Novel Technologies Enabling Flexible Drug Dosing of Enalapril Maleate and Hydrochlorothiazide For Paediatric Use

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-The world breaks everyone and afterward many are strong at the broken places.-

Ernest Hemingway

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List of Abbreviations

ADA	Advanced drop shape analysis
API	Active pharmaceutical ingredient
BATA	Brief access taste aversion
BCS	Biopharmaceutics classification system
CHMP	Committee for Medicinal Products for Human Use
CH	Charrière
CI	Confidence interval
CPP	Critical process parameter
CQA	Critical quality attribute
CYP	Cytochrome P
DPI	Dots per inch
EDQM	European Directorate for the Quality of Medicines
EM	Enalapril maleate
EMA	European Medicines Agency
EU	European Union
EuPFI	European Paediatric Formulation Initiative
ExM	Extensive metaboliser
FCR	False colour representation
FDA	Food and Drug Administration
FDC	Fixed-dose combination
GC	Gas chromatography
HCT	Hydrochlorothiazide
HIV	Human immunodeficiency virus
HME	Hot melt extrusion
HPC	Hydroxypropylcellulose
HPLC	High performance liquid chromatography

HPMC	Hydroxypropylmethylcellulose
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
JS	Jetting station
LADME	Liberation, absorption, distribution, metabolism and excretion
LENA	Labelling Enalapril from Neonates to Adolescents
NGT	Nasogastric tube
NIH	National Institute of Health
ODF	Orodispersible film
ODMT	Orodispersible mini-tablet
ORL	Oral lyophilisates
PAT	Process analytical technology
PCAST	President's Council of Advisers on Science and Technology
PDCO	Paediatric Committee
PDE	Permitted daily exposure
PEG	Polyethylene glycol
PeM	Personalised medicine
PG	Propylene glycol
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PM	Poor metaboliser
PP	Polypropylene
PSP	Paediatric study plan
PUMA	Paediatric-use marketing authorisations
PUR	Polyurethane
PVA	Polyvinyl alcohol
PVC	Polyvinyl chloride
QTPP	Quality target product profile
RH	Relative humidity

RSD	Relative standard deviation
SD	Standard deviation
SEM	Scanning electron microscopy
STEP	Safety and toxicity of excipients for paediatrics
UM	Ultra-rapid metaboliser
US	United States
WFT	Wet film thickness
WHO	World Health Organisation

Chapter I – Introduction

1. Personalised Medicine

1.1. Definition and Development

Since the industrial production of solid drug dosage forms has been developed, the medical treatment of patients has changed fundamentally. Tablets could be produced at a large scale and thousands of patients could be treated with one batch. This approach is based on the idea that a patient group gets one diagnosis and the illness can be treated with the same active pharmaceutical ingredient (API) for the entire patient group. This kind of therapy was practised for a long time and at the beginning of the 21st century, two-thirds of all dosage forms have been solid and about half of these have been tablets [1]. Especially adults were seen as one large patient group providing the same requirements for the treatment of a disease. In the past years, medical and biomolecular research made great progress [2, 3] and it was discovered that not all patients with the same disease should receive the same medical treatment. Huge differences in patient reactions on several APIs were discovered. Due to different genetic conditions, enzymatic activity or simply due to the patients' age and state of physical development, one patient may need a higher or lower dose of an API. Some patients even do not respond at all to the specified API treatment (Figure 1).

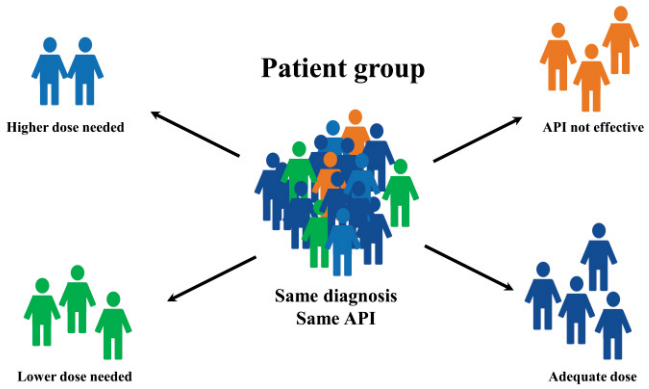

Figure 1: Schematic depiction separating a patient population into smaller sub-groups with special needs requiring a different treatment.

These discoveries led to the idea of personalised medicine (PeM), often also called individualised medicine [4, 5]. This approach was mainly characterised by the development of methods, which can analyse complex DNA sequences and determine the enzymatic expression of the individuals. Initially, the term "personalised medicine" referred only to the gene-based health care provision for a long time [6]. Many definitions related to the pharmacogenomics are available in literature [3, 7]. Ginsburg et al. defined personalised medicine as "the use of marker- assisted diagnosis and targeted therapies derived from an

individual's molecular profile" [8]. Jain et al. described personalised medicine as the "prescription of specific therapeutics best suited for an individual based on pharmacogenetics and pharmacogenomc information" [9]. These definitions do not cover all the cases of personalised medicine and literature reported about inconsistent definitions for the term and criticised the lack of a distinct definition to prevent confusion and misunderstandings [5, 10-12]. More general definitions were published like Abrahams et al. who described the term as an "extension of traditional approaches to understanding and treating disease, but with greater precision" [13]. Based on this paper, the term "precision medicine" has been introduced. The President's Council of Advisers on Science and Technology (PCAST) defined personalised medicine as the tailoring of medical treatment to the individual characteristics of each patient [14] and the European Commission defined PeM as "a medical model that aims to provide tailor-made prevention and treatment strategies for defined groups of individuals" [15]. This development indicates a distinct shift and a clear extension of the term of PeM, which does not only refer to the pharmacogenomics and pharmacogenetics any more, but is extended to a larger, not further defined patient collective. Nevertheless, the term "personalised medicine" is still not clearly specified and the National Institute of Health (NIH) of the United States indicated that the term could lead to the assumption medicine has to be designed for each patient, which is not true. Instead, the patient population should be divided in several subpopulations regarding their genetic constitution or stage of physical development [16]. Therefore, some experts call it "stratified medicine" instead [17, 18].

Beginning at the time point of birth, children are the first patient population, which have to be separated into sub-populations because they cannot be seen as small adults [19]. Growing older, response to the API is determined by both genetic polymorphisms and enzymatic constitution as of the adults [8]. In further development, people often gain co-morbidities leading to co-medications and polypharmacy, which both may influence the absorption, metabolism or excretion of a drug and therefore need individualised treatment, considering all these co-factors [20]. In literature, PeM is described as new paradigm and according to Terkola et al. PeM has "the potential to allow patients to receive drugs specific to their individual disease and to increase the efficiency of the healthcare system" [5]. Despite it is seen that the field of PeM is rapidly expanding [2] and the shift from reactive treatments to proactive, preventive healthcare management could be evaluated as beneficial [7, 12, 21], the economic advantages of the implementation of PeM in healthcare systems are disputable and not proven until now [21, 22]. Overall, the interest in PeM still lasts. Abrahams et al. [13] claimed 7 promises of PeM:

- shift in medicine from reaction to prevention,
- selection of optimal therapies,
- avoidance of adverse drug reactions,
- increase of patient compliance to treatment,
- reduction of time, cost and failure rate of clinical trials,
- revival of drugs failing in clinical trials
- reduction of the cost of health care.

Therefore, PeM is still a promising model for improving the medical care for special patient populations.

In the following sections, the three patient populations (adult population divided in subpopulations according to their genetic equipment and the paediatric as well as the geriatric population) are shortly described and the differences to "normal" adults are highlighted.

1.2. Impact of Pharmacogenomics and Pharmacogenetics on Drug Treatment

In the past 50 years, it was discovered that there is an inter-individual variability in drug response, mainly caused by genetic polymorphisms resulting in variable expression of drug metabolizing enzymes and drug transporters or targets [23]. This resulted in the field of pharmacogenetics and pharmacogenomics. Nebert defined pharmacogenetics as the "study of variability in drug response due to heredity" whereas pharmacogenomics were described as "the field of new drug development based on our rapidly increasing knowledge of all genes in the human genome" [24]. Both fields deal with the different inter-individual genetic equipment and their effects on drug response and the occurrence of adverse drug reactions. The terms are mainly characterised by the development of genetic analysis in the recent years. Pharmacogenomics deal with the genetic variation on drug response in patients by correlating gene expression with a drug's efficacy [25]. This could comprise a pharmacodiagnostic profiling for targeted medicine or the analysis of expressions of drug metabolizing enzymes. It was found that special enzymes, which are responsible for many drug metabolisms are variable expressed in the population. Depending on the amount of active enzymes, different metabolisers were defined. Patients are categorised as poor metaboliser (PM), extensive metaboliser (ExM, "normal" metaboliser) and ultra-rapid metaboliser (UM) [26]. Figure 3 displays plasma concentration curves of the different types of metabolisers. The black line represents an extensive metaboliser, whose enzymatic expression of the metabolising enzyme is "normal". This leads to a concentration curve within the therapeutic window. The green line displays a concentration curve of a patient, whose metabolising enzyme is highly expressed. The API is metabolised faster because more enzymes are available to transform the API molecules. A therapeutic concentration cannot be achieved and no therapeutic effect would occur. The patient characterized as ultra-rapid metaboliser would need a higher API dose to receive therapeutic effects. The orange line represents a patient with poor metabolising capacities, whose metabolising enzyme is rarely expressed. The API needs longer to be processed leading to a higher plasma concentration. The higher API concentration exceeds the therapeutic window resulting in potentially toxic API levels within the body. Lower doses of the API are necessary to prevent adverse drug reactions.

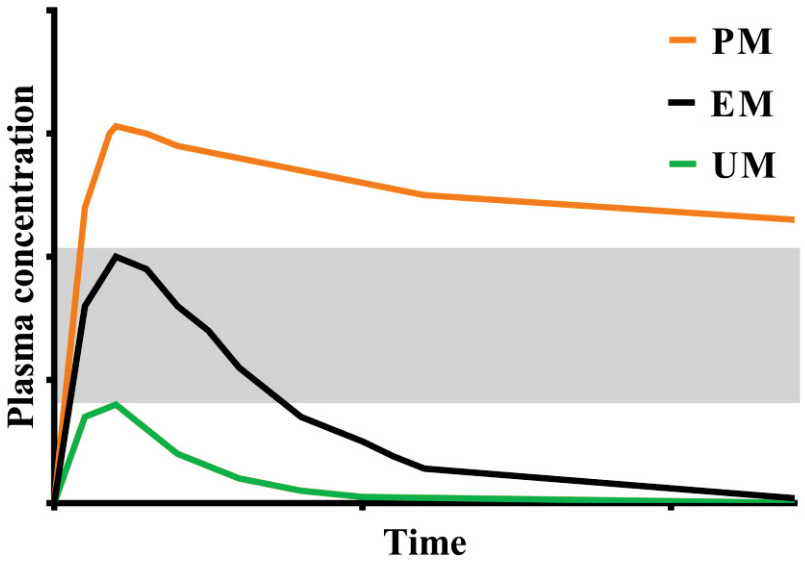

Figure 8: Schematic view of plasma concentration curves after oral administration of a model drug displaying the differences between poor metabolisers (PM), extensive metabolisers (ExM) and ultra-rapid metabolisers (UM). Grey area marks the therapeutic window.

One prominent example of different metabolisers is the pharmacotherapy with the anticoagulant warfarin, which is processed by cytochrome P (CYP) 2C9, an enzyme belonging to the cytochrome P450 family, which plays an essential role in drug metabolism [27]. A correlation between a poor expression of CYP2C9 and the higher incidence of adverse drug reaction could be shown caused by a higher warfarin plasma concentration. In comparison to higher expressions of CYP2C9, the relationship could be confirmed, leading to lower warfarin concentrations than therapeutically indicated. Another prominent example is the prodrug tamoxifen, which is indicated for the prevention and treatment of steroid hormone receptor-positive breast cancer [28]. As a prodrug, tamoxifen has to be activated by CYP2D6 enzymes to their active metabolites 4-hydroxytamoxifen and endoxifen, which provides a significant higher affinity to the oestrogen receptor and is therefore more effective in inhibiting cell proliferation. Variations in the expression of CYP2D6 can lead to an ineffective pharmacotherapy. PM will not be able to activate tamoxifen leading to a higher plasma concentration of tamoxifen and a lower concentration of the active metabolites. Brauch et al. stated that with the help of personalised medicine, utilizing genotyping assays can improve the cancer therapy with tamoxifen [29].

These two examples should only exemplarily show the potential advantages of the growing field of pharmacogenomics and -genetics in personalised medicine. Phillips et al. claimed that a drug therapy tailored to the individual's genetic make-up could generally result in a clinically relevant reduction of adverse drug effects [30]. Determining the variations of genetic enzymatic expression results in the need of variable drug dosing tailored to the metabolic capacity of the individual patient. Pharmacogenomics and related topics are not only challenging for the health care system and the medical treatment of the patients, but

also demand changes in the development of pharmaceutical formulations taking into account that patient groups need various amounts of the API.

1.3. Paediatric population

The medical treatment of the paediatric population is very challenging. Paediatric patients are no small adults and may sometimes not be treated with the same APIs and are usually medicated with lower doses. From birth to adolescence, the physical state of the body passes many changes [31]. Several physiological characteristics in children can alter drug absorption.

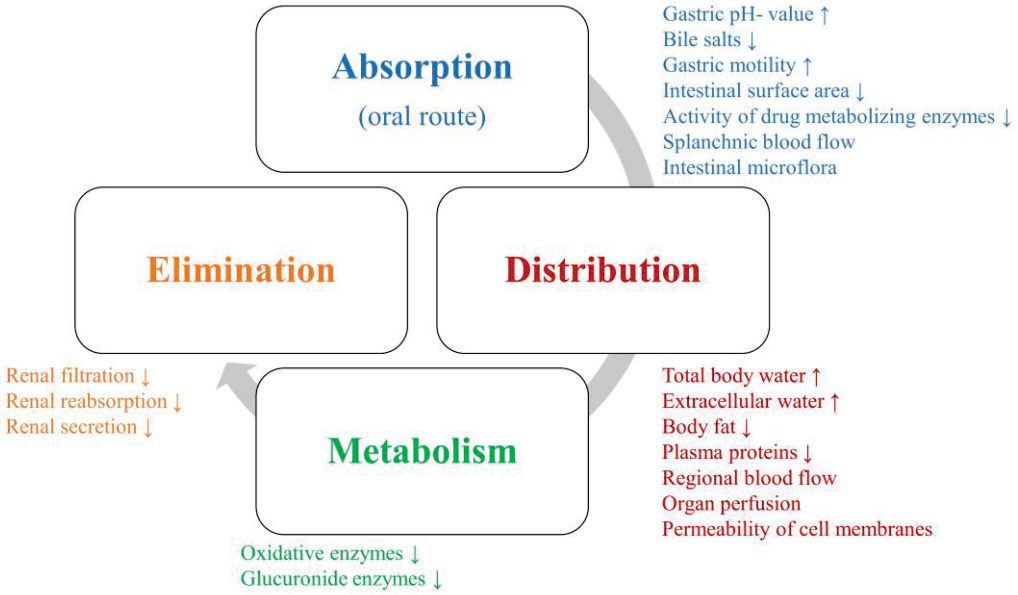

Figure 2: Paediatric drug disposition: Impact factors of a drug administration via the oral route. Influence factors displayed in comparison to the young adult population (↓↑). Figure modified from Kearns et al. [32].

There are several routes of drug administration to the paediatric population. Apart from the oral route, the percutaneous, intramuscular and inhalative routes are named as examples. Whereas several products are available and investigated for adults [33-35], the percutaneous route of administration is not very well explored for the paediatric population. Due to the different body surface /body mass ratio and the altering composition of the skin layers [36], a therapeutic and safe administration via the skin is challenging. The intramuscular application of drugs also varies in children from the adult patients due to a reduced skeletal- muscle blood flow, which may reduce the absorbance rate [32]. Furthermore, the infant lung develops more alveoli until adulthood [37]. This leads in an increasing surface area in the lung, which influences the inhalative uptake of drugs. Regarding the oral route of administration, the physiological differences within the gastrointestinal tract highly influence the drug absorption (Figure 2). The gastric pH value in neonates and infants is higher than the pH of the adult population. Varying gastric pH

values may influence the solubility of drug substances (especially the ionization of the APIs) and therefore can alter the intestinal absorbance [31]. The reduced secretion of bile salts may influence the absorption in dependency of the lipophilic properties of the API. Furthermore, the increased motility of the stomach and intestine in addition with the smaller intestinal surface area in comparison to adult patients may lead to a reduced exposure time of the drug and change the amount of absorbed API. Other points to consider are the reduced activity of metabolizing enzymes (e.g. hydrolases and peroxidases), the altering splanchnic blood flow and the evolving intestinal microflora [32]. The paediatric drug disposition is also dependent on the drug distribution, which can significantly differ from the one in the adult population. It is dependent on the size of body water in comparison with the adipose compartment and the degree of plasma protein bindings [38]. The distribution is further altering with varying regional blood flow or organ perfusion. These changes during development may result in different API doses per kg body weight to calculate therapeutic doses. Furthermore, their enzymatic condition differs from the ones in adults, which leads to variations in metabolic capacities of chemical drug substances (e.g. expression of cytochrome P 450 enzymes, which play an important role in drug metabolism) [39]. The early paediatric drug elimination is characterised by a reduced glomerular filtration rate and renal reabsorption leading to a reduced excretion of several APIs. The body may be longer exposed to the drug substance.

Beside these organic and enzymatic developments during childhood, physical abilities also play a very important role. During the first months after birth, children cannot swallow intentionally [40]. New-borns are not able to coordinate sucking, swallowing and breathing, whereas older children show better coordination skills [41]. Moreover, medicine often has a bitter taste. As children are more sensitive to bitter substances and have less understanding of medical related topics, this often results in a bad patient compliance [42, 43]. An investigation with schoolchildren (7-14 years) revealed that the understanding of medical topics is low and that children have a general negative attitude towards medicines [44]. Therefore, the oral application of a drug preparation is often very difficult. These additional challenges lead to difficulties in developing paediatric medicines. The lack of age-appropriate dosage forms and medicinal products, which is mainly caused by ethical concerns regarding clinical studies in children, was also recognized by the competent authorities leading to a few programs aiming to increase the number of age-appropriate medicine for children [45]. The EMA states in the guideline "clinical investigation of medicinal products in the paediatric population" [46], that one main goal is the obtaining of knowledge of the effects of medicinal products in the paediatric patients. They suggest the partition of this patient groups in several sub-groups according to their age considering the different states of physical development: preterm, newborn (0-27 days), infants/toddlers (28 days – 23 month), children (2-11 years) and adolescents (12-16/18 years). Whereas e.g. the renal and hepatic clearance mechanisms are immature in premature infants, the renal clearance of infants/toddlers often exceed the one of the adults.

The legal efforts and new regulatory frameworks underline the importance in developing new medicines for children. Therefore, the present thesis focuses on the development of

paediatric formulations, which provide the potential of individual dosing also for the other subpopulations.

Recent advances in paediatric drug development are provided in Chapter II. The impact of the EU regulation on the field of cardiovascular drugs is described in Chapter III.

1.4. Geriatric population

The geriatric population is an extremely heterogeneous population. With increasing age, a number of physical changes occur. Furthermore, co-morbidities lead to co-medication and polypharmacy and the medication management of elderly people becomes challenging due to potential drug interactions and adverse drug reactions caused thereby [47]. Age-dependent physiological changes may affect the drug absorption, distribution, metabolism and excretion of the active drug substance (Figure 4). Stegemann et al. described the geriatric patient and the challenges associated with the physiological, cognitive and further age-related changes [20]. In contrast to the paediatric population, age is not a good factor to distinguish into sub-populations for personalised medicine.

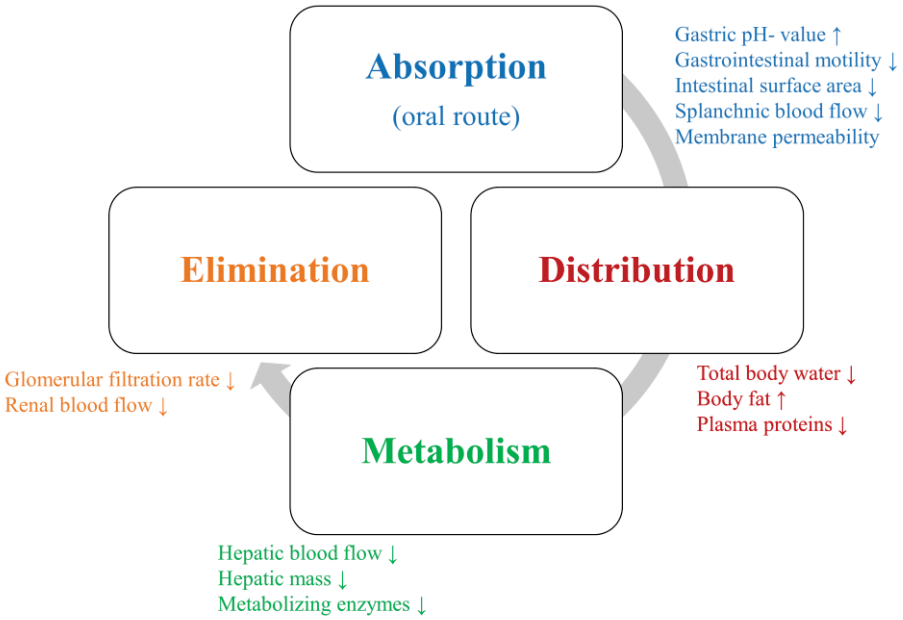

Figure 4: Geriatric drug disposition: Impact factors of an administration via the oral route. Influence factors displayed in comparison to the young adult population (↓↑). Figure modified from Klotz et al. [48].

Klotz et al. described the physiological changes caused by ageing processes [48]. Elderly patients exhibit higher gastric pH values, which may influence the drug absorbance and alter the bioavailability of certain drugs. Furthermore, changing membrane permeability reduced splanchnic blood flow and reduced gastrointestinal motility may affect the drug absorbance capacity. The drug distribution may alter in dependency of the lipophilic characteristics of the API because the total body water is reduced and the body fat content increased. Less plasma proteins are available resulting in changing distributions of APIs

with high plasma protein bindings [20]. The metabolism of active drug substances may be influenced by the reduced hepatic mass and blood flow. A decline of various hepatic metabolizing enzymes was observed resulting in a reduced hepatic clearance of some APIs [49]. Furthermore, the renal function changes by a decrease of the glomerular filtration rate. This can affect the elimination of APIs because the kidney provides an essential function in drug excretion. Physiological changes may also affect essential functions for drug handling or administration of medicine. The age-related decrease of visual functions [50] can affect the ability to identify the correct medicine and less strength and finger force can make a dosage form manipulation (like tablet splitting) difficult [51]. The decline of coordination skills (e.g. dexterity or swallowing processes) may lead in a reduced compliance of the patient. On top of physiological, cognitive and coordinative changes, the geriatric population is also affected by the genomic expression and genetic equipment (1.2.), which turns this special patient population a huge challenge with regard to personalised medicine. This was also recognised by the competent authorities resulting in an ICH guideline on studies in support of special populations: geriatrics [52].

2. Pharmaceutical Drug Development for Personalised Medicine

2.1. General aspects

One mail goal of personalised medicine is to obtain an effective plasma concentration of an API for the specified disease within the therapeutic window, excluding ineffective (too low) or toxic (too high) concentration levels for the individual patient. The effective concentration of the API is varying in the particular patient groups (e.g. children, adults with varying enzymatic expression, "normal" adults and geriatric patients). Parameters that influence the plasma concentration are described by the Liberation, Absorption, Distribution, Metabolism and Excretion (LADME) model. As described in the previous section, absorption, distribution, metabolism and excretion are highly dependent on the physical state and the genetic and enzymatic constitution of the patient. The pharmaceutical formulation development can intervene in the liberation of the API the location of drug release. Liberation can either be controlled by the route of administration (oral, parenteral) or via the dissolution profile of a drug (conventional-, delayed-, modified, prolonged- or pulsatile-release) [53]. Moreover, the pharmaceutical formulation development can consider particular physical characteristics of the patient groups, e.g. their ability to swallow dosage forms and the situation of their cognitive functions. Developing the right dosage form for the right patient population with the right characteristics and dose is of crucial importance for realising the concept of personalised medicine. This can also be observed in literature, where the term of personalised medicine has been extended to the field of pharmaceutical formulation development [54-57].

2.2. Dosage forms

2.2.1. Potential dosage forms for personalised medicine

For the choice of the best suitable dosage form, several factors have to be considered. A high variability of dosing should be enabled with ideally one drug preparation to cover the needs of all patients. Furthermore, special needs dependent on the patient population to be treated should be taken into account. Mental state or physical development of the patient and the effects on the compliance (e.g. refusal to take dosage form because of the taste or lack of understanding), swallowing difficulties (geriatric and paediatric patients) and special requirements on the dosage forms derived by the kind of illness are important points to consider. This could e.g. relate to immediate release dosage forms for the treatment of sunburst pain of cancer patients [56] or the treatment of nausea of migraine patients [58]. Hereafter, the oral route of administration should be focussed due to the fact, that it is the main and preferred route of applying medicine [59-61]. Wening et al. described potential dosage forms, which could be considered for personalised medicine (Figure 5) and suitable dosing devices for delivering the individual dose to ensure proper and safe drug administration to the patient [54]. The dosage forms were divided into two groups, one group where the dosing is achieved by accumulation of multiple API carriers and the second group where the dosage form has to be partitioned into the desired size.

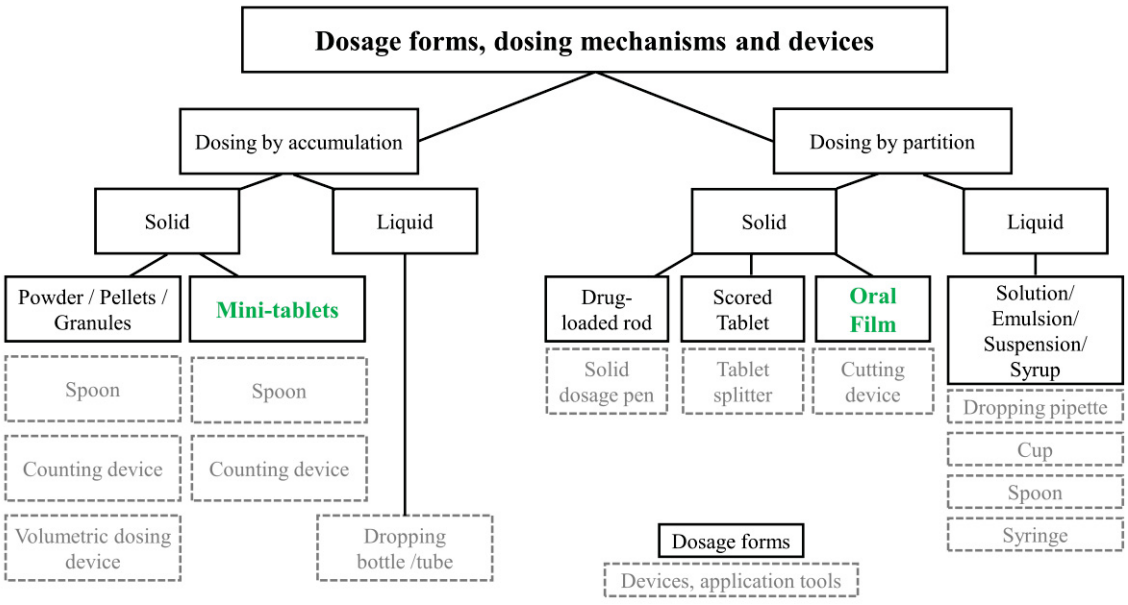

Figure 5: General classification of oral dosage forms and dosing approaches for individualized therapy modified from Wening et al [54]. The dosage forms used in the present studies are highlighted in green.

Both groups can be classified into solid and liquid formulations, which should be shortly described subsequently.

2.2.2. Liquid dosage forms and related devices

Liquid dosage forms comprise solutions, drug emulsions and suspensions, which all provide the advantage of flexible dosing utilizing a suitable dosing device. Depending on the viscosity of the liquid dosage form, common dosing devices are dropping pipettes, cups, spoons and syringes. For an accurate dosing, a homogenous distribution of the API within the liquid formulation is indispensable. Regarding solutions and syrups, the solubility of the API is the limiting factor. Emulsions and suspension are heterogeneous systems that are more complex and consist of at least two phases. A homogenous API distribution within suspensions is dependent on e.g. the viscosity of the liquid phase, the particle size distribution, difference in density between the phases and the characteristics of the sediment. An accurate dosing is here more difficult and patients and parents have to be trained how to apply the dosage form correctly. Another huge compliance issue for liquid formulations is the limited ability to mask a bad taste. Often, sweeteners or flavours are added which are limited in their taste masking properties. Furthermore, the dosing accuracy is dependent on the dosing device. Droppers were found to be very challenging to handle for caregivers. Depending on the angle of the dropper, the amount of applied dose highly varies [62]. Hermanns-Clausen et al. reported about severe events after dosing codeine with a dropper and stated that droplets might have a weight variability about 90 % [63]. Measuring spoons were tested utilizing different antibiotic suspensions [64]. The lower the height of the spoon and with increasing base area, the higher is the failure by measuring the dose. Syringes were stated as the most precise measuring device. Beside the difficulties in dosing and the limitations in taste masking opportunities, liquid formulations are often not suitable for APIs, which are sensitive to hydrolysis and are unstable in aqueous formulations. Furthermore, the microbiological stability is often an issue as well and there are only limited data on preserving agents for the paediatric population [65], which is a large patient group for application of liquid dosage forms. Still, oral drug solutions are widely used in paediatric. In geriatric patients, the use of solid oral preparations is dominant.

2.2.3. Solid dosage forms and related devices

Powder, pellets, granules and mini-tablets can be utilized as solid dosage forms to obtain flexible drug dosing by accumulation of the multipaticulates. Powder, pellets and granules are often filled into capsules at the accumulated, desired dose. They normally reveal a medium to high uniformity and often require technically demanding production processes [62]. Mini-tablets and orodispersible mini-tablets (ODMTs) are a relatively new dosage forms, which gained more and more interest recently in the paediatric population [66]. They combine the advantage of easy manufacturing (optimally by direct compression) and precise dosing opportunities with the advantages of multiparticulates (e.g. dosing flexibility) [67]. In line with two review articles, they are further described in detail in Chapters II and III.

Wening et al. [50] described drug-loaded rods, scored tablets and oral films as the dosage forms of highest potential for personalised medicine, enabling flexible dosing by partition of the dosage forms. Whereas scored tablets reveal only a limited flexibility in dosing, orodispersible films (ODFs) can be cut into various sizes providing higher flexibility. Furthermore, tablet splitting is a procedure demanding a certain dexterity of the patient. This dosage form manipulation can also easily lead to unprecise dosing [68-70]. However, ODFs were introduced as monolithic dosage forms for the paediatric and geriatric population [55, 71-73], but still providing the capability of very flexible dosing, which makes them a dosage form with high potential for personalised medicine in future. In line with two review articles, ODFs and their characteristics are described in detail in Chapters II and III.

Recently, new manufacturing processes were transferred from other industry branches to the pharmaceutical applications enabling flexible drug dosing. Three-dimensional [74] as well as two-dimensional printing [75] have been introduced as potential tools for producing individualised medicine [76]. Three-dimensional printing of various tablets providing modified release characteristics was proven to be feasible [77, 78]. Not only academical research gained interest in three-dimensional printing processes. The industry proved the feasibility of producing a 3D-printed product in an industrial-scale and the United States Food and Drug Administration (FDA) recently approved the printed drug product [79]. However, the 3D printed product (Aprecia®) does not provide features for PeM. Whereas the potential of individual dosing and flexibility in producing modified release kinetics for the drug product is high, 3D printing often offers only a low throughput. Regarding two-dimensional printing, several printing techniques are applicable. Flexographic and ink-jet printing have been performed onto edible substrates including ODFs [80, 81]. The printing process was only conducted by stand-alone inkjet printers, which do not operate in a continuous way. Therefore, a scale-up to industrial scale is challenging to achieve and was discussed in literature by utilizing numerous print heads or a print head providing more nozzles [76]. Another way to scale-up ink-jet printing to an industrial scale is the implementation of a jetting print head into a continuous manufacturing process of orodispersible film preparations. The potential of two-dimensional printing implemented in a continuous production process resulting in a pharmaceutical dosage form is further discussed in two research articles in Chapters VII and VIII.

In the following thesis, ODMTs and ODFs should be investigated as both solid technology platforms providing the advantage of flexible and personalised drug dosing. Furthermore, the ink-jet printing technology should be closer examined as potential tool for optimizing the dosing flexibility and production process of ODFs.

2.3. Fixed-dose combinations

Personalised medicine often concerns patient populations with co-morbidities needing more medications e.g. the geriatric population. This often leads to polymedication. Kaufmann et

al. described in his survey in the United States (US) that 23 % of women, aged > 65 years took at least 5 prescription drugs and 12 % of them took even more than 10 medications [82]. Fialová et al. reported in their survey about the potentially inappropriate medication use in the European geriatric population: 51 % of the investigated population took more than 6 drugs and 19.8 % took at least one potentially inappropriate medication [83]. The high number of medication taken per day can lead to a reduced compliance of the patients, which can potentially be negotiated utilizing fixed-dose combinations (FDCs). Furthermore, some illnesses require the treatment with multiple APIs to achieve a successful recovery. The model list of essential medicine of the World Health Organisation (WHO) lists some fixed-dose combinations in particular for bacterial (e.g. amoxicillin and clavulanic acid) and viral infections (e.g. lopinavir and ritonavir). Especially the treatment of antituberculosis medicine requires fixed-dose combinations and a recommendation is given to develop new tuberculostatic FDCs [84]. FDCs can therefore be used either to increase patient compliance or to improve the response in comparison to a monotherapy. They have been investigated for diabetic patients [85], hypertensive patients [86] and patients infected with the human immunodeficiency virus (HIV) [87]. Even "polypills" containing various APIs have been tested. Malekzadeh et al. introduced a dosage form containing aspirin, enalapril, atorvastatin and hydrochlorothiazide as an all-round package for cardiovascular diseases. Despite a reduction of blood pressure and lipids was observed, the effects were less than expected [88]. In terms of personalised medicine, a "polypill" is disputable. Nevertheless, fixed-dose combinations consisting of two APIs can be advantageous by increasing the patient compliance and the response or safety of the therapy [89, 90]. Due to the lack of age-appropriate formulation and ethical concerns regarding clinical studies in children, fixed-dose combinations are rarely used in the paediatric population. Nevertheless, they could also provide advantages for this patient group, in particular regarding the treatment of HIV and tuberculosis, but also in the field of cardiovascular drugs where a product with fixed-dose combination of bisoprolol and hydrochlorothiazide has been tested for elevated blood pressure in children [91].

The following thesis investigates whether fixed-dose combinations containing the ACE inhibitor enalapril maleate (EM) and the diuretic hydrochlorothiazide (HCT) can be produced as a dosage form enabling dosing flexibility and the treatment of all patients from paediatric to geriatric sub-populations. Furthermore, the FDC should be produced in a continuous manufacturing approach adapted to industrial production offering the opportunity to produce large batches and simultaneously preserve the potential of dose individualisation. The choice of the APIs has been made after a thorough analysis of published information on PIP procedures (Chapter III). Whereas EM is under development by three PIP holders (Pharmathen, Poveca and Ethicare), there is neither a filed PIP for HCT nor for the fixed-dose combination of EM and HCT.

Nevertheless, both APIs are listed on the WHO model list of essential medicines for children's [92]. Whereas EM is listed as tablet with dose strength of 2.5 and 5 mg, the registered HCT tablets provide a content of 25 mg HCT. Both APIs are indicated for chronic heart failure from the day of birth to adolescence and dosed 1mg/kg weight/day

(HCT) and 0.5mg/kg body weight/day (target dose for EM) [93]. The medical treatment of these substances is divided in a titration phase, where the dose is slowly increased, and the maintenance therapy. This dosing scheme necessitates a flexible, personalised dosing for all paediatric age groups. Until now, there is no product commercially available, fulfilling these needs and requirements.

3. Aims of the thesis

The field of personalised medicine has gained increasing attention in the past years. In particular, special patient populations like paediatric patients need new dosage forms to enable individual and precise dosing. The EMA responded to these needs by implementing Paediatric Investigation Plans (PIPs) for new medicines aiming for marketing authorization. The aim of this thesis was to investigate new solid dosage forms with regard to the potential of industrial production of personalised medicines with a focus on the applicability for the paediatric population. Especially orodispersible films should be developed in a small industry adapted scale and evaluated concerning their characteristics.

More specific aims of the presented investigations were:

- To generate a current overview over the current state of research and the novel changes in formulating paediatric medicines (Chapter II).

- To analyse all published information on PIP procedures with cardiovascular drugs in order to rationally identify and select appropriate drugs and their fixed-dose combinations for personalised medicines (Chapter III).

- To develop a flexible administration regimen of previously developed enalapril maleate orodispersible minitablets in line with a Paediatric Investigation Plan and evaluate their applicability with beverages or via nasogastric tubes (Chapter IV).

- To develop a continuous manufacturing process for ODFs and scaling it up to an industrial manufacturing scale (Chapter V).

- To develop continuous ODF production processes for fixed-dose combinations enabling flexible dosing for personalised medicine (Chapter VI)

- To implement the ink-jet printing technology into the continuous production process of ODFs (Chapter VII).

- To develop a continuous ODF manufacturing process with incorporated inkjet printing technology for production of fixed-dose combinations and subsequently evaluate the production techniques (Chapter VIII).

4. Outline of the thesis

An overview over the current state of research in paediatric formulation development is presented in the second chapter of this thesis in the form of an invited review article. The potential administration pathways as well as the applicable dosage forms are described. Further points to consider like the choice of pharmaceutical excipients, taste sensation and the acceptability of different dosage forms in children and their handling and administration are depicted. Furthermore, the future perspectives have been concluded.

The third chapter reveals a deeper insight into the current regulatory situation by analysing Paediatric Investigation Plans. The Paediatric Committee is introduced at the EMA and PIPs of the field of cardiovascular diseases are evaluated regarding their route of administration and dosage form. By means of these results, innovative platform technologies like multiparticulates and orodispersible dosage forms are described in detail. This invited review article offers an insight into regulatory plans to improve formulation development in children over the past 10 years. As cardiovascular diseases were found to be an important topic for the paediatric population, further publications were focused on cardiovascular drugs, in particular the selected APIs EM and HCT.

The development of paediatric medicine does not only include the pharmaceutical development of an age-appropriate formulation. The PIPs also comprise data of the acceptability of the dosage form and investigations concerning alternative ways of administration (e.g. the administration in combination with various beverages). Furthermore, the PIP has to cover all age groups from birth to adolescence. An adequate administration regimen – even for new-born is essential as well as the applicability of the dosage form via nasogastric tubes. Within the LENA development program, an EU funded project on the development of ODMTs containing EM, a novel methodology has been developed to enable more flexible drug dosing manipulating minitablets within an oral syringe to obtain doses of less than 0.03 mg EM in a reliable manner. These regulatory requirements are described and experiments conducted in line with a PIP of EM orodispersible minitablets, which have been developed in previous studies.

The following chapters focus on orodispersible films, another child-appropriate dosage form. They provide among the previous mentioned ODMTs the potential of personalised drug dosing. Nevertheless, most conducted experiments in literature only deal with small-scale batches and the production cannot be simply transferred to industrial scale. The aim of this research article is to transfer the production of HCT films from a small-scale approach to a continuous manufacturing process adapted for industrial production to enable flexible drug dosing.

Chapter VI depicts the development of a continuous manufacturing process of fixed-dose combination ODFs containing EM and HCT. A continuous production of fixed-dose ODFs is a promising approach for the manufacturing of personalised medicine in an industrial scale by cutting the FDC into variable sizes. Patient groups from paediatrics to geriatrics can be addressed.

Chapter VII deals with the implementation of an inkjet jetting station into a continuous ODF production process with the subsequent aim to prove the ability of ink-jet printing as potential tool for flexible, but continuous production of personalised medicines. In this chapter, the advantage of an increased dosing flexibility is utilized by transferring the inkjet printing technology from a small-scale inkjet printing system to a pilot-scale process. An inkjet print head is incorporated into the continuous manufacturing machine for orodispersible film preparations enabling a direct imprinting during continuous production. Optimal production settings are defined to subsequently transfer the process to an imprinting of ODFs with EM containing ink. As proof-of-concept, various printing concepts are realised.

Chapter VIII describes the development of an EM containing ink and the imprinting of a drug-free film during continuous production to obtain an ODF with flexible doses of EM. Furthermore, HCT films are imprinted with the developed ink to produce fixed-dose combinations. The FDC produced by inkjet printing are compared to the FDC obtained by the solvent casting method from Chapter VI. Both manufacturing techniques are evaluated and the resulting films characterized concerning their morphological and mechanical properties, their disintegration times, their content uniformity and residual solvents. Furthermore, the migration behaviour of the utilized APIs is analysed with confocal Raman microscopy. Subsequently, a recommendation for the production of fixed-dose combination ODFs is given.

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Chapter II – Advances in Paediatric Drug Formulations

Pretext

Formulation development for the paediatric population is a complex issue. Beside the lack of data concerning safety of dosage forms and their potential excipients, also an adequate taste of the dosage form and the administration to the young patients can be challenging. The subsequent review highlights the recent advances in paediatric formulation development focused on solid dosage forms, which provide a few advantages over liquid formulations. This paper creates an overview of the points to consider during formulation development and emphasises the regulatory aspects and the fields where further investigations are needed to ensure an adequate supply of medicine for the paediatric population.

Evaluation of the authorship

The following review paper has been written on invitation by the Journal of Clinical Pharmacology (impact factor 2016: 2.812) and is currently under review (submitted 2017). The first author Yasmin Thabet was mainly involved in design, data evaluation and writing of the manuscript. The second author Dr. Viviane Klingmann mainly worked on data evaluation and the chapter on acceptability studies. Prof. Dr. Jörg Breitkreutz as a senior author was responsible for the idea, the design, the writing and the revision of the manuscript according to the referees' comments.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Yasmin Thabet	20	30		40	30
Viviane Klingmann	0	10		40	20
Joerg Breitkreutz	80	60		20	50

Drug Formulations: Standards and Novel Strategies for Drug Administration in Pediatrics

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Abstract

Child-appropriate drug formulations are a prerequisite of successful drug therapy in children. Efficacy and safety must be given for the active pharmaceutical ingredient, but safety also for the used excipients, components of primary packaging materials, and devices. We are presently experiencing exciting times for pediatric drug development, stimulated by previous governmental incentives in both the European Union and the United States. The most important advances in pediatric drug formulation development are reviewed and evaluated in this article. Scientific publications and recent industry strategies indicate a clear shift from liquid dosage forms to novel solid dosage forms. Solid formulations are usually composed from excipients generally regarded as safe, whereas many liquid formulations contain excipients such as preservatives, antioxidants, or taste-masking agents that raise concerns. Further, some recent clinical studies on swallowability, acceptability, and preference indicate superiority for small-sized tablets, so-called mini-tablets, over conventional liquids .In general, multiparticulate solid dosage forms could partly replace the liquids and provide more stable and cheaper alternatives to existing drug products or new developments. Dispersible solid drug dosage forms like orodispersible tablets, mini-tablets and films are even better opportunities for efficient and safe use in pediatrics. Novel measuring and administration devices may facilitate the handling and drug administration of these modern drug dosage forms. Combination products (drug-device combinations) can easily be linked with new e-health technologies in near future to further improve pediatric drug therapy.

Chapter III – 10 years EU Regulation of Paediatric Medicine

Pretext

Since 2007, the European Medicines Agency (EMA) demands Paediatric Investigation Plans (PIPs) for new medicines, which should gain marketing authorization. They aim to ensure the child-appropriateness of drug dosage form and drug administration procedure through clinical studies in children and support the marketing authorization of a medicine for children. The PIP has to cover the needs of all age groups for children from birth to adolescence and only in exceptional cases, waivers are granted by the EMA. 10 years after the introduction of this regulatory requirement, trends are visible indicating that new paediatric dosage forms are needed. The following article analyses all available PIPs for cardiovascular diseases regarding their routes of administration and dosage forms. Newly introduced dosage forms for the paediatric population are discussed and the progress in research and development of the past 10 years is evaluated.

Evaluation of the authorship

The subsequent review has been written on invitation by the Expert Opinion on Drug Delivery (impact factor 2016: 5.567) and has been accepted in 2017. The first author Yasmin Thabet was responsible for the design, the data evaluation and the writing of the manuscript. The second author Dr. Marta Slavkova was involved in the design, evaluation and writing of the manuscript. Prof. Dr. Joerg Breitkreutz as senior author was responsible for idea, design, data evaluation, writing and review of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Yasmin Thabet	10	20		50	50
Marta Slavkova	10	20		10	10
Joerg Breitkreutz	80	60		40	40

10 years EU regulation of paediatric medicines – Impact on cardiovascular drug formulations

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Abstract:

Introduction: Child-appropriate drug formulations are mandatory for an efficient and safe drug therapy in children. Since the implementation of supportive legislations development of novel drug formulations has significantly been enforced despite the fact that children are a heterogeneous group of patients with varying needs according to age, maturation and disease.

Areas covered: In this review, recent advances and current strategies are evaluated how to overcome the specific hurdles in paediatric drug development. For cardiovascular diseases as an example, EMA's decisions on paediatric investigation plans (PIPs) have been evaluated. New developments with innovative platform technologies such as mini-tablets and orodispersible preparations have been identified indicating a clear shift from liquid preparations to small-sized solid (multiparticulate) or orodispersible dosage forms. Reasons for this shift of paradigm are discussed.

Expert opinion: Innovative platform technologies for solid drug dosage forms such as mini-tablets, orodispersible tablets or film preparations will continue to conquer the pharmaceutical market. Still, there are some major issues to be resolved, e.g. how to ensure quality of the new dosage forms and dose accuracy in flexible dosing, but the governmental incentives will continue to accelerate development of paediatric medicines and will bridge the still existing gaps in the near future.

Chapter IV – Increasing Drug Flexibility for the LENA Project

Pretext

The analysis of the PIPs regarding cardiovascular diseases showed a trend to solid dosage forms and also a need for new, age-appropriate dosage forms. Within the LENA (Labelling Enalapril from Neonates to Adolescents) project, enalapril orodispersible minitablets (ODMTs) have been developed and clinically investigated. Nevertheless, a PIP considers not only the development of the dosage form and the clinical studies which have to be conducted, but also includes the administration route and evaluates alternative ways of administering the dosage form. This study enlightens, which additional investigations have to be performed within a PIP like administration and drug stability with age-appropriate beverages and applicability via nasogastric tubes. Furthermore, a dosing regimen for a dilution of a minitablet directly at the bedside of the patient has been developed to ensure an adequate dose in the dose titration phase of the therapy for each age group also premature and newborn infants.

Evaluation of the authorship

The following research paper has been accepted by the International Journal of Pharmaceutics in February 2018 (impact factor 2016: 3.649). The research presented in this article has been conducted in context of the LENA Project (Grant Agreement No. 602295) in line with a Paediatric Investigation Plan for enalapril maleate orodispersible minitablets. The first and corresponding author Yasmin Thabet was responsible for the study design, the experimental work, the evaluation and the writing of the manuscript. The second author Dr. Jennifer Walsh was involved in the idea, in the PIP correspondence with EMA, the study design of this paper and in the revision of the manuscript. Prof. Dr. Joerg Breitkreutz as senior author of this research paper was responsible for the idea, study design and revision of the manuscript. He is also a shareholder of Ethicare GmbH, which is a beneficiary of the LENA project and holds the PIP agreed by the EMA.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Yasmin Thabet	20	20	100	80	70
Jennifer Walsh	30	40	0	10	20
Joerg Breitkreutz	50	40	0	10	10

Flexible and precise dosing of enalapril maleate for all paediatric age groups utilizing orodispersible minitablets

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Abstract:

Enalapril is an off-patent angiotensin-converting enzyme inhibitor for which no paediatric age-appropriate formulation is commercially available in Europe, and enalapril maleate (EM) orodispersible minitablets (ODMTs) have previously been formulated within the LENA (labelling enalapril from neonates to adolescents) project. In this study, a dilution method has been developed by dispersing the lowest dose strength ODMTs to enable flexible and precise EM dosing during the dose titration phase of the therapy. Furthermore, the physicochemical stability of the ODMTs has been investigated in child-friendly beverages and the administration of ODMTs via nasogastric tubes (NGT) of different sizes and materials has been evaluated. The results for the ODMT dilution procedure reveal that dispersion within an oral syringe is preferred over dispersion in a separate container, leading to flexible and precise dosing down to 0.025 mg EM. Although ODMTs were stable in the beverages over the investigated time period, dispersion in tap water only is recommended due to prolonged disintegration times within the other beverages. Dispersed ODMTs can be administered through NGT of CH 5. Almost no adsorption of EM on silicone, polyurethane or polyvinyl chloride could be observed. The ODMT concept together with the investigated dispersion method enables the safe administration of EM for all paediatric subpopulations from new-borns to adolescents.

Chapter V – Continuous manufacturing of ODFs

Pretext

Orodispersible films have been evaluated as a potential age-appropriate dosage form for children, which enable precise and very flexible dosing. In literature, only non-continuous processes of the solvent casting method have been described. Huge differences in production settings of the two processes are present, especially concerning the requirements for dynamic viscosities of the casting solutions, the way of drying the film and mechanical exposure during coiling up. The following research paper points out the differences between a non-continuous and continuous production of orodispersible films and the effect of the production conditions on the characteristics of the resulting films. This study introduces a scale-up process for orodispersible film formulations from lab-scale to a continuous manufacturing approach, which is a very important issue for the industrial ODF production.

Evaluation of the authorship

The following research paper has been published by the International Journal of Pharmaceutics in 2017 (impact factor 2016: 3.649). The first author of the manuscript Yasmin Thabet is responsible for the idea and study design as well as for the experimental work. Furthermore, she has been in authority for the data evaluation and the writing of the manuscript. Prof. Dr. Joerg Breitkreutz as senior author is responsible for the idea and study design as well as for the revision of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Yasmin Thabet	60	80	100	90	80
Joerg Breitkreutz	40	20	0	10	20

Orodispersible films: product transfer from lab-scale to continuous manufacturing

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Abstract:

Orodispersible films have been described as new beneficial dosage forms for special patient populations. Due to various production settings, different requirements on film formulations are required for non- continuous and continuous manufacturing. In this study, a continuous coating machine was qualified in regards of the process conditions for film compositions and their effects on the formed films. To investigate differences between both manufacturing processes, various film formulations of hydrochlorothiazide and hydroxypropylcellulose (HPC) or hydroxypropylmethycellulose (HPMC) as film formers were produced and the resulting films were characterized.

The qualification of the continuously operating coating machine reveals no uniform heat distribution during drying. Coating solutions for continuous manufacturing should provide at least a dynamic viscosity of 1 Pa*s (wet film thickness of 500 µm, velocity of 15.9 cm/min). HPC films contain higher residuals of ethanol or acetone in bench-scale than in continuous production mode. Continuous production lead to lower drug content of the films. All continuously produced films disintegrate within less than 30 s. There are observed significant effects of the production process on the film characteristics. When transferring film manufacturing from lab-scale to continuous mode, film compositions, processing conditions and suitable characterization methods have to be carefully selected and adopted.

Chapter VI - Development of fixed-dose, multilayer ODFs

Pretext

In the previous paper, a continuous production of orodispersible films containing hydrochlorothiazide has successfully been performed. In the subsequent research paper, the potential of a continuous production of fixed-dose combinations for the paediatric population should be explored. Due to the limited availability of age-appropriate dosage forms, which provide the facility to process two active pharmaceutical ingredients, only a few fixed-dose combinations for children are disposable. Therefore, also few clinical data for paediatric combination products are available. The following research paper aims to develop and analyse fixed-dose orodispersible films in a continuous manufacturing approach for all subpopulations with regard to personalised medicine. Different therapeutic doses can be achieved by reducing the size of the orodispersible film.

Evaluation of the authorship

The subsequent research paper has been submitted to the European Journal of Pharmaceutical Sciences in September 2017 (impact factor 2016: 3.756) and resubmitted in February 2018. As the first author of this paper, Yasmin Thabet was responsible for the idea and the concept of the study as well as for the experimental work and data evaluation and writing of the manuscript. Dr. Dominique Lunter as the second author was responsible for the experimental setup involving confocal Raman microscopy and the evaluation of the obtained data. Furthermore, she was involved in manuscript writing and revision of the paper. Prof. Dr. Joerg Breitkreutz as senior author was responsible for the idea and the study design as well as for the revision of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Yasmin Thabet	40	80	80	90	80
Dominique Lunter	0	10	20	10	10
Joerg Breitkreutz	60	10	0	0	10

Continuous manufacturing and analytical characterization of fixed-dose, multilayer orodispersible films

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Abstract:

Various drug therapies require more than one active pharmaceutical ingredient (API) for an effective treatment. There are many advantages, e.g. to improve the compliance or pharmacodynamic response in comparison to a monotherapy or to increase the therapy safety. Until now, there are only a few products available for the paediatric population due to the lack of age appropriate dosage forms or studies proving the efficacy and safety of these products. This study aims to develop orodispersible films (ODFs) in a continuous solvent casting process as child appropriate dosage form containing both enalapril maleate (EM) and hydrochlorothiazide (HCT) separated in different film layers. Furthermore, they should be characterised and the API migration analysed by confocal Raman microscopy (CRM).

ODFs were successfully produced in a continuous manufacturing process in form of double- and triple- layer formulations based on hydroxypropylcellulose (HPC) or a combination of HPC and polyvinylalcohol (PVA). CRM revealed that both APIs migrate within the film layers shortly after manufacturing. PVA inhibits the migration inside the double-layer film, but is not able to prevent the API migration as an interlayer inside a triple- layer ODF. With increasing film layers, the content of residual solvents and the disintegration time increases (mono-layer films: < 10 s, triple-layer films: 37 s). In conclusion, it was feasible to produce fixed-dose combinations in therapeutic doses up to 9 mg HCT and 3.5 mg EM for the double- layer film with adequate mechanical properties, which enable coiling up onto jumbo rolls directly after production. The best separation of the two APIs was achieved by casting a double- layer ODF consisting of different film forming polymers, which can be beneficial when processing two incompatible APIs.

Chapter VII - Printing Pharmaceuticals by Inkjet Technology

Pretext

Orodispersible films (ODFs) provide several advantages for special patient populations. Beside the ease of swallowing the particles of the fast-disintegrated polymer layer, the easy application without water and the individual dosing by adjusting the size of the film are main advantages of this dosage form. However, there are also limitations like the constricted drug load and the high production costs, which are resulting from the expensive packaging and the high waste due to film cutting. One way to overcome these disadvantages is the imprinting of orodispersible films with inks containing active pharmaceutical ingredients (APIs). The dosing flexibility can be even increased and API waste can be reduced. In literature, only stand-alone inkjet printing has been performed by now, which is not feasible for industrial production. The subsequent research paper provides a method transfer from an inkjet-printing process of orodispersible films from a stand-alone printer to an in-line imprinting directly after continuous ODF production. This transfer will enable API printing in a continuous manufacturing approach suitable for industrial production.

Evaluation of the authorship

The following research paper has been submitted to the Journal of Manufacturing Processes in November 2017 (impact factor 2016: 2.322). The first and corresponding author Yasmin Thabet was responsible for the idea and study design as well as for the experimental work. Furthermore, she was in authority of the data evaluation and the writing of the manuscript. Dr. Rok Sibanc as a second author was responsible for the idea and study design concerning image analysis tool, also evaluating the results of the image analysis. Moreover, he reviewed the manuscript. Prof. Dr. Joerg Breitkreutz as senior author was responsible for the idea and study design as well as for the review of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Yasmin Thabet	40	80	100	90	80
Rok Sibanc	20	10	0	10	10
Joerg Breitkreutz	40	10	0	00	10

Printing Pharmaceuticals by Inkjet Technology: Proof of Concept for Stand-Alone and Continuous In-Line Printing on Orodispersible Films

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J. Manuf. Process. 2018, doi: 10.2016/j.jmapro.2018.07.018

Abstract:

Orodispersible films (ODFs) are promising dosage forms for special patient populations like paediatrics or elderly persons. By printing active pharmaceutical ingredients (APIs) onto orodispersible films, the flexibility of drug dosing is increased and therefore provides potential for personalized medicines. Until now, only small-scale experiments have been conducted, where continuous jetting was performed,but no continuous ODF production was realized. This study deals with the technology transfer from a small-scale inkjet printing system to a pilotscale process by incorporating the same print head assembly into a continuous ODF production process. ODFs made from hydroxypropylcellulose were non-continuously printed multiple times with test ink containing a blue colorant as model drug and were compared to continuously printed ODFs. To identify optimal manufacturing conditions, parameter settings like firing frequencies, resolution, voltage, etc. were varied and these effects were analysed by UV–Vis spectroscopy, image analysis and light microscopy. During continuous production, a linear correlation between firing frequency (100 to 600 Hz) and deposited colourant content could be observed (R=0.999) as well as for the applied voltage (90–110 V) and the ink content (R=0.998). A minor impact of the distance between the print head and the substrate was observed. By increasing the natural resolution (50 dpi) of the print head, the deposited ink amount could be doubled. A transfer from the non-continuous production (1 layer of 1 cm x 2 cm with a resolution of 750 dpi x 750 dpi) to the continuous production (corresponding to 380 Hz firing frequency on 6 cm^2 ODF) was successfully performed. Furthermore, image analysis was proven as useful tool for process analytical technology (PAT) of the continuously printed ODFs. The continuous ODF production with direct printing enabled various printing concepts, which may serve for individualized dosing in personalized medicine treatment in the near future.

Chapter VIII - Continuous Inkjet Printing of Enalapril Maleate onto ODFs

Pretext

The previous paper showed a successful transfer from a stand-alone printing process to an in-line printing during continuous production of orodispersible films. For the first time, the following research paper displays the imprinting of orodispersible films with an active pharmaceutical ingredient in-line during the continuous film production. In response to the previous paper (Chapter VI) producing continuously fixed-dose combinations, imprinting of ODFs should be evaluated as potential alternative tool for generating fixed-dose combinations for the paediatric population. The fixed-dose combination produced by multi-layer solvent casting revealed an API migration into the film layers. The subsequent research paper should further investigate whether the migration could be restrained by imprinting the orodispersible film.

Evaluation of the authorship

The subsequent research paper has been submitted to the International Journal of Pharmaceutics in December 2017 (impact factor 2016: 3.649). As the first and corresponding author of this paper, Yasmin Thabet was responsible for the idea and the concept of the study as well as for the experimental work, data evaluation and writing of the manuscript. Dr. Dominique Lunter as the second author was responsible for the experimental setup involving confocal Raman microscopy and the evaluation of the obtained data. Furthermore, she was involved in manuscript writing and revision of the paper. Prof. Dr. Joerg Breitkreutz as senior author was responsible for the idea and the study design as well as for the revision of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Yasmin Thabet	60	80	90	80	80
Dominique Lunter	0	10	10	10	10
Joerg Breitkreutz	40	10	0	10	10

Continuous Inkjet Printing of Enalapril Maleate onto Orodispersible Film Formulations

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Abstract:

Piezoelectric inkjet printing onto orodispersible films (ODFs) was proven to be a successful technique applying flexible doses of active pharmaceutical ingredients (APIs) onto edible substrates. The reported API printing and ODF production was conducted in a non-continuous production approach. Within this study, drug-free and hydrochlorothiazide (HCT) containing ODFs should be imprinted in-line with enalapril maleate (EM) ink during continuous ODF production.

Macrogol inks based on various solvents and solvent-water mixtures were developed providing dynamic viscosities from 7 to 17 mPa*s. Water based inks contained 1.25 %, methanol based inks up to 10 % EM. Both inks could be printed (500-1000 Hz) during continuous ODF production. No EM recrystallization was observed for water-based inks. Mechanical properties were not affected by drug printing using various firing frequencies. ODF imprinted with water-based EM inks contained 0.04 mg EM / 6 cm^2. EM amount can be increased to a paediatric therapeutic dose of 0.5 mg EM utilizing methanol-based inks. These inks were successfully printed onto HCT ODFs resulting in a therapeutically relevant fixed-dose combination. No EM migration into the HCT layer could be observed. In conclusion, it was feasible to print EM doses onto drug-free and HCT ODFs during an in-line continuous manufacturing process.

Chapter IX - Conclusions and Outlook

The era of personalised medicine has been claimed as new paradigm for the health care system. The knowledge of individual genetic expression, regulating enzymes and metabolic processes led to the conclusion that different people may need different amounts of APIs. In particular the paediatric population has special needs because the body development is not completed and the therapeutic dose cannot be easily transferred from the adult to the paediatric population. The EMA increasingly asks for age-appropriate dosage forms, which led to the development of new solid dosage forms suitable for paediatric patients. Orodispersible dosage forms (especially mini-tablets and films) turned out to be the most promising ones, covering all age groups, from birth to adolescence and even to the geriatric population. To improve the patient compliance and the efficacy and safety of the medical treatment of patients who need to take several APIs per day, FDCs can be utilized. Due to limited clinical studies in the paediatric population, almost no FDCs are available despite they provide several advantages. A fixed-dose combination consisting of EM and HCT providing the possibility of flexible drug dosing could be beneficial for a wide range of sub-populations from paediatric to geriatric patients.

1. Advances in Paediatric Drug Formulations

Recent developments in pharmaceutical formulation development have introduced new technologies and novel dosage forms to the market. As multiparticulate dosage form, where the flexible dosing is achieved by accumulation, mini-tablets are the most promising innovation. The ease of production and new available data on acceptability and swallowability in children led to gaining interest by the competent authorities and pharmaceutical industry. Orodispersible films are the current innovation considering dosage forms, where the dosing flexibility is accomplished by partition of the dosage form. High dosing flexibility in combination with the ease of application even to patients with swallowing difficulties result in more research on this dosage form. Clinical acceptability studies are ongoing with promising results. This is also reflected by the currently available Paediatric Investigation Plans, where an orodispersible film preparation is present. These new innovative dosage forms might reduce the amount of paediatric liquid formulations significantly in the future.

2. EU Regulation of Paediatric Medicine

The introduction of paediatric investigation plans 10 years ago led to an increase of research in paediatric formulation development and a huge progress can be observed in this field. An ongoing shift from liquid to solid formulations can be monitored including new and innovative dosage forms like orodispersible formulations or multiparticulates. More data concerning acceptability of dosage forms and modification of the medicine will be available due to the new requirements of the regulatory authorities. The development of an age-appropriate dosage form covering all age groups from birth to adolescence may require the design of an adjusted dosing regimen or the manipulation of the dosage form (e.g. dispersion and dilution of tablets). Investigations considering the simultaneous administration of age-appropriate beverages are of essential importance because the disintegration time, acceptability and bioavailability can be influenced. Furthermore, applicability via nasogastric tubes have to be investigated to ensure an application also within this patient population. The EMA demands in the PIP procedure various additional tests and clinical studies but ensure the development of new medicine for children.

3. Continuous Manufacturing of ODFs

A huge discrepancy has been reported between the lab-scale production and industry-scale production of orodispersible films. Whereas many scientific publications are based on lab-scale manufacturing, industrial development and production includes scale-up procedures to continuously operating equipment. Scale-up experiments were reported to be difficult. These reports could be confirmed by the conducted experiments. Several points have to be taken into account when transferring a small-scale ODF production to a continuous process: The film-forming polymer exert a high influence on the scale-up process, depending on the drying conditions during manufacturing and surface phenomena on the intermediate liners. Surface tensions and resulting spreading on the intermediate liner affect the dosing of the film when the area of the wet film is altered. Depending on the solvent of the polymer solution, morphology of the films as well as the content of residual solvents can be influenced. Incorporated organic solvents can lead to the formation of air bubbles during the drying process, which can disturb mechanical stability and dosing accuracy. Residual solvents have to be limited and analysed to ensure a complete evaporation and eliminate toxicological side effects for the patients. When developing an orodispersible film formulation, only few first experiments should be conducted in a lab-scale approach. The transfer to the continuous process should be executed as early as possible due to poor scale-up conformities.

4. Development of fixed-dose, multilayer ODFs

As fixed-dose combinations gaining more importance due to polymedication in the elderly and the higher amount of APIs, which are necessary for the treatment of one disease (like HIV or tuberculosis), new age-appropriate dosage forms are essential which also enable the administration for the paediatric population. Fixed-dose orodispersible films provide the advantage of an easy application for all age-groups as well as the fast disintegration time and flexible dosing due to the dosing via the area of the film. By cutting fixed-dose ODFs in various sizes, several patient populations could be treated individually. In this thesis, the production of fixed-dose combinations containing therapeutic doses of EM and HCT in a continuous manufacturing process via the solvent casting method was proven to be feasible. Multilayer films were successfully manufactured offering a fast disintegration within the mouth and acceptable mechanical properties. Nevertheless, a migration of the APIs, which was observed by Raman imaging technologies is disadvantageous for fixed-dose combinations of incompatible APIs. A distinct separation of the APIs in the particular layers would be desirable in terms of reducing potential interactions and ensuring long-term stability of the dosage form.

5. Printing Pharmaceuticals by Inkjet Technology

The imprinting of orodispersible films has been conducted in various laboratories according to the literature. Inkjet printing has been performed in a non-continuous production process offering new opportunities in concerns of personalised dosing. A higher dosing variability is achieved and API waste can be reduced. Whereas these approaches are practicable in hospital or community pharmacies, an industrial production of larger scales is not feasible by the reported approaches. A transfer from a non-continuous process to a continuous imprinting would be necessary. This transfer has been successfully performed in the present thesis, showing the complexity of the printing process and the difficulties of a scale-up process. Especially the number of printing nozzles of the print head is of crucial importance for the continuous printing. Whereas the stand-alone printings described in literature were often performed with one printing nozzle, a continuous manufacturing requires optimally multiple nozzles jetting to ensure an adequate API application. For the utilized ink, optimal production settings could be defined and as a proof-of-concept, several printing processes could be conducted in a continuous manufacturing approach.

The ink development containing active pharmaceutical ingredients is the most challenging part considering the process. Each print head has its own requirements depending on its construction and the printing technique (e.g. piezo ink-jet printing vs. thermal ink-jet printing). Small variations in viscosity and surface tension can lead to an insufficient printing. Polymer molecules, which are necessary to adjust the viscosity, may block the nozzles and inhibit them to jet the liquid. The development of pharmaceutical inks is therefore customised to the utilized print head. The development of a pharmaceutical ink

containing EM has been successfully performed. Furthermore, drug-free as well as HCT containing ODFs were imprinted. The imprinted films exhibit acceptable characteristics concerning mechanical stability, content uniformity and disintegration time. No migration of EM could be observed, which makes the imprint of ODFs a promising tool in industry-adapted production of fixed-dose combinations. Nevertheless, the continuous ink-jet printing is limited in its applicability of higher ink amounts. Whereas the stand-alone printing allows the printing of various layers to obtain the desired API dose, the imprinting during continuous production is limited to only one printing step (despite several print heads are connected in series). Only 0.5 mg EM could be applied onto the ODFs during continuous production, which is a therapeutically indicated dose for young children, in particular during the titration period. To cover more patient populations, the amount of imprinted API has to be further increased.

6. Future Perspectives

With regard to personalised medicine, pharmaceutical formulation development has made huge progress within the past years. Regulatory interventions as well as the demand for higher dosing flexibility led to the development of various new dosage forms. Orodispersible minitablets were found to be a promising dosage form for administering flexible doses to several patient populations. Studies revealed that even children can swallow higher amounts (up to a few hundred) of tablets. Nevertheless, content uniformity could only be ensured for doses within the mg range and therefore the processing of high potent drugs is difficult. Furthermore, suitable administration devices are needed. There are several companies, which are offering mechanically or electronically dosing multidose containers. Due to the novelty of this dosage form, adequate tests and requirements regarding this dosage forms are still not available in the European Pharmacopoeia. Research in this field is still ongoing further improving the production and the applicability of the dosage form in future.

Orodispersible films are also gaining more interest for special patient population. Due to the challenging scale-up, formulation development is very difficult. Furthermore, the high production costs (mainly caused by API waste due to the cutting process or the expensive packaging) prevent an expansion on the pharmaceutical market. This may be changed by currently ongoing acceptability studies in the paediatric population or the development of multidose containers reducing the packaging costs. Nevertheless, a high limitation of ODFs is still the limited drug load of the film, which could be overcome by casting suspensions and increase therefore the drug load. The API waste can be reduced by imprinting the ODFs in the centre of the film area.

Pharmaceutical printing has also been proven as suitable technique for producing personalised medicines. Regarding the inkjet printing technique there are several challenges, which have to be mastered. More knowledge and deeper understanding of the printing process is required to improve ink development and increase the applied drug

amount. Enabling a printing of high concentrated drug inks with all print head nozzles jetting, imprinting during a continuous manufacturing process of edible substrates could lead to an industrial adapted production of personalised medicine for all subgroups – from the paediatric to the geriatric population.

To optimise the casting and printing process of orodispersible films, a well-structured investigation of potential in-process controls would be desirable. This thesis showed the facility to utilize image analysis as potential tool for in process control of applied ink amounts. Nevertheless, this technique is limited to coloured inks. The implementation of a Raman probe or utilizing infrared light as process analytical technologies could also visualise colourless APIs inside the ODF. Considering the industrial production, an implementation of a process analytical technology in the continuous production process would significantly improve the process control, especially with regard to the simultaneously ongoing printing process.

Summary

The era of personalised medicine has been claimed as new paradigm for the health care system. The knowledge of individual genetic expression, regulating enzymes and metabolic processes led to the conclusion that different people may need different amounts of active pharmaceutical ingredients (APIs) depending on the enzymatic equipment of the patient. Not only adults, but in particular the paediatric population has special needs because the body development is not completed and the therapeutic dose cannot be easily transferred from the adult to the paediatric population. Due to the lack of studies in children, only few child-appropriate dosage forms are available. The European competent authorities reacted by introducing Paediatric Investigation Plans (PIPs) as a requirement for medicines aiming for marketing authorization. This led to the development of new dosage forms suitable and specially designed for paediatric patients. Orodispersible dosage forms (especially minitablets and films) turned out to be the most promising ones, covering all age groups, from birth to adolescence and even to the geriatric population. However, the PIP does not only cover the formulation development of new medicines, but also compromise the pre-clinical and clinical studies and the evaluation of adequate and precise dose administration for each age group. Furthermore, a potential dosage form manipulation (e.g. administration with characteristic beverages) has to be closer investigated.

In line with a PIP of enalapril maleate (EM) orodispersible mini-tablets (ODMTs) the development of a suitable administration regimen covering all age groups has been conducted, which enable an easy and precise dosing directly at the bedside of the patient. Furthermore, the API stability in child-appropriate beverages was investigated. The simultaneous administration with beverages is not recommended based on the obtained results despite the API was stable over the investigated time-period. However, disintegration time is a major quality attribute for orodispersible tablets. The beverages influenced the disintegration time of the tablets, which may compromise the bioavailability and increase the risk of choking. Furthermore, the administration via nasogastric tubes was investigated and proven to be feasible and a recommendation for the required rinse volume could be given. These investigations allow a deeper insight into the regulatory requirements regarding the study design of acceptability and applicability of the dosage form and may be used as protocol for future PIPs.

Processes for manufacturing personalised medicine were often reported as small batch processes suitable for the production in a hospital pharmacy or a community pharmacy. However, the growing field of personalised medicine needs processes adapted for industrial production to cover all subpopulations. Therefore, the continuous production of orodispersible films (ODFs) has been closer investigated. A simple transfer from a non-continuous to a continuous production is not feasible. Characteristics of the formulation like viscosity of the casting solution, drying conditions during manufacturing and mechanical properties of the resulting product have to be adapted for each product.

Nevertheless, the continuous production of hydrochlorothiazide (HCT) and EM films as well as fixed-dose combinations (FDCs) containing both APIs was proven to be feasible. FDC produced via the solvent casting technique in form of multi-layer films provided dose uniformity, adequate mechanical strength and fast disintegration times. During the manufacturing process, APIs were migrating in the other layers, which makes the process unsuitable for film-based fixed-dose combinations consisting of incompatible APIs.

Another technique to produce FDCs is the imprinting of ODFs with API containing ink. Inkjet printing was reported to be a suitable process to increase dosing flexibility and reduce API waste. Nevertheless, pharmaceutical inkjet printing was conducted only in a small-scale process, not suitable for industrial production. By implementing an ink jet print head into the continuous production process of ODFs, this technique has been made accessible for the industrial continuous manufacturing. The inkjet printing process was successfully transferred from a stand-alone printing process utilizing a commercial industrial printer to a direct imprinting during continuous ODF production. Optimal production conditions for this setup (like distance of the print head, firing frequency, applied voltage, pulse shape settings etc.) could be defined. This led to the realisation of various printing concepts: symmetric and asymmetric lines, central printings as well as complete printings with the natural resolution of the print head could be performed during a continuous ODF production.

EM inks were developed utilizing various ink bases and solvent mixtures until the viscosity range and the surface tension range are appropriate for the utilized print head. EM was successfully printed onto drug-free and HCT orodispersible films resulting in mono- and fixed-dose combination products revealing acceptable characteristics concerning mechanical properties, content uniformity and disintegration time. A recrystallization of EM could be observed, which may influence the bioavailability and mechanical stability of the films. A migration of the API into the ODF cannot be observed. Therefore, this manufacturing technique should be preferred over the multi-layer production for the fabrication of FDCs of incompatible APIs.

With regard to personalised medicine, new production techniques could successfully be introduced in the present work enabling flexible drug dosing and FDCs in a single dosage form at an industrial adapted scale.

Zusammenfassung

Die Ära der personalisierten Medizin wurde zum neuen Paradigma des Gesundheitssystems erklärt. Das Wissen über individuelle Genexpressionen, Enzymregulationen und metabolische Prozesse führte zu dem Schluss, dass verschiedene Patienten in Abhängigkeit ihrer enzymatischen Ausstattung unterschiedliche Wirkstoffmengen benötigen, um einen therapeutischen Erfolg zu erzielen. Nicht nur die Erwachsenen, sondern insbesondere die pädiatrischen Patienten weisen jedoch spezielle Bedürfnisse auf, da ihre körperliche Entwicklung noch nicht abgeschlossen ist und die therapeutische Dosierung nicht einfach von einem erwachsenen Patienten auf ein Kind übertragen werden kann. Aufgrund mangelnder Studien in Kindern sind jedoch nur begrenzt Arzneimittel in altersgerechten Darreichungsformen verfügbar. Die zuständige europäische Behörde reagierte darauf mit dem Einführen des pädiatrischen Prüfkonzepts, welches Voraussetzung für das Erlangen der Marktzulassung wurde. Dies führte zur Entwicklung neuer Arzneiformen, welche mitunter speziell für die pädiatrischen Patienten konzipiert wurden. Orodispersible Arzneiformen (insbesondere Minitabletten und Filme) stellten sich als die vielversprechendsten Darreichungsformen heraus. Sie decken von der Geburt bis zum Erwachsenenalter alle Altersgruppen ab und sind darüber hinaus ebenfalls für die geriatrische Population geeignet.

Die pädiatrischen Prüfkonzepte umfassen jedoch nicht nur die Formulierungsentwicklung neuer Arzneimittel, sondern auch die Durchführung präklinischer und klinischer Studien sowie die Evaluation der adäquaten und präzisen Verabreichung der Dosis. Außerdem werden Untersuchungen zu potenziellen Manipulationen der Arzneimittel (z.B. gleichzeitige Applikation mit kindgerechten Getränken) gefordert.

Im Rahmen eines pädiatrischen Prüfkonzeptes von orodispersiblen Enalapril Minitabletten wurde in dieser Arbeit ein geeignetes Dosierschema entwickelt, welches alle Altersklassen umfasst und ein einfaches und präzises Dosieren ermöglicht. Außerdem wurde die Wirkstoffstabilität in diversen kindgerechten Getränken untersucht. Die gleichzeitige Applikation der Minitabletten mit Getränken kann nach den vorliegenden Ergebnissen nicht empfohlen werden. Enalapril war zwar über den untersuchten Zeitraum in allen untersuchten Getränken stabil, jedoch beeinflussten die verschiedenen Getränke die Zerfallszeit der Tabletten. Die Zerfallszeit ist jedoch ein qualitätsbestimmendes Merkmal von orodispersriblen Tabletten und kann die Bioverfügbarkeit des Wirkstoffes beeinträchtigen und das Risiko des Verschluckens erhöhen. Darüber hinaus wurde die Arzneistoff-Applikation über nasogastrale Sonden untersucht. Die Gabe von Enalapril Minitabletten über nasogastrale Sonden war möglich und eine Empfehlung für ein Spülvolumen nach Applikation konnte gegeben werden. Die durchgeführten Untersuchungen erlauben einen tieferen Einblick in die regulatorischen Anforderungen für die erforderlichen Studien, welche hinsichtlich der Akzeptanz und Anwendung von Darreichungsformen durchzuführen sind und können als Muster für zukünftige PIPs dienen.

Die Produktionstechniken von Arzneimitteln, welche für die personalisierte Medizin geeignet sind, sind oft auf die Herstellung kleiner Chargen beschränkt und daher ideal für die Herstellung in öffentlichen Apotheken und Krankenhausapotheken. Um alle Patientenpopulationen ausreichend versorgen zu können, benötigt der stetig wachsende Bereich der personalisierten Medizin jedoch Prozesse, die ebenfalls in industriellem Maßstab Anwendung finden können. Daher wurde im Rahmen dieser Arbeit die kontinuierliche Herstellung orodispersibler Filme näher untersucht. Ein einfaches Übertragen des Prozesses von nicht-kontinuierlicher zu kontinuierlicher Herstellungsmethode ist nicht möglich. Charakteristische Kenngrößen der Zubereitung (z.B. Viskosität der Gießlösung, Trocknungsbedingungen und die mechanischen Eigenschaften des resultierenden Produktes) müssen individuell angepasst werden. Die kontinuierliche Produktion von Hydrochlorothiazid (HCT)- und Enalaprilmaleat (EM)-Filmen, sowohl einzeln als auch in Form eines Kombinationspräparates, wurde erfolgreich durchgeführt. Kombinationspräparate, die in Form von Mehrschichtfilmen mit dem Gießverfahren produziert wurden, wiesen homogene Arzneistoffverteilungen und adäquate mechanische Stärke sowie schnelle Zerfallszeiten auf. Während der Produktion wanderten die Wirkstoffe in die verschiedenen Filmschichten. Dieser Produktionsprozess ist daher nur eingeschränkt anwendbar für filmbasierte Kombinationspräparate bestehend aus inkompatiblen Arzneistoffen.

Eine weitere Produktionstechnik zur Herstellung von Kombinationspräparaten ist das Bedrucken orodispersibler Filme mit wirkstoffhaltiger Tinte. Der Tintenstrahldruck wurde bereits als geeigneter Prozess zur Erhöhung der Dosis-Flexibilität und Reduzierung des Wirkstoffabfalles eingeführt. Jedoch wurde pharmazeutischer Tintenstrahldruck bislang nur im kleinen Maßstab durchgeführt, welcher ungeeignet für die industrielle Produktion ist. Durch die Implementierung eines Druckkopfes in eine kontinuierliche Filmziehbank wurde diese Technik der industriellen Produktion zugänglich gemacht. Der Druckprozess wurde erfolgreich von einem alleinstehenden Druckverfahren unter Verwendung eines kommerziellen Industriedruckers auf die kontinuierliche Produktion während der Filmherstellung übertragen. Optimale Produktionseinstellungen (z.B. Abstand des Druckkopfes zum Substrat, Druckfrequenz, angelegte Spannung) konnten definiert werden. Dies führte zu der Realisierung verschiedener Druckkonzepte: Symmetrische und asymmetrische Linien, zentrale Aufdrucke sowie eine komplette Bedruckung des Films mit der natürlichen Auflösung des Druckkopfes konnten während der kontinuierlichen Filmherstellung produziert werden.

Basierend auf verschiedenen Polymeren und Lösungsmittelmischungen wurden EM-Tinten entwickelt, welche die vom Druckkopfhersteller geforderten Bereiche für Viskosität und Oberflächenspannung erfüllen. EM wurde erfolgreich auf wirkstofffreie und auf HCT-haltige orodispersible Filme gedruckt. Es wurden Mono- und Kombinationspräparate hergestellt, die akzeptable mechanische Eigenschaften, homogene Arzneistoffverteilungen und ausreichend schnelle Zerfallszeiten aufwiesen. Eine Rekristallisation des EMs wurde

nach dem Druckprozess beobachtet. Dies kann Einfluss auf die Bioverfügbarkeit und mechanische Stabilität der filmförmigen Zubereitungen haben. Eine Wirkstoffwanderung während oder nach der Herstellung konnte im Gegensatz zu den im Gießverfahren hergestellten Kombinationspräparaten nicht beobachtet werden. Zur Verarbeitung zweier inkompatibler Wirkstoffe sollte daher bevorzugt diese Herstellungstechnik verwendet werden, um Kombinationspräparate herzustellen.

Hinsichtlich der Herstellung von pädiatrischen Arzneimitteln, die in der personalisierten Medizin Anwendung finden konnten in der vorliegenden Arbeit neue Produktionstechniken erfolgreich etabliert werden, die ein flexibles Dosieren und die Herstellung von Kombinationspräparaten im industriellen Maßstab ermöglichen.

Original publications

1. V. Klingmann, Y. Thabet, J. Breitkreutz
   „Arzneiformen für Kinder“
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2. Y. Thabet, V. Klingmann, J. Breitkreutz
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   Int. J. Pharm. 2018; doi.org/10.1016/j.ijpharm.2018.02.037.

5. Y. Thabet, J. Breitkreutz
   “Orodispersible Films: Product Transfer from Lab-Scale to Continuous Manufacturing”
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7. Y. Thabet, R. Sibanc, J. Breitkreutz
   „Printing Pharmaceuticals by Inkjet Technology: Proof of Concept for Stand-Alone and Continuous In-Line Printing on Orodispersible Films”
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8. Y. Thabet, D. Lunter, J. Breitkreutz
   „Continuous Inkjet Printing of Enalapril Maleate onto Orodispersible Film Formulations”
   Int. J. Pharm. 2018; doi.org/10.1016/j.ijpharm.2018.04.064.

Contributions to meetings

1. Oral presentations

1. Y. Thabet, J. Breitkreutz
"Development of a continuous manufacturing process for double-layer orodispersible films containing cardiovascular drugs for children"
6th European Paediatric Formulation Initiative (EuPFI) meeting, GR - Athens (17-18.09.2014)

2. Y. Thabet, I. Speer, K. Bartscher, W. Wiedey, J. Breitkreutz
„Flexible dosing of enalapril by orodispersible minitablets: Paediatric concept, drug development and approved PIP“
10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, UK - Glasgow (04.-07.04.2016)

2. Poster presentations

1. Y. Thabet, J. Breitkreutz
"Development of a continuous manufacturing process for double-layer orodispersible films containing cardiovascular drugs for children"
6th European Paediatric Formulation Initiative (EuPFI) meeting, GR - Athens (17-18-09.2014)

2. Y. Thabet, J. Breitkreutz
"Influence of different drying conditions on mono-and double-layer orodispersible films during continuous manufacturing"
1st European Conference on Pharmaceutics, FR - Reims (13.-14.05.2015)

3. Y. Thabet, J. Breitkreutz
"Characterization of orodispersible films concerning the effects of drying temperatures during continuous manufacturing"
8th Polish-German Symposium on Pharmaceutical Science, DE – Kiel
(29.-30.05.2015)

4. Y. Thabet, L. Krainitzki, D. Dietzel, M. Preis
„Impact of different drying conditions on mechanical properties of orodispersible films"
DPhG Annual meeting 2015, DE - Duesseldorf (23.-25.09.2015)

5. Y. Thabet, J. Breitkreutz
"Orodispersible film formulations: points to consider for product transfer from bench-scale to continuous manufacturing"
American Association of Pharmaceutical Scientists Annual Meeting, US - Orlando (25.-29.11.2015)

6. Y. Thabet, R. Krampe, M. Graband, A. Wieber, D. Lubda, J. Breitkreutz
„Drug-loaded silica particles in orodispersible films: a feasibility study"
10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, UK - Glasgow (04.-07.04.2016)

7. Y. Thabet, J.Breitkreutz
"Investigation of Applicability and Compatibility of Enalapril Minitablets in Various Beverages"
8th European Paediatric Formulation Initiative (EuPFI) meeting, PT- Lisbon (20.-22.09.2016)

8. D. Kottke, Y. Thabet, J. Breitkreutz
„Individual Drug dosing by Printing Enalapril Maleate onto Orodispersible Films using Various Devices"
8th European Paediatric Formulation Initiative (EuPFI) meeting, PT - Lisbon (20.-22.09.2016)

9. Y. Thabet, J. Breitkreutz
"Characterization of Various Printing Devices as Tools for Individual Dosing"
American Association of Pharmaceutical Scientists Annual Meeting, US - Denver (13.-17.11.2016)

10. Y. Thabet, J. Breitkreutz
"Orodispersible Films: continuous manufacturing and direct imprinting of enalapril maleate"
9th Polish-German Symposium on Pharmaceutical Science, PL – Krakow (26-27.05.2017)

11. Y. Thabet, D. Kottke, J. Breitkreutz,
„Continuous inkjet printing of enalapril maleate onto orodispersible films"
9th European Paediatric Formulation Initative (EuPFI) meeting, PL – Warsaw (20.-21.09.2017)

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Erklärung

Hiermit versichere ich an Eides Statt gemäß § 5 der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Heinrich-Heine Universität Düsseldorf, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Die vorliegende Arbeit wurde in dieser oder ähnlicher Form noch bei keinen anderen Instituten eingereicht.

Düsseldorf,