration exceeding the equilibrium solubility in the small intestines was found to significantly increase the permeation [26,37,38]. Among nano-technologies or lipid-based formulations (LBFs), amorphous solid dispersions (ASDs) show by far the widest application. This becomes apparent by several marketed products available for different therapeutic indications such as human immunodeficiency virus (HIV), cancer, or mycotic infections just to name a few of them. Exemplarily, the commercial products Kaletra®, Zelfboraf® and Sporanox® can be mentioned here [38-40].

If the focus is placed on the development of child-appropriate DFs containing poorly soluble APIs, far less products and related literature is available. Reasons for this could be the inherent challenges in the field of paediatric drug development as pointed out in chapter *1.1.1*, the age-dependent biopharmaceutical challenges (see chapter *1.1.2*) and the selection of a suitable solubility enhancement technique [23,33]. Additionally, a more comprehensive safety evaluation of APIs and excipients is required, as the impact of disposition of various substances throughout the different age groups is still not well understood yet [30,41]. Nevertheless, much research is being conducted in this area with the aim to expand on the available opportunities for children. Recently, Salunke and co-workers from the European Paediatric Formulation Initiative (EuPFI) and industry companies have published a very informative review focusing on paediatric oral drug delivery for poorly soluble APIs, which could serve as beneficial basis for future studies [23].

Physicochemical profiling of the API is usually performed as initial action in formulation development since the suitability of the solubility enhancement technique strongly depends on the API properties like lipophilicity, molecular weight, melting point, crystallization behaviour, polymorphism and ionic charge [42,43]. However, to finalize the product development and also evaluate on the final oral DFs the formulation scientist also need to be aware of the targeted population group since the desired dose, acceptability, as well as the GIT status of children can commonly vary considerably [24,44]. Therefore, to cover the large width of developmental stages, different drug loads and more than one DF should be considered to enable high flexibility throughout the development route [23].

With regard to the market situation only a few oral solid DFs containing a poorly soluble drug substance are marketed for children [23]. Today, oral liquid DFs are still widely used for the administration of poorly soluble drugs [45]. The use of inclusion complexes with cyclodextrines (e.g. in Sporanox®) or cosolvents like propylene glycol and ethanol (e.g. in Kaletra®) are most common, whereas the formulation for example as LBF (as present in Neoral®) is a rarity [23]. Despite enabling dose flexibility and ease of administration, several concerns were pointed out for the use of oral liquids such as, instability, bad taste, low drug solubility and safety concerns for the high quantity of used excipients for solubilization [2,23,45,46].

In recent years, the production and further downstream processing of an ASD into a tablet has emerged as a promising alternative to enable the development of solid DFs for poorly soluble APIs [47,48]. Shortly summarised, ASDs can be described as a molecular (or amorphous) dispersion of an API in a polymeric carrier [22,38]. The solubility enhancement is achieved by the appearance of a high energetic state with a disordered structure of the API molecules, leading to an increased apparent solubility. As ASDs are the solubility enhancement technique investigated in this work, more detailed descriptions about ASD principles are presented in chapter *1.3*. ASDs are most frequently formulated into conventionally sized tablets [47]. The high proportion of excipients, predominantly a polymer, results in high tablet masses, which causes difficulties in the administration, especially for paediatric and geriatric patients [47,49]. In order to prevent the need for an extemporaneous compounding prior to administration, innovative DFs for children like mini-tablets, granules or pellets based on ASDs are a point of current research interest [50-52]. Niessen et al. [53] recently showed the feasibility for ritonavir (RTV) containing ASDs to be formulated as mini-tablets. In the scope of this work a biorelevant dissolution assessment revealed no significant differences between the developed mini-tablets, the marketed oral powder Norvir® and conventionally sized tablets. Consequently, the advantages in the ease of administration of mini-tablets can be beneficially used while possible dissolution differences hypothetically caused by the DF could be excluded.

Regarding industrial drug product development, a preferred approach is trying to convert the formulation technique used for the marketed tablet for adults, into a child-appropriate DF like oral powders. Exemplarily, the marketed RTV film tablet Norvir® from AbbVie could be taken here into account [23]. In the case of the paediatric product a further milling step and a polymer coating were implemented prior to packaging the powder into stick packs [23,54]. The beneficial attributes of the oral powder formulation were additionally demonstrated by Morris et al. [54]. The authors reported on an improved acceptability due to reduced bitterness of the ASD powder compared to the Norvir® oral solution. Furthermore, the study showed that the use of different food vehicles to improve the acceptability had no influence on the BA.

Selected oral solid DFs where the technology transfer from the adult to the paediatric product was successful is exemplarily shown in Table 1. Here, every marketed product is formulated as an ASD and afterwards processed downstream into a different DF [23].

In many cases, where poorly soluble APIs were formulated as LBFs or nanocrsytals, this procedure was only possible for adults, equivalent formulations suitable for children have not been realised to date. As example the products Agenerase® (Glaxo Smith Kline) and Emend® (Merck Sharp & Dohme) could be mentioned. In both cases the same solubility enhancement technique was applied during paediatric development as used for the adult product, however, the final DF was changed into a liquid [23].

Table 1 Selected marketed solid oral products for paediatrics based on the same solubility enhancement technique as present for the marketed product for adults. Modified according to Salunke et al. [23].

Product name, company	APIs	Formulation technique	Adult formulation	Paediatric formulation
Kaletra®, AbbVie	Ritonavir, Lopinavir	ASD via Hot-melt extrusion (HME)	Film-coated tablet	Scaled down film-coated tablet
Lopinavir Ritonavir oral pellets, Cipla	Ritonavir, Lopinavir	ASD via HME	not available	Oral pellets
Norvir®, AbbVie	Ritonavir	ASD via HME	Film-coated tablet	Oral powder
Kalydeco®, Vertex	Ivacaftor	ASD via Spray drying (SD)	Film-coated tablet	Oral granules
Orkambi®, Vertex	Lumacaftor, Ivacftor	ASD via SD	Film-coated tablet	Oral granules

Nevertheless, the successful implementation of child appropriate ASD products could only be accomplished for a few products, explainable by several formulation challenges ASDs tend to show. Physical drug stability is crucial since most of the ASDs can be classified as metastable systems and are at risk for recrystallization [36,55]. Therefore, careful handling and packing is required as for example moisture contact can influence stability of the amorphous system [56]. Based on this, ASDs are hardly feasible to be formulated as an oral liquid formulation. However, if APIs with low tendency for crystallization such as RTV are considered, tablets, granules, or powders can be at least dispersed in a liquid prior to administration [54,57]. Morris et al. demonstrated even a higher relative BA for the previously suspended ASD powder compared to the oral solution [54].

1.1.4 Reference product Kaletra®: Paediatric HIV therapy

The API combination of RTV and lopinavir (LPV) will be used in the scope of this work as model drugs developing a child-appropriate DF for poorly soluble drugs. As a reference, the marketed product Kaletra®, by Abbvie was considered for the investigations. Kaletra® is a fixed dose combination (FDC) for the treatment of HIV for both, adults and children [58]. According to the WHO Guideline from 2016 the use of co-formulated protease inhibitors is first line therapy for HIV infections in infants, children, and adults [59].

The two APIs belong to the same group of HIV protease inhibitors. LPV is thereby characterised as main component for the blockade of HIV-1-protease which is essential for the replication of the virus. However, due to the rapid metabolism of LPV via cytochrome P (CYP) 450 enzymes, RTV is added to slow down the metabolism of LPV by blockage of the CYP enzymes [60]. Depending on the administered dose and concentration of RTV, Eichbaum et al. [61] reported on a complex mechanism of inhibition by RTV mainly caused by an irreversible mechanism, usually induced by a clinical daily dose of 100 to 300 mg [62]. In addition to the already complex pharmacokinetics, both APIs tend to interact with each other during dissolution which further hampers the prediction of the systemic exposure and finally the available quantity in blood circulation. Therefore, sufficient drug monitoring of the blood plasma needs to be applied to verify an adequate API exposure and preventing possible adverse drug effects (ADE) during the therapy [7,63].

Currently there are three different products of Kaletra® on the market. Giving emphasis to the paediatric population, most commonly a liquid solution of Kaletra® is part of the therapy [64]. The product is authorized for children older than 14 weeks and is dosed by body surface area or body weight. Despite the dosing advantage, the use of the oral solution is linked to several concerns. The oral solution contains high amounts of propylene glycol (15.3 %) and ethanol (42.3 %) which are associated with an increased risk for gastrointestinal ADEs or even worse alcohol toxicity especially for newborns and infants [7,52]. Consequently, there is a tendency for reduced patient adherence, which in turn can lead to therapeutic failure or the accumulation of viral resistances [52]. The broad application of the oral solution is furthermore complicated by the bad taste as well as by stability aspects (recommend storage conditions < 8 °C), a major issue for the use in countries with poor resource settings [52].

Alternatively, if oral solid DFs can be administered, there are two tablet formulations of Kaletra® with different dosage strengths of LPV/RTV (100 mg/25 mg) and (200 mg/50 mg) on the market. Considering the recommended daily dose for adults and children above 12 of 800/200 mg this would end up by 2 x 2 200/50 mg or 1 x 4 200/50 mg tablets a day. This goes along with an immense number of tablets to be taken and demands a high level of compliance for the patients to finally achieve a successful therapy. Both products consist of the same

qualitative composition and solubility enhancement principle. The tablets are prepared by the MELTREX® technique by AbbVie [65]. In brief, this manufacturing approach consists of a hot-melt extrusion step with extremely short residence times to avoid thermal degradation of the APIs prior to be shaped with forming rolls (calendaring) to the final product geometry. Within the hot-melt extrusion a composite ASD of both APIs with the polymer polyvinylpyrrolidone vinylacetate co-polymer (PVPVA) is formed [65,66].

Extremely relevant for the administration of Kaletra® is that these tablets are only intended to be swallowed intact, without being crushed, broken, or dispersed prior to the administration. Reason for this were collected results by Abbott Pharmaceuticals (the legal predecessor of AbbVie) during the development. A decreased absorption in animals for both APIs was reported when crushed tablets were administered [7]. Moreover, a pharmacokinetic study by Best et al. [7] reported on the susceptibility of crushed Kaletra® in humans. The study compared the systemic exposure of RTV and LPV in a paediatric population with HIV infection when either intact Kaletra® or crushed Kaletra® were administered to children aged from 10-16 years. As a major output the study has revealed a significant decrease of the mean systemic exposure for both APIs for the crushed formulations by approx. 40 % compared to the intact tablets.

Considering swallowability as one of the major issues paediatric patients may have, the intended use of Kaletra® is a major challenge. The swallowability issue predominantly for the 200/50 mg Kaletra® tablet becomes apparent looking at the tablet dimension (see Figure 2*).* The Kaletra® tablet has a mass of approximate 1 g, a length of 19 mm and a width of 10 mm (self-collected measurement data). In Figure 2 a comparison of a) Kaletra® b) self-produced 8 mm ODT and c) seven 2 mm mini-tablets is provided to highlight the differences in tablet dimensions. The availability of the down-scaled Kaletra® tablet with 100/25 mg dose strength, however, has improved the acceptability for children, but still a huge proportion of patients is not able to swallow this tablets intact [7].

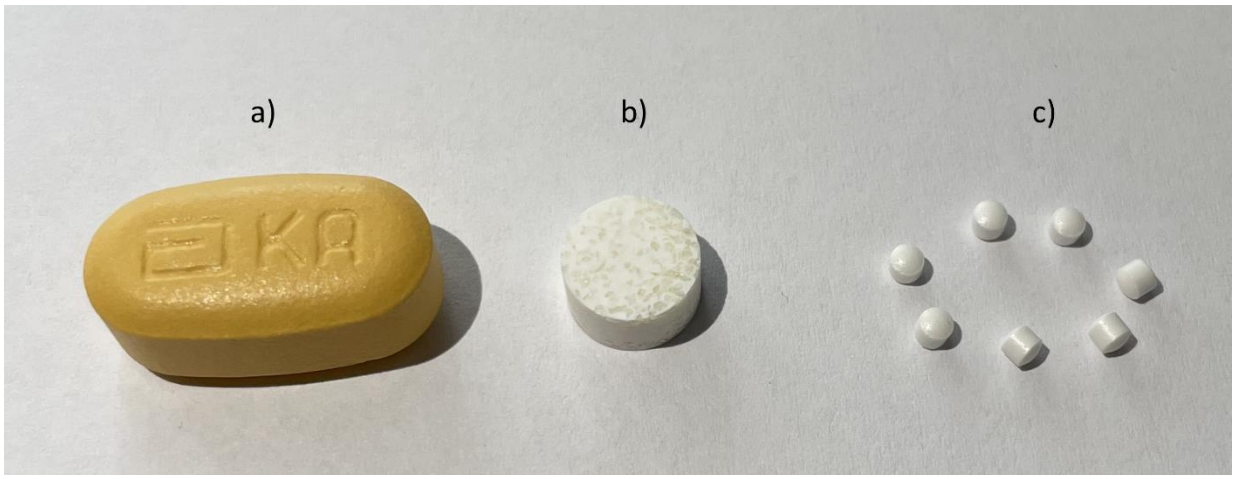

Figure 2 Comparison of a) commercially available 200/50 mg Kaletra® b) self-produced 8 mm ODT c) seven 2 mm mini-tablets

To overcome these challenges experienced with previously available tablet formulations or oral liquids, LPV/ RTV 40/10 mg pellets have been developed by CIPLA. and approved by the FDA in 2015. The pellets are authorized for the use in children above 14 days of age and > 5 kg of body weight [67]. To investigate the possible benefit the pellet formulation might have, an acceptability study was conducted by Pasipanodya et al. comparing the use of pellets and the oral solution in infants [64]. The study revealed that a large proportion of caregivers preferred the use of pellets, however, still challenges in the administration were reported. The authors, however, concluded that current challenges in the administration could be overcome by an appropriate training of the caregivers [64]. It is also worth noting that the pellets are also based on the same formulation approach as the tablets and may not be crushed or altered in any way [67]. Undoubtedly, this is by far much less relevant for pellets than for tablets, but still poses risks to be considered.

Currently quite a lot of activity is ongoing for the development of suitable DF for the FDC of LPV and RTV. Nanoparticle-based systems were investigated by two different research groups [45,52]. In the work of Pham et al. [52] solid granules were formed that induce self-assembled nanoparticles after encountering water. It was possible to encapsulate both APIs and consequently covering the unpleasant taste. Further, Deng et al. [45] investigated a nanoparticle based orodispersible system for RTV and LPV produced via lyophilization. In both cases sufficient stability was proven, and in-vivo data were presented, showing that the nanoparticle-based systems exceeded the plasma levels of Kaletra®. One major drawback, however, is the limitation in the production scaling since these concepts have been investigated in lab scale dimensions and will present a challenge when it comes to scaling up for industrial relevant batch sizes.

Lopinavir

For this work LPV was selected as model API for a poorly soluble molecule which plays an important role in the field of paediatric HIV therapy. Despite presenting a high efficacy in the inhibition of HIV protease 1 LPV is commonly used in combination with the booster agent RTV due to the strong CYP 3A4-mediated metabolism. The consequence of the rapid metabolism combined with a poor aqueous solubility is a low BA of LPV after oral administration [68,69].

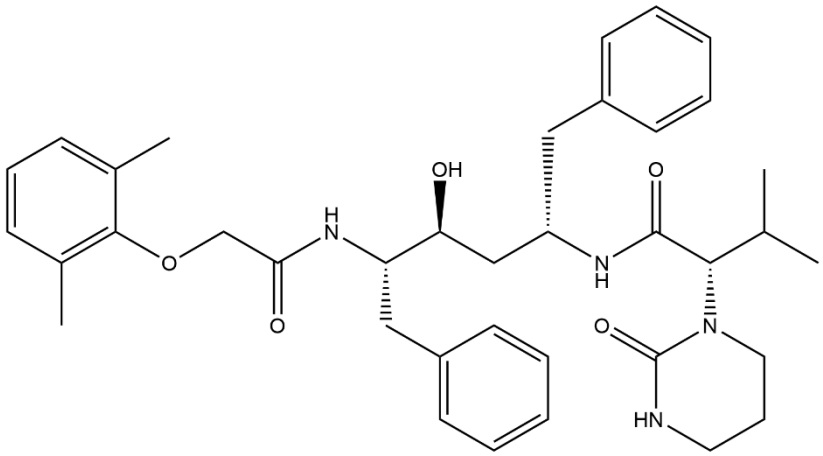

Figure 3 Chemical structure of LPV

LPV is a white to yellowish, slightly hygroscopic powder. The chemical structure shown in Figure 3 depicts a relatively large peptidomimetic molecule with a molecular weight of 628 g/mol. LPV can be described as a highly lipophilic molecule [69]. LPV is practically insoluble in water and freely soluble in methanol or dichloromethane. The solubility is pH independent, at least for the biopharmaceutically relevant range from 1 to 6.8 [63]. According to the BCS, LPV can be classified as class II drug [69]. Furthermore, it needs to be considered that due to the high flexibility of the molecule, LPV can adopt different molecular conformations allowing for amorphous as well as crystalline forms [70].

Ritonavir

For this work, the poorly water-soluble API RTV was chosen as the second model substance. RTV also belongs to the class of HIV Protease 1 inhibitors, however, to date predominantly considered as booster agent in combination with more potent HIV protease inhibitors. RTV is characterised as one of the most potent CYP 3A4/5 inhibitors and is therefore of high clinical relevance, especially in combination with APIs suffering from a poor BA due to the CYP-mediated metabolism. The reason given for not using RTV solely as protease inhibitor is on the one hand, the rapid metabolism, and on the other hand, the rapid creation of viral resistances [68].

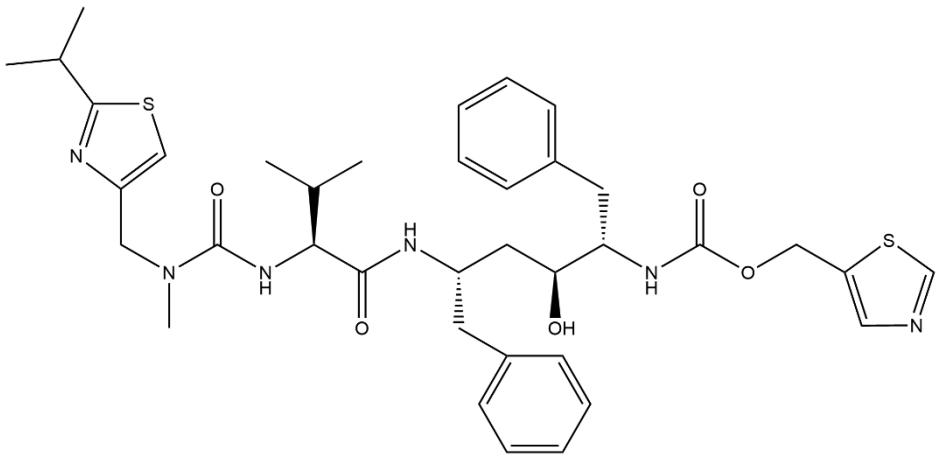

Figure 4 Chemical structure of RTV

RTV can be described as white to tan light powder. The chemical structure of RTV is depicted in Figure 4 and reveals a relatively large peptidomimetic molecule with a molecular weight of 721 g/mol. The chemical nature of RTV can be described as highly lipophilic with a LogD value of 4.3 at neutral pH of 6.8 [71]. RTV is practically insoluble in water or phosphate buffers at pH 4-7 (solubility approx. 1 µg/ml), however, provides significantly higher water solubility (400 µg/ml) in acidic conditions (pH < 2) [71]. According to the BCS, RTV can be assigned to class IV due to its poor aqueous solubility as well as low permeability [54]. Regarding the chemical structure the two basic thiazole moieties will lead to an ionization in acidic environment thus, increasing the solubility of RTV. The pK_a values for the respective thiazole structures are 1.8 and 2.6 [71,72]. Attention should be given to polymorphism since two polymorphs were described in literature (I & II), significantly differing in their physicochemical properties such as solubility [70,73].

1.2 Orodispersible tablets

1.2.1 General aspects

Despite many beneficial aspects conventional tablets may have, there are several limitations that do not allow a convenient use for every patient group, mostly connected with swallowing difficulties predominantly for paediatric and geriatric patients [16,74]. ODTs can be seen as a promising therapeutic alternative to overcome swallowability issues while still enabling both, the preferred oral administration as well as stability benefits of solid DFs [15,75]. ODTs rapidly disperse after contact with saliva, forming a liquid dispersion or solution which can be swallowed easily. After disintegration the released API may act locally or show a systemic effect, either via an intestinal or transmucosal absorption. The possibility to affect the BA due to the transmucosal absorption route was exemplarily shown for the two APIs naratriptan and valsartan [76,77]. The potential of ODTs in the context of paediatric therapy, particularly focusing on acceptability as well as on numerous formulation aspects, is described more in detail in the review article in *chapter II.*

According to the Ph.Eur., ODTs are uncoated tablets intended to be administered to the oral cavity, disintegrating rapidly without the need for further intake of any liquids. A disintegration time of 180 s in a conventional disintegration tester is required by Ph.Eur., whereas the FDA stated in a guidance for industry a more biorelevant time of 30 s relying on the application in the oral cavity [78]. Despite some heterogenous terms in literature as well as in regulatory specifications, the nomenclature of Ph. Eur. will be used in this work. DFs such as dispersible tablets and lyophilisates must be distinguished from ODTs. Dispersible tablets are dispersed in water prior to application, whereas lyophilisates are produced based on API containing solutions or suspensions via freeze drying preferably directly in the blister. Controversially, ODMTs firstly prepared by Stoltenberg and Breitkreutz [79] are still classified under ODTs, despite providing relevant differences in the aspects of quality control and product specifications [15].

1.2.2 ODT manufacturing and excipients

By far the most commonly used technique for the manufacturing of ODTs is direct compression (DC). This is generally attributed to the ease of manufacturing combined with time and cost efficacy. Furthermore, the limited number of process steps needed, including only weighing and blending of the excipients and the API(s) prior to compression on a tablet press also led to the establishment of DC as preferred manufacturing technique. In addition, lower variability in the process and a lower risk for stability issues of the API were highlighted [15,80,81].

Many different studies in literature were performed either on a compaction simulator for initial formulation development or e.g. in terms of up-scaling approaches on industrial like rotary

tablet presses [82]. Despite a broad knowledge and a high expertise in DC, still several challenges are present. The majority is linked to the properties of the APIs. In both cases, for low dosed as well as for high dosed ODTs different aspects are needed to be addressed. For low dosed formulations the content uniformity, whereas for higher drug loaded ODTs the balance between a sufficient mechanical strength and a fast disintegration were found to be most important [80,81,83]. To overcome the difficult properties of the API, while still ensuring the required quality attributes of ODTs such as disintegration time, mechanical strength, content uniformity and finally sufficient acceptability, suitable excipients must fulfil high requirements [75,81,84]. For initial research many cellulose derivates e.g. microcrystalline cellulose (MCC) and L-Hydroxypropyl cellulose (L-HPC) were screened for suitability, but mostly excluded either due to an insufficient disintegration or an unpleasant mouthfeel [85]. Instead, sugar alcohols became the most relevant material group. Especially mannitol is by far the most frequent used material in the field of ODTs [85]. The reason for that could be predominantly attributed to the pleasant mouthfeel providing a slightly sweet taste, a cooling effect during dissolution and the high porosity of the resulting compacts [85]. Despite many beneficial characteristics of mannitol, the major drawbacks which strongly limit the sole use of native mannitol is the poor flowability, compressibility and tableting difficulties such as capping and sticking [86]. Due to the low bonding capacity of the mannitol crystals the resulting compacts exhibit a low mechanical strength [85,87]. To counterbalance the poor bonding capacity, but still maintaining the benefits of mannitol, different co-processed excipients (CPEs) have been developed to provide a good flowability, compactability, fast disintegration and a pleasant mouthfeel within one ready-to-use powder [84,85,88]. According to Rojas et al. [84] co-processing leads to an interaction of two or more excipients on a subparticular level, resulting in a synergy of powder functionality. The physical alteration of a mostly mannitol-based combination of a filler-binder and a superdisintegrant leads to a modification of powder properties like particle size, particle shape, porosity, and density, which all have a significant influence on the desired ODT properties. Commonly used processes are spray drying (SD), granulation, co-grinding, and co-crystallization [85,88-90].

Among others, Draskovic et al. [80] pointed out the superiority of CPEs, especially for the incorporation of high amounts of APIs like caffeine or ibuprofen. The challenging behaviour of the APIs often cause an insufficient compaction or a poor disintegration. Many studies in literature compared the performance of CPEs and could aid in the selection since the variety of CPEs is high [80,83,84,91]. Exemplarily, the study of Bowles et al. [81] and Dziemidowicz et al. [75] could be taken into consideration. They highlighted many different aspects in their studies and evaluated different CPEs either regarding manufacturability or acceptability aspects. In Table 2 selected commercially available products are summarised. Special grades of the respective products differing for example in characteristics such as particle size

distributions, however, are not considered in this overview. Even though much useful literature is available the final selection of the best suitable CPE is commonly evaluated on a case-by-case basis.

Table 2 Examples of mannitol based CPEs for the direct compression of ODTs (adapted and modified from Bowles et al. [81]).

CPEs	Supplier	Ingredients
Hisorad®	Daicel Corporation, Japan	D-mannitol MCC croscarmellose sodium
Granfiller D®	Daicel Corporation, Japan	D-mannitol MCC carmellose crospovidone
Ludiflash®	BASF, Germany	D-mannitol (90 %) crospovidone (5 %) polyvinyl acetate dispersion (5 %)
Parteck® ODT	Merck KGaA, Germany	mannitol sorbitol croscarmellose
Pearlitol® Flash	Roquette, France	mannitol (80-85 %) maize starch (15-20 %)
SmartEx®	Shin-Etsu, Japan	D-mannitol polyvinyl alcohol L-HPC
F-Melt®	Fuju Chemical Industry, Japan	D-mannitol (55-70 %) MCC (10-25 %) xylitol (2-9 %) crospovidone (5-13 %) magnesium aluminometasilicate (2-9 %)
Prosolv® ODT	JRS Pharma, Germany	mannitol (60-70 %) MCC (15-30 %) fructose and silicon dioxide (< 10 %) crospovidone (5 %)
Compressol® SM	SPI Pharma, USA	mannitol (80-90 %) sorbitol (10-15 %) silicon dioxide (< 2 %)
Pharmaburst® 500	SPI Pharma, USA	mannitol (85 %) silicon dioxide (< 10 %) sorbitol (< 10 %) crospovidone (5 %)

1.3 Amorphous solid dispersions

1.3.1 General aspects

The principle of solid dispersions was firstly considered by Sekiguchi and Obi in 1961. The authors observed an increased dissolution rate by preparing eutectic mixtures of the poorly soluble API sulfathiazole with urea [92]. The term “solid dispersion” has been firstly introduced by Chiou and Riegelman [93] having defined it as “a dispersion of one or more active ingredients in an inert carrier at the solid state“ [93]. Nowadays, many different schemes for the categorization of solid dispersions can be found in literature [38,94]. To give some examples, eutectic mixtures, glass suspensions, crystalline suspensions, crystalline solid solutions, and ASDs can be allocated to the group of solid dispersions. However, a distinct definition for one system is not necessarily possible since several types can be present within one solid dispersion.

In the scope of this work, the term ASD will be used following the definition by Huang and Dai [95], characterising systems where an API is predominantly embedded in amorphous state into a solid matrix, commonly a polymer. The relevance of ASDs in modern oral drug delivery is justified by the possibility to improve the BA of poorly soluble drugs [38]. This is attributed to an increase in dissolution rate and the generation of supersaturation of the API when exposed to biological fluids [38].

The typical dissolution profile of an ASD has been described as *spring and parachute* by Guzman et al. [96]. Due to the lower density and the lack of long range order, the amorphous API is at higher energetic state, which results in a sharp increase in dissolution exceeding the equilibrium solubility [97]. The initial spring is either followed by rapid precipitation or a parachute phase, meaning that supersaturation can be maintained over a certain time. According to Taylor and Zhang [98], every concentration of an API dissolved above the equilibrium solubility of its most stable polymorph can be defined as supersaturated. For quantification, the degree of supersaturation can be easily applied and be calculated by the ratio of the concentration at certain time point and the equilibrium solubility in the same media at same conditions such as temperature and pressure [98]. The supersaturated state of the API after initial dissolution can be stabilised via different mechanisms, strongly influenced by the selection of the polymer, as could be pointed out by Curatolo et al. [99]. The relevance for the generation and the maintenance of supersaturation can be explained by the findings of Raina et al. [100] and Borbas et al. [101] defining the extent and amount of supersaturation as prerequisite for an increased flux across the membrane. A correlation was found between the increase of flux and the extent of supersaturation up to a defined threshold called “amorphous solubility”.

From a thermodynamic point of view the supersaturation can be regarded as unstable since no thermodynamic equilibrium can be formed, as this system exists between the amorphous form and its solution in the absence of crystalline material [38]. To stabilise supersaturation while preventing the dissolved API from crystallization, the adequate selection of a polymeric crystallization inhibitor is crucial [22]. Besides a desirable increase in permeation, the higher energetic state of the API also acts as driving force for possible precipitation and crystallization of the API [102]. Consequently, the amount of molecularly dissolved drug substance which is available for permeation would continuously decrease until finally equilibrium solubility is reached. As a result, this would counteract the benefit of an ASD formulation and would automatically lead to an insufficient in-vivo performance [103].

The complex dissolution interplay during ASD dissolution as well as critical formulation aspects will be discussed in the following chapters.

1.3.2 Drug Dissolution from ASDs

Besides the appearance of molecularly dissolved API during dissolution of ASD formulations, a multitude of colloidal structures, such as drug-rich particles, micelles, nanoaggregates, are formed simultaneously, leading to a complex interplay between those structures [98,104]. Therefore, to describe the maximum amount of detectable API in solution, the term apparent solubility is widely accepted, as it combines both, states of molecular supersaturation as well as solubilised forms [38,105,106].

Special emphasis must be given to the formation of a separated amorphous phase during dissolution, often generalised as amorphous-liquid phase separation (ALPS) [38]. According to Ueda and Taylor [107], the phenomenon of ALPS generally occurs if a certain limit of supersaturation defined as amorphous solubility is exceeded while the crystallization tendency of the molecule is low. The formation of ALPS has additionally been described to be dependent on the combination of API and polymer [108]. Furthermore, a study conducted by Indulkar et al. [109] has shown that ALPS is likely to occur when the drug load in an ASD is low, due to the rapid increase in drug dissolution exceeding the amorphous solubility. Wilson et al. [103] reported that the desired increase in permeation is directly linked to the extent of supersaturation, however, only until the amorphous solubility is reached. From that point where the free drug concertation is at maximum, further addition of drug would just lead to an enrichment in the colloidal phase, while the degree of supersaturation remains constant. The appearance as well as the formation of the colloidal phase is not fully understood to date and controversially discussed in literature [110,111]. While the appearance of crystalline precipitates is undoubtedly correlated with a negative influence as it depletes the supersaturation, the formation of an amorphous colloidal phase is expected to be of biopharmaceutical relevance [112]. Various studies indicated that the colloidal phase is advantageous for in-vivo purposes

since it is in equilibrium with the molecularly dissolved API, thus acting as a reservoir by replenishing the permeated drug continuously [103,113]. In contrary, there is also some literature available, characterising the formed amorphous phase as precursor for precipitation with a considerable risk for subsequent crystallization [38,111]. To date, still a lot of research is ongoing in this field, for example by analysing the influence of the generated particle size of the colloids, as studies have demonstrated that smaller particle sizes could play an important role in permeation [107,112,114,115].

Besides many different postulated dissolution mechanisms for ASDs, there is accumulated evidence in literature that three different mechanisms as summarised by Schittny et al. [38] are most likely to occur when a solid ASD particle is exposed to aqueous media. The three highlighted mechanisms are schematically visualized in Figure 5.

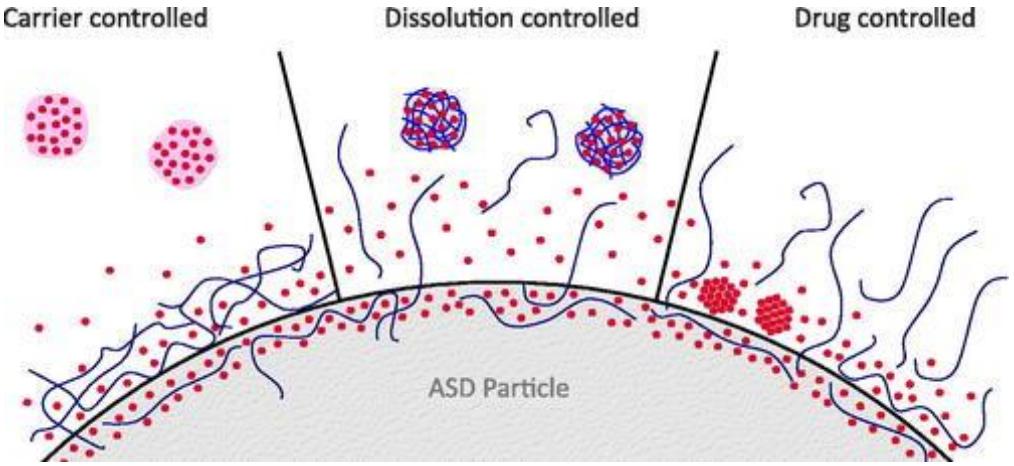

Figure 5 Overview of three different dissolution mechanism of ASDs (with permission from Schittny et al. [38])

In terms of the first scenario, the *carrier-controlled release*, the used matrix polymer starts to from a highly viscous gel layer after water ingression through which the API has to diffuse. As a result, the expected drug release kinetic is comparably slow. The release in this case is controlled by the API concentration within the ASD and the surrounding release medium. For this mechanism, however, when exceeding the amorphous solubility, ALPS can occur. The second scenario is the *congruent release* where the API and the polymer show a fast and simultaneous release inducing a strong supersaturation effect. It is crucial in this regard that the efficacy of the polymer for an immediate stabilisation is maintained as the degree of supersaturation strongly affects the crystallization rate in both aspects, the nucleation step as well as the crystal growth [116,117]. It was reported by Saboo et al. [118] that the congruent release mainly attributes to the formation of ALPS. The third mechanism described, is the *drug-controlled release* which is attributed to an initial dissolution of the polymer whereby the remaining API dissolves at a rate which is predominantly controlled by the drug itself. ASDs relying on this mechanism suffer from a high recrystallization tendency due to the lack of direct

interaction with the polymer. According to Schittny et al. [38] no reports were found in literature describing the occurrence of ALPS for this scenario. However, the clear distinction of the mechanisms is mostly based on theoretical considerations. In practice, the different occurring mechanisms cannot be clearly distinguished and therefore simultaneous occurrence can be assumed [119].

1.3.3 Formulation aspects

Defining most of the ASDs as thermodynamically metastable, challenges arise for physical stability over the intended shelf-life. To reduce the high energetic state of the amorphous API, the systems are susceptible to recrystallize forming a thermodynamically favourable polymorph [36]. To reduce the risk for recrystallization by an increased solid state stability several important ASD properties were highlighted in literature, such as polymer selection, drug load, the protection of moisture and the addition of further excipients [22,56].

For kinetic stabilisation a commonly assumed rule of thumb claims that the glass transition temperature (T_g) of an ASD should be at least 50 °C higher than the maximum storage temperature [120]. Besides the antiplasticization effect, which causes an increase in T_g of the API the use of polymers with a high T_g can also increase solid state stability by an increase in viscosity which can lead to a decrease in molecular mobility [22,121]. The polymers that have been most studied and described for ASDs are cellulose derivatives such as hydroxypropyl methylcellulose (Hypromellose, HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), poloxamers, polyvinylpyrrolidone (Povidone, PVP) and polyvinylpyrrolidone vinyl acetate (PVPVA) [122]. Within each development process, however, the appropriate polymer has to be selected fitting the API properties best [22,116,123].

Besides solid-state stabilisation the ideal polymer should also aid to the desired dissolution profile, followed by stabilisation of the supersaturation, and finally prevent the drug to precipitate. The polymer selection for a given API aimed for being developed as an ASD, is generally assessed first in small scale high throughput dissolution assays [39,124]. Most commonly ASDs are formulated as binary systems including an API and the polymer only [125]. The effectiveness of polymers to influence the respective ASD performance varies significantly as pointed out by Curatolo et al. [99]. This could be attributed to multiple possible mechanisms the polymers aim to maintain drug in supersaturation. In general, this is mainly enabled by kinetic stabilisation and merely slow the thermodynamically unavoidable process of nucleation and crystal growth [126].

Conceivable mechanisms would be [122,126]:

- changes in solution properties either via solubilisation or viscosity increase
- steric hindrance

- hindering crystal growth by adsorption on the newly built surfaces
- molecular interactions such as hydrophobic interactions or hydrogen bonds

Khan et al. [127] found out that polymers with intermediate hydrophilicity/hydrophobicity were most effective in the inhibition of crystallization during dissolution. This is potentially attributed to the ability of these polymers to interact with the hydrophobic drug rich phase formed within the process of ALPS as well as with the molecularly dissolved drug in the aqueous phase [123,128]. Besides intermediate hydrophobicity, the appearance of ionizable groups, number of hydrogen bond donors and acceptors as well as a sufficient molecular weight were reported to be most favourable for stabilising drug supersaturation [38]. By far PVPVA and HPMCAS play the most important role in ASD development apparent from most of the marketed products [22]. In terms of PVPVA, a fast onset of drug release at least until the threshold for drug load is reached and the ability for strong molecular interactions can be highlighted [109,123,129]. In the case of HPMCAS, the high relevance is mostly related to the huge potential of crystallization inhibition [130]. Curatolo et al. [99] analysed 41 polymers regarding the ability for achieving and maintaining supersaturation including nine structurally different hydrophobic drugs. The results of the study revealed the highest effectiveness of stabilisation when HPMCAS is used. A crucial point to bear in mind, when HPMCAS is selected, is the use of the HPMCAS grade suitable for the specific formulation approach. The grade has a remarkable impact on the resulting pH dependent solubility, crystallization inhibition and dissolution rate, caused by a different ratio of acetyl to succinoyl groups in the polymer [128]. The different onsets of dissolution for example at different pH, can be taken as advantage for a tailored dissolution profile. Exemplarily, gastric resistance and sustained release principles could be mentioned here [128,131].

It is well known that the API load directly impacts the ASD dissolution behaviour. Indulkar et al. [109] performed a study to investigate the dissolution of ASDs with RTV and PVPVA with rising drug loads starting form 10 % w/w up to 50 % w/w. Interestingly, the authors observed rapid and complete release for ASDs up to 25 % w/w, with a subsequent formation of ALPs and described a congruent release of API and polymer up to a drug load of 25 % as limit of congruent release. It is also confirmed by other research groups that the congruent release of API and polymer can be seen as prerequisite for ALPS to occur. Higher drug loads thereby decreased dissolution with no indication for ALPS [109,112,118]. This circumstance poses an immense risk for recrystallization, however, not observed in the study of Indulkar et al. [109] possibly due to the low crystallization tendency of RTV. The hypothesis was made by the authors, that in terms of higher drug loads, the dissolution mechanism has changed to be finally dominated by the hydrophobic nature of the lipophilic drug [109]. The relevance for the dissolution mechanism can be even strengthened by the study of Tres et al. [132] taking

felodipine as a fast-crystallizing API. Likewise, the change in dissolution mechanism by increasing the drug load was also described, however, in this case re-crystallization was found to occur. The authors compared the dissolution behaviour of 2 different PVPVA based ASDs, first, with a drug load of 5 % and second with a drug load of 50 %. In the case of the lower loaded ASD, the release was shown to be polymer dependent with felodipine dissolving with the same dissolution rate as the polymer. In contrast for the 50 % drug loaded option, significantly lower dissolution rates were observed for the polymer as well as for felodipine. Additional analytical investigations via Raman spectroscopy served to find detectable reasons for these different dissolution performances. For the 5 % loaded ASD no changes in Raman spectra were detected during dissolution, indicating a dissolution of the ASD as single entity, dominated by the hydrophilic polymer. However, the picture obviously changed for the 50 % drug-load of the ASD. Here, the investigation revealed an initial loss of the polymer from the ASD extrudate with the consequence of drug re-crystallization. The authors concluded that the dissolution behaviour has changed to be now strongly dominated by the hydrophobic felodipine [132]. Even though, higher drug loads are principally desired, a careful evaluation is mandatory to ensure well performing ASD products.

A further critical aspect could potentially be the addition of another poorly soluble drug to the product as it is often present in FDCs. A well-described system is the combination of LPV and RTV. A significant decrease in dissolution is reported in literature when both APIs were combined in one polymer matrix. A physicochemical API-API interaction during dissolution was suggested as possible explanation. The authors hypothesized a significant reduced amorphous solubility for each drug, due to the mixing tendency in the drug-rich phase. This mixing tends to stabilise the colloidal phase, causing a shift in the balance with the molecularly dissolved API and hence reducing the concentration of dissolved drug molecules [63,133]. Besides this system of RTV and LPV further API combinations were also investigated. As far as miscibility was present in the amorphous state, a substantial decrease in amorphous solubility was also detectable [134].

For completeness, many other formulation aspects may affect the drug dissolution from ASDs to name a few, the degree of ASD homogeneity, further addition of excipients such as surfactants or a second polymer as apparent in ternary ASDs, and residual crystallinity [38].

1.3.4 Biorelevant dissolution testing for ASDs

Dissolution testing according to the standardized methods of the United States Pharmacopeia (USP) and Ph.Eur. is usually performed to assess the quality of the drug product and to prove the batch-to-batch consistency [135]. In principle, the basket or the paddle methods can be used for solid oral DFs, usually with media volumes in the range of 500-1000 ml to achieve sink conditions for enabling a complete drug release. Besides quality control aspects, in-vitro

dissolution testing has been established to predict changes in drug release that may have an impact on in-vivo performance [136]. In case of immediate release DFs for highly soluble APIs in-vitro dissolution testing has been entered in approval procedures and can be used as a replacement for bioequivalence studies in order to file a biowaiver [137]. However, this is mostly not applicable for poorly soluble drugs since the used volumes for in-vitro dissolution testing are prone for false in-vivo prediction due to overestimation of dissolution.

The prediction of in-vivo performance for ASDs is by far more complex since the dissolution process relies on different mechanisms such as solubilization, supersaturation and precipitation which all influence the exposure and finally, the absorption in the small intestine [37,138]. To nevertheless draw possible conclusions on in-vitro-in-vivo correlations (IVIVC) for ASDs more advanced dissolution models were proposed. These models were either based on USP I and II apparatus or flow through cells (USP IV) [37,135,139,140]. The implementation of non-sink conditions (in a one-phase setup) is of great importance for the dissolution assessment of ASDs as pointed out by Sun et al. [141]. Only when the possibility is given to assess the extent and maintenance of a supersaturated state, as well as ongoing precipitation and recrystallization, biopharmaceutically relevant conclusions could be made.

In order to better simulate in-vivo conditions, the model must be physiologically adapted [135,138]. One major aspect in this regard is the use of biorelevant media, firstly proposed by Dressman et al. [136]. Especially for systems which induce supersaturation, biorelevant media like fasted state simulated gastric fluid (FaSSGF), fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) were found to have a good prediction compared to human intestinal fluids as pointed out by Bevernage et al. [37]. Physicochemical key aspects in the development of these media were the adjustment of pH, osmolarity, surface tension and buffer capacity [136]. Schittny et al. finally summarised the use of biorelevant media during the development stage as one of the most crucial points and defined it as indispensable [38].

Besides the implementation of non-sink conditions and the use of biorelevant media the simulation of the physiological pH gradient must be also considered, especially for formulations that rely on the gastrointestinal pH gradient to induce supersaturation such as weak bases [37,142]. However, the consideration of gastric residence is not only noteworthy for APIs providing pH dependency but can be also critical for neutral molecules as recently pointed out by Müller et al. [130]. A significant decrease of supersaturation was observed when the exposure time in acidic media was increased, despite the absence of acidic or basic properties of the API. To simulate the transfer out of the gastric environment into the small intestine, Kostewicz et al. developed a two-compartment gastric intestinal transfer model [142]. Many

different transfer setups are described in literature, among other aspects they exemplarily differ in the technique the transfer is applied, or medium volumes considered [130,143,144].

To further increase the in-vivo reliability Bevernage et al. [37] among others pointed out the absence of an absorptive sink compartment as an important cause for poor IVIVC for supersaturating systems [103,145]. The permeation can affect precipitation by lowering the Gibbs free energy of the supersaturated state by a continuous removal of dissolved molecules. Furthermore, the supersaturation is at risk for overestimation in single phase setups, due to misinterpretations of the effect of precipitation inhibitors [37]. An easy principle for first trials, which could potentially provide first insights for possible in-vivo behaviour is the use of a biphasic dissolution approach. In this setup an organic layer e.g. octanol or decanol as absorptive sink compartment is added [146,147]. Like the previously described simple transfer model there are also many modifications of this procedure published. Most commonly either USP I, USP II apparatus or models based on flow through cells (USP IV) were used [148]. Worth to mention in this regard is the developed biphasic dissolution assay (BiPHa+) used in the study of Denninger et al. [149]. Besides the implementation of the sink compartment the model additionally ensures a continuous control and adjustment of pH throughout the simulated gastrointestinal transit. Despite promising in-vivo correlations found by Xu et al [72], and Shi et al. [146] there are numerous limitations that restrict the broader use of the biphasic model. For example, it remains unclear to what extent the direct contact between the drug and the organic solvent is affecting the dissolution. Furthermore, it must be mentioned that the partition of the API is mainly driven by the partition coefficient between the aqueous and organic phase and does not rely on the properties of a physiological membrane. Despite difficulties in the in-vivo prediction, valuable insights especially in early-stage development could be gained. Of greatest relevance thereby is the discriminative power between ASD formulations or even between different manufacturing techniques as pointed out by Silva et al. [150] or Thiry et al. [151]. In practice, the simulation of an absorptive compartment has also been established by several other experimental setups, the well-established Caco-2 model using human colorectal adenocarcinoma cells [34], the parallel artificial membrane permeation assay (PAMPA) [152] or the TNO Gastro-Intestinal Model (TIM) [153] were documented in literature. Despite years of intensive research, to date none of the above-mentioned models is able to fully simulate GIT conditions, yet [135,138].

1.4 Challenges in the downstream processing of ASDs

1.4.1 Manufacturing techniques

Several ASD production techniques have been developed in recent years. The four most described techniques in literature are, SD, HME, fluid-bed technology and KinetiSol© technology. Processes like HME require the application of high temperatures to reach the

molten state of the compounds, whereas the Kinetisol© technology is working with mechanical stress to reach the required energy. SD and fluid-bed technology thereby involve the evaporation of solvent or solvent mixtures [22,48,139]. Each of the listed techniques offers different advantages and opportunities, however, also go along with individual limitations which usually need to be thoroughly evaluated before choosing the appropriate technique on a case-by-case basis. An important key parameter in this regard is the physicochemical nature of the API [48,154]. Taking the API characteristics into account, scientists often follow two possible manufacturing routes: the solvent- or the melt-based route. By far the two most prominent processes are SD as solvent-based and HME as melt-based option [22,155]. This point can be further emphasised by taking a closer look at the FDA approved ASD products, which are predominantly produced via SD or HME as emphasized in the review of Baghel et al. [22].

In 1961, Sekiguchi and Obi firstly reported on the melting technology to produce solid dispersions, at that time mostly investigating eutectic or monotectic mixtures of an API and a carrier [92]. A physical mixture was heated to obtain a melt which was afterwards solidified via cooling and finally crushed to reduce the particle size. As a modern industry-related version, HME has emerged nowadays as the most relevant technique, highlighted by a rising number of patents and several marketed products available [139,156,157]. This process combines feeding of the components, and an intensive mixing of polymer and API under heating in an extruder before the melt is pressed out of the nozzle(s). Besides the high temperatures applied and the subsequent melting of the substances the additional introduced mechanical force further supports a homogenous dispersion of the API in the polymer. As already pointed out, ASD homogeneity has a significant influence on the resulting biopharmaceutical performance [158,159]. Finally, the melt is pushed under pressure through a die forming a filament, which solidifies to the glassy state where the API molecules are entrapped in the polymer. Afterwards the filament can be either post-processed into granules via milling prior to tableting or filled into hard capsules or sachets. Rarely described, but also possible is the direct shaping of the filament into the final dosage form, so called calendaring [156].

In HME, as a solvent free process, a drying step is not necessary, leading to an increased cost-efficiency and the possibility to implement continuous manufacturing approaches [157,159,160]. Furthermore, it was shown that high drug-loaded ASDs were producible while stability issues could be excluded. Tian et al. [161] demonstrated the production of 60-70 % loaded ASDs for three selected APIs, with the use of intensive thermodynamic modelling. Despite the broad applicability of HME in ASD production several disadvantages are also present. Thermal stability must be ensured for all the ingredients since HME works at elevated temperatures and contains relatively long residence times in the extruder. Consequently, the process is not capable for heat sensitive materials. This point is not only relevant for APIs but

also for many polymers, which often need high temperatures to reduce the melt viscosity needed for extrusion [156,158]. As an alternative to overcome the thermal load and still be able to process high melting drugs, the KinetiSol© technique was developed. The heat necessary for the melting of the compounds is only generated by friction and shearing at high rotating speeds of the blades. Beneficial thereby is the comparably low processing time of under 30 s and lower processing temperatures [139]. This technique is frequently implemented in research, however, has not been implemented into industrial scale, yet [48].

Solvent based techniques start with the dissolution of the API and a polymeric carrier in a solvent or in a solvent mixture, followed by a quick removal of the solvent. The main benefit of the solvent-based techniques is the prevention of thermal degradation of the API, as only a low heat load is necessary to evaporate organic solvents [139]. However, two different challenges are needed to be addressed in the development. Firstly, a suitable solvent or a solvent mixture has to be found to dissolve both, the API and the polymer. The determination of a suitable solvent is a prerequisite for the final ASD performance, as insufficient dissolution in the solvent can significantly influence final ASD homogeneity [162,163]. The difficulty here often lies in the different polarities of the molecules [139]. As an undesired consequence, further excipients like surfactants are often required. However, their quantity in the final DF is generally strictly limited and reduces the loading capacity. Secondly, the residual organic solvent needs to be completely removed for patient safety, as these can cause ADEs [22]. Additionally, the second drying poses a risk to ASD stability since the increased temperature goes ahead with an increase in molecular mobility with the consequence of phase separation, frequently the preliminary step before the first nucleation induces [22]. Nevertheless, SD has become the most relevant solvent-based technique. This process allows for an extremely fast evaporation, enabling an entrapment of the API molecules in the polymer matrix due to the sudden increase in viscosity. Beneficial aspects additionally highlighting the relevance of SD for the manufacturing of ASDs could be the high control of process variables, the ease of up-scaling and the great potential to influence the final powder properties of the ASD [48,139].

1.4.2 Downstream processing of ASDs into tablets

A lot of research has been performed focusing on production techniques for ASDs [164] or on the dissolution performance of intermediates [38,165], however, only a few studies dealt with the downstream processing of ASDs into tablets as the final DF [47,166,167]. Possible reasons for that could be the higher complexity of the systems, attributed to a more challenging formulation development and stability assessment compared to standard formulations [155,168]. Regarding stability, it is important to bear in mind that ASDs are prone to phase separation in form of demixing triggered by mechanical energy input during tableting or dry

granulation [47]. This tendency can be even more pronounced if higher drug loads are considered as demonstrated by Ayenew et al. [169].

Most studies available in literature focusing on downstream processing of ASDs into tablets highlighted the poor flowability, compactability and later tablet properties such as disintegration and dissolution as biggest challenges [47]. Undoubtedly, the individual extent is highly dependent on the ASD manufacturing technique and the resulting properties of the intermediates [170-172]. For ASDs produced by SD one of the main challenges will be the improvement of flowability, because SD typically yields very cohesive powder with a low bulk density and a large surface area, hampering subsequent direct compression. Reports on direct compression of spray dried ASDs are often limited using single punch equipment and a manual die fill to firstly study the compaction behaviour of the powder [173,174]. To overcome this, another intermediate step such as dry granulation is often necessary [167].

Regarding this work, the focus will lay on the downstream processing of ASDs produced via HME. To achieve a tablet as desired oral solid DF, the obtained filaments need to be first milled in an additional process step. In contrast to SD powders, milled powders obtained from filaments generally have the tendency to show a better flowability, due to the higher bulk density. However, this is strongly dependent on the particle size distribution and particle morphology [47,170]. The resulting particle size of the milled extrudates was found to be a relevant aspect as it influences the flowability [47,160], tabletability [158,175] as well as the dissolution behaviour [175,176]. An interesting downstream approach for HME was published by Hörmann et al. [160]. With the use of strand pelletization it was possible to achieve free flowing spherical particles with a very narrow particle size distribution. In a subsequent process step the pellets could be mixed and finally compressed into tablets. The authors also provided extensive insights for the implementation of quality by design (QbD) approaches using a semi continuous process for the development of tablets containing ASDs.

The main challenges for the processing of milled extrudates towards a successful tablet formulation are the loss in compressibility and the insufficient disintegration of the tablets. Davis et al. [170] observed a significantly lower tensile strength for milled extrudates compared to spray dried products applying compression pressures in the same range. As possible reasons for that, particle size and morphology as well as the reduced compressibility of the previously densified extrudate were hypothesised [158,170]. Demuth et al. [47] suggested the use of smaller particles for an increase in specific surface area available for particle-particle bonding, however, only to a limit where the flowability is still in a processable range. In addition to the challenges caused by the powder properties of the milled extrudates the high amount of polymer included will also lead to difficulties. Many polymers tend to swell and form a gel layer after contact with water or generally suffer from poor wettability, after the extrusion process.

As a result, the disintegration of the tablet as well as the dissolution rate of the particles can be significantly influenced [158,166]. In a recently published study by Zhang et al. [177] remarkable differences in the disintegration process dependent on polymer hydrophilicity and polymer-drug ratio were reported. The authors showed that for ASDs prepared using hydrophilic polymers (like PVPVA) disintegration time increased when polymer-drug ratio increased. In contrast for less hydrophilic polymers like HPMCAS faster disintegration times were observed considering the same polymer-drug ratios.

To overcome this challenging behaviour of the ASDs, high amounts of different excipients are needed, such as filler-binders and disintegrants. However, considering that the drug load in ASDs is most commonly around 10-30 % [124], further addition of excipients will finally increase tablet mass causing pill burden or acceptability issues [47]. For this reason, the used excipients should be evaluated thoroughly and ASDs should contain as little additives as possible.

1.5 Aim of the thesis

As laid out in the previous sections, child-appropriate DFs for poorly soluble drugs are highly required for an efficient and safe pharmacotherapy. In recent years, innovative solid oral DFs like ODTs, ODMTs or immediate-release mini-tablets have gained importance since advantages in terms of stability and acceptability were proven in several studies. To date, still most available products with poorly soluble APIs are formulated as liquid oral DFs. They often contain high amounts of questionable excipients posing a considerable risk for adverse effects. Also, common practice is the manipulation of marketed products for adults, e.g., via crushing the tablets prior to dispersing them in water, or extemporaneous compounding, which is associated with a high potential for the failure of pharmacotherapy.

Aim of the thesis was to develop a child-appropriate formulation for the two poorly soluble drugs RTV and LPV. As selected technique for solubility enhancement the preparation of ASDs was chosen prior to be downstream processed into ODTs.

In a more detailed overview, the aims of the thesis are described as follows:

- To review the potential of ODTs as promising child-appropriate DF in the field of paediatric drug development. Furthermore, to provide a detailed overview about current challenges and recent advances of ODTs. Main points in this regard were the detailed analysis of acceptability and formulation challenges of ODTs *(chapter II).*

- To evaluate the performance of CPEs for direct compression of ODTs. To gain knowledge about the tableting and disintegration behaviour of the ODT formulations based on CPEs, especially for high loaded APIs with challenging properties *(chapter III).*

- To investigate new formulation approaches in several biorelevant dissolution models, with a special focus on the role of interplay between both model APIs *(chapter IV).*

- To finally determine key aspects in the downstream processing of ASDs into ODTs *(chapter V).*

1.6 Outline of the thesis

The current state of research on ODTs in paediatric drug therapy is provided in *chapter II* of this thesis in form of a review article published in *Expert Opinion on Drug Delivery*. An overview was given about recent advances and current challenges of ODTs. One of the main interests in this work was the literature-provided evidence in how far ODTs can be regarded as acceptable for children. In several case studies it was demonstrated that principally ODTs also found acceptance for pre-school children, which is controversy to the previously assumed age limits. This insight could further extend the targeted age groups. Thereby, the relevance of the tablet diameter was pointed out as crucial aspect for acceptability. Regarding the tablet size ODMTs prove to be the ideal DF for children since they even seemed to be accepted by neonates and could be used for personalized dosing. Challenges in the field of ODTs were also found since still the most assumptions are evidenced with small studies and need to be further confirmed by larger studies. Also still challenging are special formulation approaches in terms of taste masking, modified release or when poorly soluble drugs are formulated, especially relevant for high drug loads.

Chapter III focuses on the evaluation of two novel CPEs based on mannitol with already available ones used for direct compression of ODTs and ODMTs. It was investigated in how far the CPEs could overcome poor compressibility, a slow disintegration, relevant for high drug loads and the content uniformity for low-dosed formulations. Paracetamol which is well known for its poor compactability was selected for evaluation of the CPEs to what extent the inadequate bonding capacity could be conquer. High-loaded ibuprofen formulations were prepared to serve as reference for the disintegration of the tablets when poorly soluble drugs suffering from a slow disintegration are embedded. Furthermore, low-dosed enalapril maleate ODTs and ODMTs were produced on an industrial rotary tablet press Korsch XM 12 to investigate the feasibility of matching content uniformity.

Chapter IV focuses on different biorelevant dissolution approaches for the two selected model APIs RTV and LPV. First, after preparing different ASD formulations via HME, a small-scale formulation screening was carried out to get an impression of the general dissolution behaviour pointing out the extent and maintenance of supersaturation as most relevant. Second, a biorelevant transfer dissolution approach was performed to compare the dissolution profiles for selected combinations with the marketed product Kaletra® since the interaction of RTV and LPV dissolving simultaneously must be regarded critically. Here, it was suspected that a new formulation approach would perform significantly better as already existing ones in literature. Finally, a biphasic dissolution approach was implemented to analyse a more physiological environment with the addition of an absorption sink compartment to be able to possibly emphasize the superiority of the new postulated formulation approach.

Chapter V brings together the most relevant findings from *chapter III* and *IV* and focuses on the downstream processing of ASDs into ODTs. In the following study key aspects were determined to enable sufficiently performing ODTs, meaning a balance between adequate mechanical strength and a fast disintegration. Relying on the results and experiences gained from *chapter III*, two different CPEs, Hisorad® and Ludiflash®, were found to be best suitable to overcome the challenging behaviour of high loaded ASDs. Besides the involvement of two CPEs, also different particle size fractions of the ASDs, ASD loads, and the use of two different polymers have been evaluated. The final aim thereby was to analyse the effect on the critical quality attributes (CQAs), mechanical strength and disintegration of the ODTs. Finally, a biorelevant dissolution setup excluded an influence of compression, due to possible solid-state changes and proved the ability for ASDs to be downstream processed into ODTs.

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Chapter II – Orodispersible tablets for pediatric drug delivery: current challenges and recent advances

Pretext

Since many years experts are calling for a shift of paradigm in the paediatric therapy from previously preferred liquid oral DF to modern solid oral DF. Through intensive research during the last years, ODTs and ODMTs, have become much more important, evident from the increase in the number of publications in this research field. Nevertheless, still only a few drug products formulated as ODTs have achieved to be successfully authorised. Reason for this could be the small number of acceptance studies available which confirm the relevance and the possible superiority of this DF. The aim of this review article was to shed light on the current research situation and pointing out existing challenges for ODTs. The authors highlighted the acceptability of ODTs throughout different developmental stages and formulation challenges as most relevant in this article.

Evaluation of authorship

Author	Idea [%]	Study design [%]	Evaluation [%]	Writing [%]
Raphael Wiedey	0	50	50	50
Marcel Kokott	0	30	40	40
Jörg Breitkreutz	100	20	10	10

JB has been invited to submit a review on orodispersible tablets for paediatric drug delivery to the journal Expert Opinion on Drug Delivery. MK assisted in manuscript setup, literature evaluation and writing. RW worked on the manuscript setup, evaluation, and writing. JB as senior author was responsible for the study design, the evaluation and revision of the manuscript.

Orodispersible tablets for pediatric drug delivery: current challenges and recent advances

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Abstract

Introduction: Child appropriate dosage forms are indispensable in modern medicine and are a prerequisite for successful and efficient pediatric drug therapy. For years experts call for a paradigm shift, from formerly preferred liquid dosage forms to novel oral solid dosage forms. Orodispersible (mini-) tablets are a promising formulation approach due to the ease of administration and their relatively high acceptability.

Areas covered: Current challenges as well as recent advances of orodispersible tablets for pediatric drug delivery are critically discussed in this review. Highlighted aspects are evidence for acceptability by children and advances in special ODT formulations (taste masking, modified release, enabling formulations).

Expert opinion: Innovative solid dosage forms like OD(M)Ts are gaining more importance in pediatric drug therapy because of various benefits discussed in the review. Especially to be emphasized is the high acceptance even in pre-school children, that has not been fully recognized by clinicians, yet.

Despite the presented evidence and recent advances, notable challenges remain: More clinical acceptance studies with ODTs are needed to learn about the acceptability of different ODT sizes within certain age groups.

Numerous formulation advancements have been made, but challenges remain where several issues (e.g. poor taste) have to be addressed and the required drug loads are high.

Chapter III – Evaluation of two novel co-processed excipients for direct compression of orodispersible tablets and mini-tablets

Pretext

Besides the importance of children's acceptability, as highlighted in *chapter II* still challenges in the formulation development and manufacturing are needed to be addressed, especially relevant for formulations with a high drug load. The scope of this publication was to critically evaluate the potential of two novel CPEs for direct compression when highly challenging APIs are included. Key points were mechanical strength, disintegration behaviour and content uniformity. Three different model drugs, paracetamol, ibuprofen and enalapril maleate were selected to specifically challenge the CPE. Based on this knowledge a more formulation realistic data set should be generated which in the following could attribute to a fast and suitable selection of a CPE adapted to the respective properties of the API.

Evaluation of authorship

Author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Writing [%]
Marcel Kokott	20	50	80	70	70
Ard Lura	0	0	20	0	0
Jörg Breitkreutz	40	10	0	0	10
Raphael Wiedey	40	40	0	30	20

The following research article has been published in European Journal of Pharmaceutics and Biopharmaceutics in 2021. The first author of the manuscript MK was responsible for the idea and study design as well as for the execution of the experimental work. Data evaluation as well as writing of the manuscript was performed by MK. AL was involved in the execution of experimental work. JB and RW as senior authors were responsible for the idea and the study design as well as for the revision of the manuscript.

Evaluation of two novel co-processed excipients for direct compression of orodispersible tablets and mini-tablets

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Abstract

Pediatric, geriatric, and other patients who suffer from swallowing difficulties represent a special patient group, where an increased need in appropriate formulation development is required. To overcome these mostly swallowability linked issues, orodispersible tablets (ODTs) and orodispersible mini-tablets (ODMTs) can be seen as a suitable alternative to improve compliance. Orodispersible tablets are oral solid dosage forms which rapidly disintegrate after contact with saliva, leaving a liquid dispersion, which can be easily swallowed. To fulfil the required quality criteria and optimize the formulations regarding tensile strength and disintegration time, co-processed excipients (CPE) based on mannitol are frequently used in the manufacturing of orodispersible tablets. This study aimed to systematically compare two new CPEs, namely Granfiller-D® and Hisorad® and evaluate their potential in future OD(M)T formulations with already marketed products. The performance of the CPEs was examined in combination with three different APIs. Disintegration time, sufficient mechanical strength and content uniformity for low dosed formulation were chosen as main quality aspects. Conventionally sized tablets (9 mm) with 50 % drug load of ibuprofen and paracetamol were produced with each CPE. Low dosed OD(M)Ts with a drug load of 4 % enalapril maleate were manufactured to study content uniformity. Large differences were visible in the formulations containing ibuprofen and only Hisorad® allowed to compress ODT fulfilling the specifications of Ph.Eur. and FDA regarding disintegration times (180 s and 30 s, respectively). For the poorly binding model drug paracetamol, none of the studied excipients showed a satisfactory performance, with maximum tensile strengths < 1 MPa. To reach content uniformity in low dosed ODMTs, Ludiflash® seems to be the most preferable alternative, as the formulation showed the lowest AV (< 4) combined with the smallest variation in API content (c.v. < 2 %). In conclusion, the study revealed that none CPE is the ideal choice for all approaches, but different CPEs should be selected dependent on the different challenges during formulation development of OD(M)Ts.

Chapter IV – The interplay of poorly soluble drugs in dissolution from amorphous solid dispersions

Pretext

Before the gained knowledge from *chapter III* could be further transferred to the overall aim to develop a child appropriate DF for RTV and LPV the interaction of both APIs predominantly relevant during dissolution needed to be investigated more in detail. This interaction is of great relevance in the context of paediatric therapy, emphasised by several published in-vitro as well as in-vivo data. This research article aimed to present a new formulation approach for the combination therapy by gaining a deeper understanding of the interplay of both APIs during dissolution. Starting from a small-scale dissolution approach for first formulation screening, followed by a more biorelevant dissolution either performed in single- or biphasic setups. The formulation concept was based on a separate embedding of the APIs into two different behaving polymers. In addition to the use of PVPVA for RTV, HPMCAS grades were evaluated for LPV in order to analyse the influence of a modified onset of release. Finally, a comparison to the marketed product was performed.

Evaluation of authorship

Author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Writing [%]
Marcel Kokott	70	80	100	80	70
Jörg Breitkreutz	10	0	0	0	10
Raphael Wiedey	20	20	0	20	20

The following research paper was submitted to International Journal of Pharmaceutics: X in 2024. MK as first author is responsible for the idea, study design as well as for the execution of experimental work. Data evaluation as well as writing of the manuscript was done by MK. JB as senior author is responsible for the idea and revision of the manuscript. RW as senior author is responsible for the idea and study design as well as for the revision of the manuscript.

The interplay of poorly soluble drugs in dissolution from amorphous solid dispersions

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Abstract

In recent years, the application of fixed dose combinations of antiretroviral drugs in HIV therapy has been established. Despite numerous therapeutic benefits, this approach poses several challenges for the formulation development especially when poorly soluble drugs are considered. Amorphous solid dispersions (ASD) thereby have gained considerable interest in the pharmaceutical field, however, mainly including binary systems containing only one drug and a polymer. The co-formulation of two amorphous drugs is accompanied by an immense increase in the complexity of the system as exemplarily reported for ritonavir and lopinavir embedded in a composite polymer matrix of PVPVA. The present study aims to present a new formulation approach to overcome the well-documented interaction during dissolution. Two different polymers, PVPVA and HPMCAS were used to produce ASDs for both drugs individually via hot-melt extrusion. The embedding of lopinavir in the slower dissolving polymer HPMCAS, while using PVPVA for ritonavir was found to significantly improve the overall dissolution performance compared to the individual use of PVPVA as well as to the commercial product Kaletra®. In addition, the use of different grades of HPMCAS demonstrated the possibility to further modify the dissolution profile. For a preliminary biorelevant assessment, the selected formulations were tested in a biphasic dissolution setup.

Chapter V – Downstream processing of amorphous solid dispersions into orodispersible tablets

Pretext

The last publication has the aim to finalise the development of a child-appropriate DF for RTV and LPV. Key aspects in the downstream processing of ASDs into ODTs were investigated. The findings in *chapter III* enabled an efficient selection of suitable CPEs, whereas the best performing combination approach found in *chapter IV* was chosen for the final downstream processing. The hot-melt extruded ASDs were milled, sieved, blended either with Hisorad® or Ludiflash® and finally tableted on a compaction simulator. In particular, the effect of the used matrix polymer, the ASD load, the used ASD particle size as well as the CPE selection were pointed out as critical factors for well performing ODTs. The aim was to develop ODTs with the highest achievable ASD load while balancing out a fast disintegration with a sufficiently high mechanical strength.

Evaluation of authorship

Author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Writing [%]
Marcel Kokott	70	90	80	70	70
Stefan Klinken	10	0	20	0	0
Jörg Breitkreutz	10	0	0	0	10
Raphael Wiedey	10	10	0	30	20

The research article was published in International Journal for Pharmaceutics in 2023. MK as first author is responsible for the idea, study design as well as for the execution of experimental work. Data evaluation as well as writing of the manuscript was performed by MK. SK was involved in the execution of experimental work and in the generation of the idea. JB and RW as senior authors are responsible for the idea and the study design as well as for the revision of the manuscript.

Downstream processing of amorphous solid dispersions into orodispersible tablets

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Abstract

The formulation development of amorphous solid dispersions (ASDs) towards a patient-friendly oral solid dosage form is proving to be still challenging. To increase patient's compliance orodispersible tablets (ODTs) can be seen as promising alternative. Two different ASDs were prepared via hot melt extrusion (HME), using PVPVA as polymer for ritonavir (RTV) and HPMCAS for lopinavir (LPV). The extrudates were milled, sieved, and blended with Hisorad® (HRD) or Ludiflash® (LF), two established co-processed excipients (CPE) prior to tableting. Interestingly, the selected ASD particle size was pointed out to be a key parameter for a fast disintegration and high mechanical strength. In terms of PVPVA based ASDs, larger particle sizes > 500 µm enabled a rapid disintegration even under 30 s for 50 % ASD loaded ODTs, whereas the use of smaller particles went along with significant higher disintegration times. However, the influence of the CPE was immense for PVPVA based ASDs, since it was only possible to prepare well performing ODTs, when Hisorad® was chosen. In contrast for HPMCAS based ASDs the selection of smaller particle sizes 180-500 µm was beneficial for overcoming the poor compressibility of the ASD matrix polymer. ODTs with LPV could be produced using both CPEs even with higher ASD loads up to 75 %, while still showing remarkably fast disintegration

Chapter VI – Conclusion and outlook

This work provides new insights in the field of paediatric drug development for poorly soluble active pharmaceutical ingredients (API). In detail, this thesis addressed two current major challenges in pharmaceutical development which are brought into a relevant context, overcoming poor aqueous solubility and final post processing into a child-appropriate dosage form. Advanced dosage forms such as orodispersible tablets (ODTs) and mini-tablets became increasingly important and stated their relevance in several clinical studies and scientific publications.

The review of existing literature demonstrated that ODTs have mostly been claimed as a highly promising alternative, predominantly for school children (> 6 years). The acceptance of ODTs was generally summarised to be high throughout different age groups of children, pointing out the tablet size as most important characteristic. Therefore, many articles have highlighted the use of orodispersible mini-tablets (ODMTs) as ideal option since they combine the inherent advantages of oral solid dosage forms and are well accepted even by neonates. It was also evident in literature that the full potential of ODTs especially regarding acceptability in the paediatric therapy has not been fully utilised, yet. As one of the main reason the very limited number of direct acceptance studies is hypothesized as the resulted knowledge is therefore mainly based on anecdotal reports. Besides the acceptability, immense research has been done to solve formulation issues concentrating mostly on taste masking, modified release, and solubility enhancement. Despite many outstanding formulation concepts published in the field of taste masking and modified release dosage forms, available data for ODTs containing poorly soluble APIs is rare.

Of greatest relevance in the production of ODTs are mannitol based ready-to-use co-processed excipients (CPEs). In order to be able to select the suitable CPE for the following formulation development a systematic comparison with different CPEs was carried out. The current literature has already presented several comparisons of CPEs, however, mostly without or only with low API loads. The performance of the CPEs was evaluated with three different APIs. Mechanical strength, disintegration time and content uniformity were chosen as critical quality attributes. Each of those aspects could be a relevant parameter with the first two being mostly challenging at high API loads. Paracetamol was selected in order to evaluate the ability of the CPEs to overcome the widely known insufficient compactability. Ibuprofen was chosen as model substance for a poorly soluble drug, causing a poor disintegration due to hydrophobicity and low resulting porosities. Enalapril maleate was selected to evaluate the potential to enable adequate content uniformity in low dose formulations. The conducted study successfully revealed differences between the selected CPEs. It was shown that Parteck® ODT, Hisorad® and Ludiflash® performed extremely well at low drug loads. However, the

picture changed visibly when a high amount of hydrophobic drug was incorporated. In this case only Hisorad® allowed for a fast disintegration within the specified requirements of European Pharmacopoeia while also a sufficiently high mechanical strength was achieved. Interestingly, all the other CPEs suffered from a poor disintegration with finally failing the requirements. For paracetamol, all CPEs failed to compensate the poor compaction properties. Taking every result into account it could be stated that no excipient is the one-fits-all choice for all challenges faced in the development of ODTs. It could be concluded that the wide range of available CPEs enables several opportunities, however, the final choice is still to be made on a case-by-case basis.

After thorough investigations in the field of ODTs, the second part of this work started with the formulation of amorphous solid dispersions (ASD) for the model system ritonavir (RTV) and lopinavir (LPV). ASDs with different polymers and drug loads were produced via hot-melt extrusion and afterwards tested in different dissolution setups. First, with the aim to find the best composition of API and polymer separately. Second, to characterise the best combination when both APIs are administered simultaneously. Seperate ASDs using two different polymeric carriers, polyvinylpyrrolidone vinylacetate co-polymer (PVPVA) and different grades of hydroxypropyl methylcellulose acetate succinate (HPMCAS) were prepared since the formation of a composite ASD matrix proved to be inferior based on previously performed experiments and published studies in literature. Preliminary small-scale dissolution trials revealed superiority of HPMCAS as carrier for LPV enabling a drug load of up to 40 %. In terms of RTV, however, the polymer HPMCAS underperformed and therefore PVPVA was chosen as matrix with a maximum drug load of 20 %.

Interestingly, the following evaluation of biorelevant dissolution for several combination approaches of RTV and LPV did not show complete consistency with the literature. Here, it was previously hypothesised that the sole separation of the APIs into fast-dissolving polymers such as PVPVA compared to the use of a composite matrix seemed to be sufficient for a significant decrease of API-API interaction during dissolution. In the present study, however, still a remarkable decrease of RTV supersaturation was observed when the dissolution onset of LPV took place immediately. This led to the assumption that a separation of the dissolution onsets of both APIs might be a promising aspect to improve both profiles. It was observed that considering the slower dissolving polymer HPMCAS for LPV, both dissolution profiles could be improved significantly. By the delay of the LPV onset, the supersaturation of RTV could be maintained longer. Nevertheless, it is also worth noting that even when the separation of dissolution onsets was enabled the direct interaction was also noted after a certain time when both APIs came into contact during dissolution. Furthermore, it was also demonstrated in this study that the selection of a defined HPMCAS grade as matrix polymer for LPV can be

regarded as key for the fine tuning of RTV dissolution. Since the grades differ in their pH-dependent onset of dissolution, the beginning of LPV dissolution can be directly adjusted with the consequence of an indirect influence on RTV dissolution. Regarding the influence of the used HPMCAS grade on LPV performance, it was observed that the final degree of supersaturation was unaffected. In addition to further examine this hypothesis from a more biopharmaceutical point of view a biphasic dissolution test was performed. The most promising combination LPV_HPMCAS with RTV_PVPVA pointed out from the conducted dissolution experiments also performed best in these trials, apparent by a 3-fold higher decanol partition of LPV compared to the use of separated fast-dissolving PVPVA ASDs for both APIs. Almost no partition was detectable for the approach where both APIs were embedded in one composite PVPVA matrix as present in the marketed product Kaletra®. Although, this biphasic approach was extremely simplified, interesting differences between the investigated combinations could be detected and therefore taken as starting point for following research in this field.

After the superior ASD combination has been identified, the respective ASDs were milled, sieved, and blended with a CPE before being tableted on a compaction simulator. The CPE evaluation study defined Hisorad® as best suitable when hydrophobic drugs are considered. Additionally, Ludiflash® was also chosen for investigation as it represents a more hydrophilic CPE without MCC as crystalline material. It was demonstrated that many different aspects were necessary to be considered to finally achieve a well performing ODT. The study revealed that the selection of the CPE, the polymer and the used ASD particle size fraction were of greatest relevance for balancing out a fast disintegration and a high mechanical strength. With the use of Hisorad® both, a challenging disintegration behaviour caused by the PVPVA matrix, and a reduced bonding capacity triggered by the HPMCAS matrix could be compensated best. Additionally, Hisorad® enabled highest ASD loads for well performing ODTs with 50 % for RTV_PVPVA and 75 % for LPV_HPMCAS. In contrast Ludiflash® ODTs, which proved to be a highly suitable CPE in many other aspects, showed strong limitations in disintegration with higher loaded PVPVA-based ASDs. Apart from the choice of CPE, the particle size fraction of the ASDs had a massive impact on the ODT properties, however, strongly dependent on the polymer used. In case of RTV_PVPVA ASDs it was shown that the use of smaller particles < 500 µm negatively affected the disintegration time. This was accompanied by an increase in mechanical strength, possibly due to the increase in specific surface area of the ASD particles. It is well known that a higher specific surface area correlates with a higher ability for bonding capabilities of the particles. Consequently, to load the ODTs as high as possible (50 %) while still having sufficiently strong compacts with a fast disintegration, a bigger particle size fraction of 500-710 µm had to be considered. In contrast, LPV_HPMCAS ASDs did not show limitations in disintegration, even though ODTs were loaded with ASD up to 75 %. The challenge in this

case was mainly to generate a tablet with a sufficiently high mechanical strength. To overcome this limitation, smaller particles were used in contrast to PVPVA-based systems. In this regard it was unavoidable to exploit a higher specific surface area to increase the possibility for more particle-particle interactions. Finally, for both APIs well performing ODT formulations based on Hisorad® were found. To exclude a possible influence of tableting on ASD stability, dissolution results of RTV and LPV ODTs were compared with the respective ASDs before tableting. As a result, no difference could be detected, and it was therefore verified that tableting did not have a negative impact on ASD dissolution for these formulations.

In order to be able to finally assess whether this demonstrated formulation approach could make HIV therapy for children safer and better in real life, much research has still to be performed. It should be kept in mind that all results were based on in-vitro trials. In-vivo studies would be essential to investigate to what extent the separation of the release onset is beneficial when it comes to absorption processes in the small intestine. Extremely relevant in this field would also be the execution of acceptance studies with children to investigate if the produced ODTs are well accepted. A key aspect in this regard would be the analysis of sensory perception, such as taste, the appearance and acceptance of remaining ASD particles after tablet disintegration. Finally, future research must deal with process development since an adequate scale-up from a compaction simulator as used in this work to an industrial scale rotary tablet press would be mandatory for the development of a new product.

Chapter VII – Summary

Since the shift of paradigm from previously preferred liquid dosage forms to solid dosage forms for paediatric patients, orodispersible tablets (ODT) and mini-tablets became a promising alternative. Despite a lot of research throughout the last years, still the availability of child-appropriate products is limited, especially for active pharmaceutical ingredients (API) with challenging physicochemical properties like a poor aqueous solubility. Therefore, available medicinal products authorised for adults are frequently manipulated prior to administration. The fact that the extemporaneous manipulation outside the intended use is highly concerning can be exemplarily elaborated on the film-coated tablet Kaletra®, a fixed dose combination of ritonavir (RTV) and lopinavir (LPV) showing a decrease of approximately 50 % in systemic exposure when the tablets were crushed prior to administration. The aim of the present work was to develop a new child-appropriate drug formulation for the poorly soluble protease inhibitors RTV and LPV.

The initial focus of this work was mainly set on the investigation and evaluation of ODTs as suitable dosage form for children. Literature research demonstrated that ODTs as oral solid dosage form have mostly been claimed as highly promising for child-appropriate administration. This is predominantly due to a high acceptance throughout the different age groups of children. Many different formulation concepts such as taste masking or modified release are point of interest in literature. However, reports on the use of poorly soluble APIs, formulated via a suitable solubility enhancement technique and subsequent downstream processing into ODTs are limited.

Based on the gained knowledge in the field of ODTs, a first study was conducted highlighting more the aspects of manufacturing and formulation development. For the manufacturing of ODTs mostly mannitol based co-processed excipients (CPE) are favoured. Many comparative studies for the direct compression of ODTs using CPEs are available in literature, however, mostly for placebo formulations or at low API dose. In order to define the best suitable CPEs for later formulation development a systematic investigation of available alternatives was carried out. For this purpose, specific APIs suffering from a poor disintegration and/or compaction behaviour were selected to investigate in how far the CPEs can compensate this challenging behaviour. The study revealed that the best balance between sufficient mechanical strength and fast disintegration within the pharmacopeial limits was present for the CPE Hisorad®.

After the extensive research on ODTs, the formulation development and biorelevant dissolution assessment for RTV and LPV and the following downstream processing into ODTs was focus. The preparation of amorphous solid dispersions (ASD) was selected as solubility

enhancement technique for both APIs. The model system RTV and LPV as well as the marketed product Kaletra® have already received attention in the literature. Considering the susceptibility of the marketed product to crushing, as well as the described interplay of those two APIs during dissolution, a biorelevant dissolution study was conducted. As part of this, numerous different ASD combinations and single ASDs have been tested for biorelevant dissolution to get a deeper understanding of this phenomenon and to draw possible conclusions for later formulation development. In contrast to already available studies, the only separation of the APIs using the same fast-dissolving polymer PVPVA was not sufficient to overcome the significantly decreased dissolution for both APIs. However, it could be shown that a separation of the respective dissolution onsets improved both dissolution performances. This was realised by using a slower dissolving polymer HPMCAS for the embedding of LPV and keeping the fast-dissolving polymer PVPVA for RTV. Furthermore, the selection of the HPMCAS grade, differing in the pH-dependent onset of dissolution could be seen as key parameter because the onset of LPV directly affected the supersaturation of RTV, however, did not show any influence on the achieved supersaturation for LPV.

To finally combine both conducted studies, a third one investigated the suitability of ODTs as formulation platform for ASDs. The respective ASDs for RTV and LPV were milled, sieved, and blended with a CPE prior to be tableted. The study demonstrated that the selection of the CPE, the ASD polymer and the used ASD particle size were relevant for the achievement of well performing ODTs, characterised by balancing out a fast disintegration with a sufficient mechanical strength. Depending on these key parameters ODTs with maximum ASD loads of 75 % for LPV and 50 % for RTV could be successfully manufactured. Additionally, it could be proved that the energy input during tableting did not affect the following dissolution performance of the ASDs.

In the context of this work, a development route towards a child appropriate dosage form for poorly soluble APIs was presented. A promising new combination approach of LPV and RTV was proposed. The separation of both APIs into polymers with different dissolution kinetics created a possibility to adjust and to improve both dissolution profiles in-vitro. Additionally, for the first time, it was successfully demonstrated that ASDs of RTV and LPV could be afterwards downstream processed into well performing ODTs. Furthermore, the detailed study on the evaluation of CPEs, can be used as a basis for other investigations to choose a suitable CPE for direct compression of ODTs.

Chapter VIII – Zusammenfassung

Seit dem Paradigmenwechsel von zuvor bevorzugten flüssigen Darreichungsformen zu festen Darreichungsformen für pädiatrische Patienten, stellen orodispersible Tabletten (ODT) und Mini-Tabletten eine vielversprechende Alternative dar. Trotz immenser Forschungsaktivitäten in den letzten Jahren, ist die Verfügbarkeit fester, kindgerechter Arzneimittel nach wie vor begrenzt. Dies gilt insbesondere für Wirkstoffe mit herausfordernden physikochemischen Eigenschaften, wie beispielsweise eine geringe Wasserlöslichkeit. Aus der Notwendigkeit heraus, werden oftmals für Erwachsene zugelassene Arzneimittel vor der Verabreichung modifiziert, beziehungsweise manipuliert und außerhalb der jeweiligen Zulassung verwendet. Eine solche Anwendung kann allerdings mit höchstbedenklichen Folgen einhergehen. Dies lässt sich exemplarisch anhand der für die Therapie des Humanen Immunodefizienz Virus zugelassenen Filmtablette Kaletra®, eine Kombination aus Ritonavir (RTV) und Lopinavir (LPV), aufzeigen. Im Rahmen einer klinischen Studie konnte gezeigt werden, dass die systemische Exposition beider Wirkstoffe ersichtlich geringer war, wenn die Tabletten vor der Einnahme zerkleinert wurden, im Vergleich zu der Einnahme der intakten Tablette. Ziel der vorliegenden Arbeit war es eine neue, kindgerechte Formulierung der beiden schwerlöslichen Protease-Inhibitoren LPV und RTV zu entwickeln.

Der anfängliche Schwerpunkt dieser Arbeit, lag vor allem auf der Untersuchung und Bewertung von ODTs als geeignete Darreichungsform. Die ausführliche Literaturrecherche zeigte, dass ODTs als feste, orale Darreichungsform oftmals als vielversprechende Alternative bei pädiatrischen Patienten beschrieben werden. Dies wird unter anderem mit einer hohen Akzeptanz in den verschiedenen Altersgruppen begründet. Viele verschiedene Formulierungskonzepte, wie zum Beispiel die Geschmacksmaskierung, oder die modifizierte Freisetzung sind in der Literatur von Interesse. Durchgeführte Studien, die sich jedoch mit der Verwendung von schwerlöslichen Wirkstoffen in einer orodispersiblen Matrix befassen, sind dagegen eher selten.

Auf der Grundlage der gewonnenen Erkenntnisse, wurde eine erste Studie durchgeführt, in der die Aspekte der Herstellung und Formulierungsentwicklung von ODTs näher beleuchtet wurden. Für die Herstellung von ODTs mittels Direkttablettierung werden oftmals mannitolbasierte koprozessierte Hilfsstoffe bevorzugt. In der Literatur lassen sich zahlreiche vergleichende Arbeiten zu den jeweils verfügbaren Fertigmischungen der Hilfsstoffe finden, allerdings meist für Placebo-Formulierungen oder Formulierungen, mit nur geringem Wirkstoffgehalt. Um die am besten geeigneten koprozessierten Hilfsstoffe für die spätere Formulierungsentwicklung zu identifizieren, wurde eine systematische Untersuchung durchgeführt. Für diesen Zweck wurden Wirkstoffe ausgewählt, die ein herausforderndes Zerfalls- und/oder Kompressionsverhalten aufweisen, um zu untersuchen, inwieweit die

Hilfsstoffe dies kompensieren können. Die Studie legte offen, dass die beste Balance zwischen einer ausreichenden mechanischen Festigkeit und einem schnellen Zerfall innerhalb der Grenzen des europäischen Arzneibuches, nur für den Hilfsstoff Hisorad® gegeben war.

Im Anschluss an die umfangreiche Betrachtung und Bewertung von ODTs, folgte die Formulierungsentwicklung und biorelevante Freisetzungsuntersuchung für RTV und LPV. Als Formulierungstechnik zur Erhöhung der Löslichkeit, wurde die Herstellung amorpher fester Dispersionen gewählt. In Anbetracht der bekannten Interaktion beider Wirkstoffe, formuliert in einer gemeinsamen Polymermatrix, wurde eine initiale Freisetzungsuntersuchung durchgeführt, um ein tieferes Verständnis dieses Phänomens zu erlangen und mögliche Schlussfolgerungen für die folgende Formulierungsfindung zu ziehen. Im Rahmen dieser Studie, wurde eine Vielzahl verschiedener Kombinationen von amorphen festen Dispersionen in unterschiedlichen Freisetzungsansätzen untersucht. Im Gegensatz zu bereits vorliegenden Daten, reichte die alleinige Trennung der Wirkstoffe unter Verwendung desselben schnelllöslichen Polymers PVPVA nicht aus, um die verringerte Freisetzung beider Wirkstoffe zu verhindern. Es konnte jedoch in dieser Arbeit hervorgehoben werden, dass eine Trennung der jeweiligen Freisetzungsstartpunkte eine signifikante Verbesserung des gesamtem Freisetzungsprofils ermöglichte. Dies wurde durch die Verwendung eines verzögert/verlangsamt freisetzenden Polymeres HPMCAS, für die Einbettung von LPV und die Beibehaltung des schnelllöslichen Polymeres PVPVA für RTV realisiert. Darüber hinaus konnte die Auswahl der HPMCAS-Qualität, welche sich unter anderem durch den pH-Wert abhängigen Auflösungsbeginn unterscheidet, als Schlüsselfaktor angesehen werden. Der somit variable Auflösungsbeginn des LPVs, gesteuert über die entsprechende HPMCAS-Qualität, beeinflusste unmittelbar das Ausmaß der Übersättigung von RTV, wohingegen die finale Übersättigung des LPVs unbeeinflusst blieb.

Um die beiden durchgeführten Studien final verbinden zu können, wurde in einer dritten Studie die Eignung von ODTs als Formulierungsplattform für amorphe feste Dispersionen untersucht. Die jeweiligen Dispersionen für RTV und LPV wurden gemahlen, gesiebt und mit einem koprozessierten Hilfsstoff vermengt und anschließend tablettiert. Hierbei zeigte sich, dass die Auswahl des Hilfsstoffes, des Polymers, als auch die verwendete Partikelgrößenfraktion der Dispersion von größter Bedeutung für die Qualität der ODTs war. In Abhängigkeit dieser Schlüsselparameter konnten erfolgreich ODTs mit einer maximalen Beladung der Dispersion von bis zu 75 % für LPV-Dispersionen und 50 % für RTV-Dispersionen hergestellt werden.

Im Rahmen dieser Arbeit wurde ein Entwicklungskonzept für eine kindgerechte Darreichungsform für zwei schwerlösliche Wirkstoffe vorgestellt und ein neuer, vielversprechender Kombinationsansatz beschrieben. Die Trennung der beiden Freisetzungsstartpunkte der Wirkstoffe durch unterschiedliche Polymere, ermöglichte die

Anpassung und Verbesserung beider Freisetzungsprofile. Darüber hinaus konnte zum ersten Mal erfolgreich gezeigt werden, dass amorphe feste Dispersionen von RTV und LPV anschließend zu gut funktionierenden ODTs weiterverarbeitet werden konnten. Darüber hinaus kann die umfangreiche Vergleichsstudie der koprozessierten Hilfsstoffe, als Anhalts- sowie Startpunkt für eine Vielzahl von weiteren Untersuchungen im Rahmen der Formulierungsentwicklung von ODTs dienen.

List of original publications

1. Marcel Kokott, Ard Lura, Jörg Breitkreutz, Raphael Wiedey
   Evaluation of two novel co-processed excipients for direct compression of orodispersible tablets and mini tablets
   Eur. J. Pharm. Biopharm. **2021**, 168, 122-130.

2. Ard Lura, Valentine Elezaj, Marcel Kokott, Björn Fischer, Jörg Breitkreutz
   Transfer and scale-up of the manufacturing of orodispersible mini-tablets from a compaction simulator to an industrial rotary tablet press
   Int. J. Pharm. **2021**, 602, 120636.

3. Raphael Wiedey, Marcel Kokott, Jörg Breitkreutz
   Orodispersible tablets for pediatric drug delivery: current challenges and recent advances
   Expert. Opin. Drug. Deliv. **2021**, 18, 12.

4. Tobias P. Holm, Marcel Kokott, Matthias M. Knopp, Ben J. Boyd, Ragna Berthelsen, Julian Quodbach, Korbinian Löbmann
   Development of a multiparticulate drug delivery system for in situ amorphization
   Eur. J. Pharm. Biopharm. **2022**, 180, 170-180.

5. Marcel Kokott, Stefan Klinken, Jörg Breitkreutz, Raphael Wiedey
   Downstream processing of amorphous solid dispersions into orodispersible tablets
   Int. J. Pharm. **2023**, 631,122493.

6. Marcel Kokott, Jörg Breitkreutz, Raphael Wiedey
   The interplay of poorly soluble drugs in dissolution from amorphous solid dispersions
   Int. J. Pharm.: X **2024**, 7, 100243

Contributions to meetings

Oral presentations

Challenges in downstream processing of orodispersible tablets containing ASDs; Pharmaceutical Solid State Research Cluster (PSSRC) Annual Symposium, 2022, Helsinki

Poster presentations

1. Marcel Kokott, Raphael Wiedey, Jörg Breitkreutz
   Evaluation of co-processed excipients for direct compression of low dosed orodispersible mini-tablets
   13th Meeting of the European Paediatric Formulation Initiative, 2020, online

2. Marcel Kokott, Ard Lura, Raphael Wiedey, Jörg Breitkreutz
   Granfiller-D® as new co-processed excipient for orally disintegrating tablets produced by direct compression
   12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2021, online

3. Marcel Kokott, Raphael Wiedey, Jörg Breitkreutz
   The interplay of two poorly soluble APIs in ASD combination products
   13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2022, Rotterdam

4. Marcel Kokott, Stefan Klinken, Raphael Wiedey, Jörg Breitkreutz
   Orodispersible tablets as promising alternative for pediatric HIV combination therapy
   14th Meeting of the European Paediatric Formulation Initiative, 2022, Rome

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Eidesstattliche Versicherung

Ich versichere an Eides Statt, dass die vorliegende Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität in Düsseldorf“ verfasst worden ist.

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Marcel Kokott