

**Focus of commentary** – Global Health Challenges

**Drug Delivery Innovations to Address Global Health Challenges for Pediatric and Geriatric Populations (through improvements in patient compliance)**

Joshua Boateng<sup>1\*</sup>

<sup>1</sup>Department of Pharmaceutical, Chemical and Environmental Sciences, Faculty of Engineering and Science, University of Greenwich, Medway, Central Avenue, Chatham Maritime, Kent, UK, ME4 4TB

\* Correspondence: - Dr Joshua Boateng (j.s.boateng@gre.ac.uk, joshboat40@gmail.com)

**Abstract:**

Despite significant advances in pharmaceutical and biotechnological drug discovery, the global population is plagued with many challenging diseases. These are further compounded by anticipated explosion in an ageing population, which presents several problems such as polypharmacy, dysphagia and neurological conditions, resulting in non-compliance and disease complications. For antibiotics, poor compliance, can result in development of drug resistant infections which can be fatal. Further, children, especially, in developing countries die unnecessarily from easily treatable diseases (e.g. malaria), due to poor compliance arising from bitter taste and inability to swallow currently available medication. Though, some of these challenges require the discovery of new drug compounds, a significant number can be resolved by employing pharmaceuticals approaches to reduce the incidence of poor patient compliance. Such solutions are expected to make swallowing easier and reduce the need to swallow several solid medications, which is difficult for vulnerable pediatric and geriatric patients. This commentary will explore the current state of the art in the use of drug delivery innovations to overcome some of these challenges, taking cues from relevant regulatory agencies such as the Food and Drugs Administration, the European Medicines Agency, World Health Organization and the peer reviewed scientific and clinical literature.

Keywords: Buccal, Geriatric; Global Health Challenges; Malaria; Mucosal Drug Delivery; Patient Compliance; Pediatric; Personalized Medicine.

## 1. Overview

Within the last few decades, science has made significant advances which have led to major medical and pharmaceutical breakthroughs. However, despite the many scientific, medical and pharmaceutical breakthroughs such as antibiotics and vaccinations, the global population continues to be plagued with significant health challenges. Clinicians still face the huge problem of antibiotic resistant bacteria which are not sensitive to current first line antibiotics. In the developed world, improved medical advancements means that most people live longer than a few decades, which has however, created new clinical challenges. On the other hand, developing countries are plagued by several neglected diseases including malaria, which affects mostly the pediatric population who are the most vulnerable, just like the geriatric populations in developed countries. These are compounded by the increasingly reduced number of 'block-buster' drugs coming through the pharmaceutical drug development pipeline, coupled with the increasing cost of global healthcare and high population explosions worldwide.

## 2. General pharmaceutical challenges

The pharmaceutical industry spends significant amounts of time and money in drug discovery efforts to develop and bring new drug products to market. However, these efforts are plagued with several challenges even with new compounds that are potentially active in the target site but fail to reach market. Such drugs fail mainly because of poor solubility which makes it difficult to be absorbed into the systemic circulation when administered, especially via the most commonly used oral gastro intestinal route. This is important, as sufficient solubility of the unionized form of the drug, coupled with appropriate partition coefficient, is essential to ensure absorption, systemic bioavailability and ultimately determines therapeutic efficacy.

In addition, a drug typically administered via the oral route, will go through several absorption barriers with corresponding drug loss before reaching the intended site of action, and therefore require higher initial dose to be administered than that required at the site of action, as summarized in Figure 1. Furthermore, most new drugs that successfully make it to development stage, face the challenge of bitter and unpleasant taste when administered via the oral route which presents significant challenges in terms of patient non-compliance and subsequently, low therapeutic outcomes, especially for pediatric patients. This requires added research and formulation development efforts to address such challenges. These can result in increased product costs, which ultimately affects the patient and health providers worldwide. In addition, advances in molecular biology, genomics and proteomics, have resulted in the

development of pharmaceutical biotechnology based large molecules such as peptides and proteins, which are difficult to administer via the traditional GIT route due to instability in the GI pH, proteolytic enzymes and significant first pass effect in the liver. Such complex molecules are therefore largely administered via the parenteral route (i.e. injections) which is a challenge for children and patients with chronic conditions such as diabetes, where regular injections are required but which is invasive and painful. The commonly used traditional routes of administration and their advantages and disadvantages have been summarized in Table 1.

**FIGURE 1 HERE**

**TABLE 1 HERE**

### **3 Global health challenges**

As noted above, global health challenges vary depending on the geographical and / economic region of the world.

#### **3.1 Geriatric populations**

Most developed countries with better nutrition, advanced medical facilities and better patient care generally have higher life expectancy and therefore generally an ageing population, with most projected to live beyond 65 years old. This presents unique challenges as older patients suffer from multiple diseases including neurological ones such as dementia and dysphagia. Compared to the general adult population (18 – 60 years), medicines and medication management are much more complex and challenging in the elderly (over 65 years) with the latter generally requiring different features than standard adult medications. In addition, the presence of several chronic disease conditions results in multiple therapies which require the administration of many medications. Further, most diseases of older people are chronic, requiring them to take their medication over prolonged periods. The presence of multiple medical conditions (Table 2) and prolonged medication results in another therapeutic problem which is the challenge of polypharmacy, where patients take more than 5 different types of medication in a day with different instructions. This is obviously difficult for dementia patients and will need to depend on carers or find other means of differentiating the various medications and administering them appropriately. In most cases, such medication

present in the form of tablets or capsules, which are difficult to swallow for patients with dysphagia, who stand the risk of choking. For example, older patients with chronic heart conditions and risk of thrombosis, take aspirin tablets daily which is clearly a challenge for those with swallowing difficulties. The European Medicines Agency (EMA) has identified the following problem statement: “Elderly patients may face physical and cognitive impairment and hence they may have difficulties in taking their medicines e.g. swallowing tablets, opening packaging or reading the user instruction and patient information leaflet. Older people may also more frequently require the assistance of caregivers than the overall adult population. In addition, physiological changes such as hepatic impairment, renal impairment or altered gastrointestinal motility may require a re-evaluation of the benefit/risk profile of the medicine and warrant adapted dosing regimens. The pharmaceutical development of medicines for use by older patients should take such aspects into consideration.”<sup>5</sup>

These present several age-related limitations which cause non-compliance and therefore poor health outcomes. Though this can be resolved with fast disintegrating tablets that disperse readily in water for drinking, high liquid volumes can still be difficult for dysphagia patients, especially the highly infirm and bed bound, where the risk of vomiting is high. Further, liquid formulations tend to leave a bitter after taste, even when sweeteners are present. The ultimate outcome is poor uptake and acceptance. Swallowing issues will therefore have a direct impact on medication adherence. Swallowing difficulties have been described as a major health care problem in elderly that advances with increasing age, affecting 50% of patients in nursing homes<sup>6</sup>. For example:

- a. Most older adults have less than 20 teeth which makes chewing very difficult, therefore chewable tablets though a good alternative to swallowing, presents difficulties for such patients.
- b. Effervescent tablets require the need to disperse in water which though better than tablets, do not always lend themselves to easy swallowing whilst tablets such as Vitamin D is a fat soluble vitamin will not dissolve in water and will require an emulsion such as milk.

Based on the general literature, it is quite evident that there is need for alternative formulations to tablets or capsules that are easy to swallow without the need for reconstitution with lots of water or chewing. Such formulations are expected to result in ease of acceptance and uptake by patients, carers and doctors with a resultant attainment of high patient compliance. Liu and co-workers have suggested the use of fast melt formulations such

as films and wafers for geriatric drug delivery as an alternative to traditional tablets, capsules and effervescent powders. However, most of these reports are based on normal adult data which is non-specific<sup>7</sup>.

## TABLE 2 HERE

### 3.2 Pediatric populations

There are also similar challenges associated with treatments available for pediatric populations most of whom struggle to swallow tablets and capsules, and more acutely, have an innate resistance of injections due to the pain and the fear of needles which results in significant patient non-compliance. Whilst most children's medicines come in the form of liquids or suspensions which are more easily swallowed, these are not practical in cases of vomiting. More importantly, these require the need for masking of bitter taste and unpleasant smells of some active ingredients, which also result in patient non-compliance. Current approaches using high sugar concentrations and sweeteners present dental, obesity and type 2 diabetes concerns. Poor patient compliance in pediatric patients is of particular concern in neglected diseases such as malaria which are common in developing countries where the infant mortality rates from such non-compliance is high. Some of the common pediatric conditions and the current associated therapies are shown in Table 3.

In 2007, the WHO<sup>8</sup> launched an initiative "Make medicine child size" with aimed to raise awareness and accelerate action on providing access to child – specific medicines. In the same year, the European Pediatric Formulation Initiative (EuPFI) was established in London to help promote the preparation of effective and safe children medication by facilitating sharing of expertise between key stakeholders including academic researchers, industry, clinical and regulatory professionals. Its key objectives include identifying the common challenges encountered with developing formulations for pediatric populations to achieve better medications and dosage forms that are clinically relevant for children. The European Regulation on Pediatric Medicines<sup>9</sup>, now requires suitable dosage forms for children, particularly small children, to be developed by a pharmaceutical company as part of their pediatric investigation plan<sup>10</sup>.

The WHO model formulary for children provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO model list of essential

medicines for pediatrics. The desirable features that are essential and need to be taken into consideration when designing pediatric dosage forms include:

- Convenient, reliable administration and preferably ready-to-use formulations
- Minimal manipulation by health care professionals, parents or caregivers
- Dose and dose volume/weight adjusted to the intended age group
- Acceptable and palatable dosage form
- Minimum dosing frequency
- Minimal impact on life style
- Minimum, non-toxic excipients
- Transportable and low bulk/weight
- Easy to produce and stable in a variety of climates
- Affordable
- Commercially viable<sup>10</sup>

### TABLE 3 HERE

Some of the above features are considered for certain pediatric drugs such as dose and dosage volume, while others such as transport, weight and affordability address end-user needs in developing countries. The design and selection of new pharmaceutical dosage forms involves the careful consideration and a balance between quality target product profile versus technical challenges and development feasibility. Pediatric dosage forms present particular complexity due to the diverse patient population, compliance challenges and safety consideration amongst this vulnerable patient group. The pediatric population is divided into six groups such as; pre-term new-born infants, term new-born infants, infants/toddlers, pre-school children, school children and adolescents<sup>11</sup>. Further challenges include size and physiological and biological maturation, difficulties and low tolerance to unacceptable taste, specific concerns associated with required excipients<sup>12</sup>.

In a recent study on behalf of the EuPFI, Batchelor and co-workers surveyed global experts in pediatric biopharmaceutics from academia, healthcare professionals, pharmaceutical industry scientists and regulators to understand the current views around the development of a pediatric biopharmaceutics classification system (pBCS), something which is currently lacking in the state of the art of pediatric formulation and drug delivery<sup>13</sup>. They found that there was concern, especially in the area of defining of BCS for class II and class

IV drugs. The authors concluded that further cross disciplinary discussion and research is required into evidence that will underpin the development of a suitable pediatric BCS.

Drug therapy plays a vital role in disease management for pediatric populations suffering from a variety of acute and chronic diseases. The majority of drugs approved for adults, however, have not been approved for use in children though such medicines are commonly used in pediatric patients. One of the most important impediments for their application however, is the lack of suitable alternative pediatric dosage forms<sup>14</sup>. As a result, many drugs used in pediatric populations are not available in suitable dosage forms such as thin films and must be prepared extemporaneously, while using appropriate excipients. However, it is essential to determine the stability of various drugs at clinically important concentrations and safe practical storage conditions.

### **3.3 Common routes of drug administration for pediatric and geriatric populations**

Generally, drug administration occurs via various routes with varying degrees of benefits and drawbacks. Over the last few decades, administration of drugs in the human body has been the main area of research and different types of routes have been exploited as described in Table 4. The rejection rate of oral dosage forms is higher than other routes (topical, intravenous, intramuscular), due to the unpleasant and bitter taste of the medicine<sup>15</sup> as previously noted. Administration of drug to pediatric patients' body is always a challenge as pediatric dosage forms require accurate doses based on the age and body weight<sup>16</sup>. Oral mucosa (buccal) thin films offer easy administration and handling, can provide rapid disintegration and dissolution or sustained release, bypasses first-pass metabolism, enhanced stability and taste masking for bitter drugs, local and systematic drug delivery, rapid onset of action, and no trained or professional person is required for pediatric administration<sup>17</sup>.

**TABLE 4 HERE**

### **4 Tropical diseases: Malaria as a test case**

Most tropical diseases are commonly found in developing countries in Africa, Asia and the Americas and usually linked with poverty and its associated social challenges such as poor housing and sanitation as well as inadequate healthcare facilities and poor public health provision. Most of these diseases are poorly managed and have been officially designated as neglected tropical diseases (NTDs) by the WHO.<sup>18</sup> One other well-known tropical disease is



malaria which though receives a lot of current global attention, still poses significant threats to the endemic areas and even tourists who visit such places.

Malaria is caused by infection of red blood cells with protozoan parasites of Plasmodium through feeding bites by the female anopheles mosquito. The most common human Plasmodium species include *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, depending on the region of the world. The burden of malaria remains a significant public health challenge in Sub-Saharan Africa with reported incidents of morbidity and deaths arising from plasmodial infections. In 2010, 91% of the 655,000 global deaths due to malaria occurred in Africa and 86% of these cases occurred in children below the age of five<sup>18</sup>. According to the WHO, “there were an estimated 438, 000 malaria deaths in the world, of which approximately 69% were children under the age of 5 years”.<sup>18</sup> Though proven treatment options for malaria are fully documented, poor palatability and associated compliance issues persist and results in treatment failures. Available pediatric antimalarial agents are available as suspensions, powders or as tablets to be crushed for reconstitution with water, all of which have poor acceptability among children. Malaria drugs tend to be bitter, tablets are difficult to swallow and even sweetened liquid formulations leave a bitter after taste. Injections which are used as a last resort present the problem of pain and therefore not practical for routine drug delivery, leaving the oral route as the most viable option.

However, like most other medications, clinical trials are not conducted in children and as a result, there are no antimalarial pediatric formulations, which therefore requires breaking of tablets, which in most cases result in dosing inaccuracies. Further, issues of poor stability, microbial contamination and inaccurate dosing in liquid alternatives are apparent due to the lack of appropriately designed pediatrics formulations for the African market. Given that most newly developed antimalarial drugs, eventually face the problem of ‘drug resistance’, indiscriminate and ineffective use of antimalarial drugs, especially for children, is a critical issue, requiring urgent attention. As part of its recommendations on rationale use of antimalarial drugs, the WHO notes the importance of promoting adherence to a full treatment course, which is however, significantly impeded by the bitter taste of most drugs, especially for children, resulting in high chances of poor treatment and development of more resistant and dangerous strains of the parasite<sup>18</sup>. Therefore, resolving the problem of poor pediatric patient acceptability through formulation (or re-formulation) and novel drug delivery approaches, seems to be a viable means of improving uptake and ultimately therapeutic outcomes. Current treatment options recommended by the WHO for treatment of uncomplicated malaria in children are summarized in Table 5.

**TABE 5 HERE****5 Remedies**

In response to the above challenges, the pharmaceutical industry and regulators have explored various formulation approaches to improving patient compliance, especially in the vulnerable geriatric and pediatric populations as discussed below. Most of these approaches involve re-formulation in the form of oral dosage forms as they're the simplest and cheapest to produce and administer.

**5.1 Traditional remedies****Liquids (solutions, suspensions)**

Solutions and syrups contain one or more solids dissolved in a suitable solvent, usually water or a mixture of miscible solvents such as water and ethanol or water and glycerol. Their key advantage is the assurance of uniform dosage administration because of the solutes being uniformly dispersed throughout the solution. Solutions are also more easily swallowed compared to tablets and capsules and are therefore the most popular dosage form, especially for children. However, use of solutions has major disadvantages, such as chemical, physical, or microbial instability (requiring a preservative), taste issues (requiring taste masking and flavoring agents), lack of controlled release properties, limited number of safe excipients, and unreliable dosing because of incomplete swallowing<sup>20</sup>

Unlike solutions, suspensions comprise two phases with solid particles dispersed within a liquid phase. The main reason for using suspensions is the poor solubility of the main active ingredient and also has the possibility of taste masking the drug within the particulate excipient mixture. They are used for various routes of administration including oral, topical or nasal. The most common oral suspensions tend to be prepared in the form of dry powders for reconstitution, which has the advantage of reducing the incidence of drug instability. Typical examples include antibacterial suspensions for children such as amoxicillin. Generally, measuring devices such as cups, syringes or spoons are required to ensure accurate dosing of liquids unlike tablets, which can be challenging for children on their own and for geriatric patients, especially those with conditions such as Parkinson's disease. In the case of suspensions, patients need to remember to shake the bottle before use and suspending agents are required to ensure the drug particles remain suspended long enough to allow reproducible accurate dosing.

### **Semi-solids**

The use of semi-solids is based on the principle of convenient food intake such as porridge and mashed food which are easily eaten by children in particular or adults with little or no teeth. Sometimes, powders or crushed tablets are either mixed with such semi-solid foods or hidden within them to avoid contact of the medication with the taste mechanisms (especially in children), and therefore improve patient acceptance. Common semi-solid formulations for oral delivery or local mucosa administration include gels and medicated gums<sup>21</sup>.

Medicated gums are semi-solid confectionary type dosage forms designed for chewing to release the drug into saliva<sup>22</sup>. They can deliver the active ingredient to elicit local action within the mouth (such as antibiotics to control gum disease) or for systemic absorption<sup>23</sup> across the oral mucosa (buccal and sublingual) and / or gastrointestinal routes (e.g., nicotine). Medicated gums are traditionally manufactured using a melting process adapted from the confectionary industry but could also be obtained by directly compressing insoluble gum powder. Common gum bases include polyisoprene, polyisobutylene, isobutylene isoprene copolymer, styrene butadiene rubber, polyvinyl acetate, polyethylene, ester gums, and polyterpenes. Other excipients include plasticizers and softeners (e.g. glycerin and oleic acid) to maintain pliability, sweeteners, and flavoring agents to improve taste, and dyes to enhance appearance.

### **Lozenges**

Lozenges contain one or more drugs contained within a solid dosage form designed to dissolve or disintegrate slowly in the mouth to release the active ingredient. In most cases, lozenges provide local action in the oral cavity or the throat but some (e.g. nitroglycerin) are intended for systemic absorption after dissolution. Common drug classes delivered in the form of lozenges include antiseptics, analgesics, decongestants, antitussives and antibiotics. Lozenges can be formulated with sugars such as sucrose and dextrose or sugar-free alternatives usually based on sorbitol or mannitol<sup>21</sup>.

### **Soluble (orally disintegrating) tablets**

These are fast disintegrating tablets, usually containing highly water soluble additives or effervescent materials such as hydrogen carbonate, which easily dissolve or disintegrate rapidly in water, therefore allowing the patient to swallow in the form of a solution or

suspension<sup>24-25</sup>. They are manufactured by conventional tableting means or by using freeze-drying or molding approaches.

## 5.2 Novel drug delivery approaches

Over the past few decades, there has been an increased interest in novel drug delivery systems driven by various factors including:

- Therapeutic (clinical) concerns depending on whether the formulation in question is for self-administration, dosing schedule (daily versus weekly) or hospital use, preventive or therapeutic application, local or systemic delivery as well as age and disease state.
- Biopharmaceutics factors such as route of administration which is affected by the patient, disease state and site of action.
- Physico-chemical properties of the drug and dosage such as taste, color and appearance (size and shape) which determine patient acceptability.

These factors are important and are mainly aimed to improve safety, efficacy and patient compliance and ultimately help to increase product life cycle<sup>26</sup>. Liu and co-workers have suggested the use of fast melt formulations such as films and wafers for geriatric drug delivery as an alternative to traditional tablets, capsules and effervescent powders<sup>7</sup>.

### 5.2.1 Minitablets

These are flat or slightly curved tablets ranging in diameter from 1 – 3mm for easy administration, especially to children under the age of six who cannot take conventional tablets and are generally accepted by pediatric patients. In a randomized controlled trial in children, Klingmann and co-workers evaluated the acceptability of 2mm diameter mini-tablets in comparison with standard syrup formulations. The ability of the children to swallow 2mm mini-tablets (coated or uncoated) compared to 3ml of syrup was investigated. Their results showed that though all the formulations tested were generally accepted, the uncoated mini-tablets showed significantly higher acceptability than the syrup and concluded that mini-tablets are a suitable drug delivery alternative to syrups<sup>27</sup>. Biyyala and colleagues investigated mini-tablets in a GMP environment and concluded that “mini-tablets can allow flexible dosing across a wide pediatric age/weight range with just one dosage form” whilst they can be mixed with food or dispersed in liquid to improve patient acceptance<sup>28</sup>.

Mini-tablets show great flexibility in terms of application and rate of drug disposition as they can be formulated to release the drug very quickly as well as in a controlled fashion or a combination of both. Lopes and co-workers compressed mini-tablets into a biphasic delivery system that was able to release a model drug in a zero order release fashion over a long period of 8 hours using different combinations of hydroxypropylmethylcellulose and ethyl cellulose<sup>29</sup>. On the other hand, orally disintegrating mini-tablets have been reported as novel solid drug delivery systems and noted to fulfil the ideal requirements of pediatric appropriate formulations including ease of administration, flexible (individual) dosing adaptation to suit the wide age range, good stability, low transport and storage costs and excipients generally regarded as safe (GRAS)<sup>30</sup>.

### 5.2.2 Fast dissolving films and tablets

Fast-dissolving formulations generally disintegrate or dissolve within 1 minute when placed in the mouth in the presence of only saliva without the need for liquids or chewing. Compared to fast dissolving tablets, fast dissolving films and wafers are more recent formulations, designed for patients with fear of choking (pediatric and geriatric) and in some cases used to achieve patent extensions<sup>31</sup>. Fast-dissolving films are thin polymeric sheets comprising various hydrophilic polymers usually plasticized and can be prepared by solvent casting of aqueous gels or extruding by hot-melting of the powdered mixture. The most common fast dissolving film commercially available are summarized in Table 6 below. Commonly used film forming materials investigated include pullulan, cellulose ethers, starches, gums such as xanthan, alginates, polyvinyl alcohols, polyvinylpyrrolidone and various combinations of the above<sup>32-36</sup>. Fast dissolving formulations normally always contain excipients such as dextrose or sucrose and microcrystalline cellulose, with high water affinity, which contributes to the rapid disintegration in the presence of saliva. Cilurzo and co-workers developed fast dissolving films containing maltodextrins for delivering a model insoluble drug, piroxicam using both solvent casting and hot melt extrusion approaches. The other excipients included glycerol as plasticizer as well as sorbitan monooleate and microcrystalline cellulose<sup>37</sup>.

Reiner and co-workers investigated the bioequivalence of a patented film formulation of ondansetron compared with the commercial oral dispersing tablets and showed similarities in various regulatory pharmacokinetic profiles. They suggested that compared to tablets, the fast dissolving film was easier to swallow without any need of water, no liquid intake was necessary as well as no flavor taste compared to syrups and finally they were easier to handle,

store and transported around, compared to the orally disintegrating tablets<sup>38</sup>. Khan and co, used supercritical fluid technology to convert swelling controlled omeprazole loaded Metolose based films into rapid release fast dissolving films for potential pediatric delivery. The supercritical fluid treated films released greater than 90% of the drug within 15 minutes compared to the original swelling films which released just over 60% even after one hour<sup>39</sup>.

#### **TABLE 6 HERE**

Wafers on the other hand are highly porous solid dosage forms obtained by freeze-drying of polymer solutions. Their highly porous nature allow very rapid ingress of saliva which enables them to disintegrate or dissolve in the presence of minimal volumes of saliva and form easily flowing gels that can be readily swallowed without the risk of choking. The most common fast dissolving wafer commercially available is Zydis developed by Catalent, which dissolves on the tongue almost instantly upon contact with saliva. The company lists a range of applications and indications including dysphagia, pediatric and geriatric application, fast onset, and ease of use. Therapeutic indications include anti-psychotic (Parkinson's disease, schizophrenia), anti-emetic (travel sickness), gastrointestinal (diarrhea, constipation), allergy (anti histamine, immunotherapy) and anxiolytic (anti-depressants)<sup>41</sup>. In a pilot clinical trial, an open label oral to Zydis switch study was conducted to investigate the tolerability of rapid switch from oral selegiline to Zydis selegiline for the treatment of Parkinson's disease. Patients generally preferred the Zydis selegiline preparation but the authors concluded that the difference is unclear for any clinical significance given the open label nature of the trial<sup>42</sup>. Preis and co-workers evaluated taste-masked cetirizine hydrochloride formulated in oral freeze-dried matrix based on the Zydis technology. Their study showed that a resin of cetirizine HCl and various cyclodextrins were successfully incorporated into the Zydis freeze-dried formulation and yielded a stable product with good release profile in the presence of cyclodextrin<sup>43</sup>.

#### **5.2.3 Controlled release mucoadhesive films and wafers**

More recently, there has been interest in mucoadhesive formulations such as films and wafers for drug delivery across the non-keratinized oral (buccal and sublingual) mucosal membranes to achieve systemic effect without the need for swallowing whilst also avoiding first pass metabolism, which can allow the use of lower doses to reduce potential side effects. Due to the numerous advantages of buccal dosage forms, pharmaceutical companies have adopted

various technologies to manufacture oral films on a large scale as an alternative to traditional dosage forms such as tablets and capsules<sup>44</sup>.

There have been several studies reported in the literature for such mucoadhesive formulations for various applications including pediatric and geriatric patients and for various indications and these are summarized in Table 7 below. The matrix usually comprises hydrophilic polymers with functional groups able to form suitable interactions with the mucin glycoproteins present on the buccal and sublingual mucosal surface, which ensures prolonged residence time to allow drug penetration through the membrane epithelium.

#### **TABLE 7 HERE**

### **5.3 Personalized medicine**

General drug development involves testing new drugs or products in subsets within populations without necessarily taking into consideration the genetic, physiological, biochemical, nutritional and personal variations between different (individual) patients<sup>65</sup>. This results in differences observed in therapeutic outcomes and even toxicities and side effects of administered therapies. Conventional dosage forms such as tablets or capsules, contain predefined amounts of active pharmaceutical ingredients with clinical trials testing undertaken using middle aged adult males. As a consequence, certain patient groups, particularly women, pediatric and geriatric patients could experience under- or over-dosage, which could result in reduced efficacy or side effects respectively. The objective of personalized medicine therefore is to individualize drug dosage that is specifically customized to the needs of an individual patient. This is important as several variables such as age, weight, height, race, gender and disease state of the individual patient, affect efficacy (and/or toxicity) and should therefore be considered and translated in precisely tailored oral delivery forms to allow for more individual-specific therapeutic effect.

With advances in molecular biology, biotechnology and bioinformatics tools, exemplified by the sequencing of the human genome, there has been a move towards designing drugs and dosage forms, tailored to the biochemical and physiological make-up of the patient, in a new field referred to as personalized medicine. The Personalized Medicine Coalition<sup>66</sup> defines it as “the use of new methods of molecular analysis to better manage a patient’s disease or predisposition to disease”. The European Union<sup>67</sup> defines it as “providing the right treatment to the right patient, at the right dose at the right time”. President’s Council

of Advisors on Science and Technology<sup>68</sup> defines personalized medicine as “the tailoring of medical treatment to the individual characteristics of each patient.” The American Medical Association<sup>69</sup> defines personalized medicine as “Health care that is informed by each person’s unique clinical, genetic, and environmental information”; whilst the National Cancer Institute, NIH<sup>70</sup> defines personalized medicine as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.”

The main advantage of personalized medicine as far as pediatric and geriatric patients are concerned, is that it avoids the ‘one-size-fits-all’ approach (Figure 2) which does not take into consideration the wide differences present within these patient groups as noted above. For example, pediatric patients are at different stages of development from birth right up to puberty whilst the bodies of geriatric patients begin to deteriorate at different rates and at different stages depending on age, lifestyle and body weight<sup>71</sup>.

## FIGURE 2 HERE

### 5.3.1 Drug delivery approaches to personalized medicine

According to the FDA<sup>71</sup>, personalized medicine promises to increase benefits and reduce risks for patients by improving both the safety and efficacy of medicinal products. As a result, drugs need to be designed and delivered using appropriate formulations that ensure the drug reaches the intended target to achieve the desired therapeutic effect whilst at the same time being easy to administer for the patient, to reduce the chances of non-compliance, which can have severe consequences including complications and potential fatalities. Further, such dosage forms should as much as possible be able to be produced on a large scale as well as extemporaneously on a small scale in hospital pharmacies and dispensaries and within nurse clinics. This requires use of cheap and readily available excipients, approved by regulators such as the FDA and generally be regarded as safe (GRAS). Breitzkreutz and Boos suggested that drug delivery to older patients require individualized dosing, patient adapted drug formulations and delivery devices to ensure specificity of drug efficacy<sup>73</sup>. In particular, highly potent active pharmaceutical ingredients with very narrow therapeutic windows, such as digoxin and morphine, require precise dose adaptation, including use of phased dose titration. This requires appropriate drug delivery systems to allow the selection and administration of individualized drug dose to be embedded into routine clinical pharmacy practice.



Pardeike and co-workers investigated nano-suspensions as personalized oral dosage forms using a micro-dosing technology. This was based on inkjet-type printing technique where all the active pharmaceutical ingredients and excipients for an individual patient were directly printed on an edible substrate which was easily inserted into a hard gelatin capsule for oral administration<sup>74</sup>. The advantages of this technique as spelt out by the authors include (i) the possibility of on-demand manufacturing of a personalized oral dosage for individual patients, (ii) precise dosing of low-dose drugs and/or drugs with a small therapeutic window, (iii) multi-dosing by printing multiple drug layers on one paper carrier strip using barrier coatings and (iv) no need for the development of complex formulations (e.g. multilayer tablets)<sup>74</sup>. However, practical implementation and clinical studies are required to be able to confirm the effectiveness and success of these concepts. Current practices still involve dosing liquids by droppers, spoons and syringes or splitting tablets into segments, which clearly present various risks such as inaccurate dosing (Figure 3). Though multi-particulate dosage forms (pellets) dispensers have been developed, there is only one dispenser available on the market. Other technologies such as the Solid Dosage Pen has potential for individualize dose choices<sup>73</sup>.

### **FIGURE 3 HERE**

### **6 Concluding remarks**

New developed drugs will need to be designed with the delivery to the required patient groups (including vulnerable groups such as geriatric / pediatrics) in mind and tailored accordingly. This will need to include considerations at phase II and III clinical trials in children and geriatric populations for already approved drugs that have passed stringent safety and quality checks, just for the purpose of accurate dose calibration. Of course this raises ethical dilemmas of administering therapy to one group of children, but not others. Therefore models that bioequivalently mimic pediatric populations need to be designed to avoid the need of risking drug administration to such vulnerable patient groups during clinical trials or possibly reduce the sample sizes required in such endeavors.

### **Conflict of interest**

There are no conflicts of interest to declare.

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**FIGURE LEGENDS**

Figure 1 The various absorption barriers and stages of loss encountered by a typical drug delivered in the form of an oral dosage form (e.g. tablet or capsule).

Figure 2. Representation of the trial-and-error or one-dose-fits-all approach versus personalized medicine. [Reproduced from Xie and Frueh 2005)]<sup>72</sup>.

Figure 3 Various dosage forms currently employed in personalized medicine drug therapeutics. Adapted from<sup>65</sup>

Table 1 Advantages and limitations of traditional routes of administration

Route	Type of dosage form	Advantages	Disadvantages
Oral	<ul style="list-style-type: none"> <li>• Tablets</li> <li>• Capsules</li> <li>• Liquids</li> <li>• Suspensions</li> </ul>	<ul style="list-style-type: none"> <li>• It is the most commonly used route.</li> <li>• Cheap and very economical.</li> <li>• Administration does not require special skills.</li> <li>• Self-medication is possible.</li> <li>• This route is convenient.</li> <li>• This route is painless<sup>1</sup>.</li> </ul>	<ul style="list-style-type: none"> <li>• Pediatric and geriatric patients have difficulty in swallowing.</li> <li>• Swallowing medication requires fluids and therefore the probability of nausea and vomiting is increased.</li> <li>• Absorption rate of the drug into the bloodstream after swallowing varies depending on gastric emptying rate.</li> <li>• Affected by intestinal and stomach secretions and pH<sup>2</sup>.</li> <li>• Therapeutic peptides and proteins deactivated by the presence of acidic (stomach) environment and proteolytic enzymes in the GI tract<sup>3</sup>.</li> <li>• Subject to first pass metabolism in the liver<sup>4</sup>.</li> </ul>
Parenteral (injections)	<ul style="list-style-type: none"> <li>• Solutions</li> <li>• Emulsions</li> </ul>	<ul style="list-style-type: none"> <li>• Rapid access of drug to the site of action without the risk of first pass metabolism in the liver.</li> <li>• Lower drug doses required compared to the oral route.</li> <li>• Drug rapidly disperses to various part of the patient's body before experiencing first pass effect in the liver.</li> </ul>	<ul style="list-style-type: none"> <li>• Most patients, predominantly infants and geriatrics, do not readily accept injections because of pain.</li> <li>• Rate of metabolism varies between patients and therefore repeated injections might be necessary which can increase the stress level in patients<sup>1</sup>.</li> </ul>
Topical (dermal / skin)	<ul style="list-style-type: none"> <li>• Creams</li> <li>• Ointments</li> <li>• Suspensions</li> <li>• Emulsions / lotions</li> <li>• Powders</li> </ul>	<ul style="list-style-type: none"> <li>• Practical approach for treating skin conditions</li> </ul>	<ul style="list-style-type: none"> <li>• Does not always enable medication to penetrate deeply to provide a systemic effect.</li> <li>• The rate of drug uptake across the skin is slow and therefore cannot be used in emergency situations.</li> <li>• Continuous contact with air can cause either oxidation or contamination to change the properties of the drug.</li> </ul>

Table 2: Selected common geriatric diseases and current clinical therapies

Disease	Therapy/management	Dosage form(s)
Alzheimer's Disease	Cholinesterase inhibitors e.g. Donepezil	Tablets, orally disintegrating tablets
Arrhythmia of the Heart	Beta-blockers e.g. Propranolol	Tablets
Arthritis	Disease modifying anti-rheumatic drugs e.g. Cyclosporine	Capsules, liquids
Bedsore (pressure ulcers)	Muscle relaxants e.g. diazepam	Tablets
Cancer	Chemotherapy, depending on type of cancer	Tablets, injections
Cataracts	Surgery	-
Cholesterol	Statins e.g. atorvastatin	Tablets
Chronic Kidney Damage	Diuretics e.g. furosemide	Tablets
Chronic Obstructive Pulmonary Disease	Mucolytics e.g. carbocysteine	Tablets, capsules
Diabetes (e.g. Type 2)	Biguanides e.g. Metformin	Tablets
Glaucoma	Eye drops	Liquid
Hypertension (High Blood Pressure)	Beta-blockers e.g. atenolol Calcium channel blockers e.g. amlodipine	Tablets Tablets
Incontinence, Urinary	Antimuscarinics e.g. oxybutynin	Tablets, syrup, topical gel / patch
Lymphoma, Non-Hodgkin's	Chemotherapy (e.g. vincristine) in combination with steroids (e.g. prednisolone)	i.v. injections Tablets,
Macular Degeneration, Dry	Supplements e.g. vitamins and minerals	Tablets, capsules
Multiple Sclerosis (MS)	Immunomodulators e.g. Fingolimod	Capsules
Osteoarthritis	NSAIDS e.g. diclofenac	Tablets, cream
Osteoporosis	Bisphosphonates e.g. alendronate	Tablets
Parkinson's Disease	Dopaminergic drugs e.g. levodopa	-
Stroke	Antiplatelets e.g. aspirin	Tablets

Table 3 Selected common pediatric conditions and current therapies

Disease	Treatment	Dosage form
Chicken pox	Paracetamol	Suspensions
	Kaolin	Suspensions
Ear infections	Antibiotics	Oral liquids or ear drops
	Paracetamol	Suspension
Flu	Paracetamol	Suspension
Gastroenteritis	Oral salts	Liquids
Impetigo	Antibiotics	Oral liquids
		Skin cream
Malaria	Artemether + lumefantrine	Dispersible tablets
	Artesunate + mefloquine	Tablets
	Dihydroartemisinin + piperaquine	Tablets
Scarlet fever	Antibiotics	Suspensions
Tonsillitis	Paracetamol	Suspensions
	Ibuprofen	Sprays
		Lozenges
Whooping cough	Antibiotics	Suspensions

Table 4 Different routes of drug administration and corresponding dosage forms for adults and pediatric patients.

Administration routes	Site of administration	Dosage forms
Oral	Mouth	Solution, syrup, suspension, emulsion, gels, powders, granules, capsules, tablets etc.
Sublingual	Under the tongue	Tablets, troches or lozenges
Buccal	Between gum and cheek	Orally disintegrating tablet, Film, lollipop, lozenges, chewing gum
Topical (epicutaneous/transdermal)	Skin surface	Aerosols, gels, pastes, lotions, creams
Parenteral	Vein, spine, skin, muscles, bones, arteries, heart, joint-fluid areas, joints	Injections, implants, irrigation
Rectal	Rectum	Ointments, powders, creams, suppositories, solutions
Respiratory	Nasal	Aerosols, inhalations, sprays, gases

Table 5 Antimalarial combination therapies (ACT) currently recommended by the WHO<sup>19</sup> for treating uncomplicated malaria.

Type of ACT	Available adult Formulations	Available pediatrics formulations	Target dose range	Recommended dose
Artemether + lumefantrine	Dispersible or standard tablets containing 20mg artemether and 120mg lumefantrine	Flavored dispersible tablet	5–24mg/kg body weight of artemether and 29–144 mg/kg body weight of lumefantrine	Twice a day for 3 days (total of 6 doses)
Artesunate + amodiaquine	Fixed dose combination tablet containing 25+ 67.5mg; 50+ 135mg; or 100+ 270mg of artesunate and amodiaquine respectively	None	4 (2–10mg/kg body weight per day artesunate and 10 (7.5–15) mg/kg body weight per day amodiaquine.	Daily for 3 days
Artesunate + mefloquine	Tablets containing 100mg artesunate, 220mg, mefloquine hydrochloride (200 mg mefloquine base)	A fixed dose pediatric tablets containing 25mg artesunate and 55mg mefloquine hydrochloride (50mg mefloquine base)	4 (2–10) mg/kg body weight per day artesunate and 8.3 (5–11)mg/kg body weight per day mefloquine	Daily for 3 days
Artesunate + sulfadoxine /pyrimethamine	Blister packed, scored tablets containing 50mg artesunate and fixed dose combination tablets containing 500mg sulfadoxine+25mg pyrimethamine	None	4 (2–10)mg/kg body weight per day artesunate and 25 /1.25 (25–70 /1.25–3.5) mg/kg body weight sulfadoxine/ pyrimethamine	Artesunate dose given daily for 3 days. Sulfadoxine / pyrimethamine dose given as single dose on day 1.
Dihydroartemisinin + piperaquine	Fixed dose combination tablets containing 40mg dihydroartemisinin and 320mg piperaquine.	Pediatric tablets containing 20mg dihydroartemisinin and 160mg piperaquine	4 (2–10) mg/kg body weight per day dihydroartemisinin and 18 (16 – 27) mg/kg body weight per day piperaquine for 3 days for adults and children weighing > 25kg. 4 (2.5–10)mg/kg body weight per day dihydroartemisinin and 24 (20– 32)mg/kg body weight per day piperaquine for 3 days for children weighing < 25kg.	Daily for 3 days



Table 6 Examples for fast dissolving films commercially available on the market (y = years, m = months) (Reproduced from Slavkova and Brietkretz, 2015)<sup>40</sup>

Indications	API	Product	Age	Company
Mouth freshener	Mint oil	Listerine	n.d.	Pfizer
Flatulence, nausea	Silicone oil	Gas-X-Tongue Twisters	≥ 0 y	Gas-X
Nicotine withdrawal symptoms	Nicotine	NiQuitin Strips	≥ 12 y	GSK
Iron deficiency, anemia	Ferric oxide Folic acid	Hemoramin	≥ 18 y	C.L. Pharm
Chemotherapy induced nausea and vomiting	Ondansetron	Setofilm Zuplenz	≥ 6 m ≥ 4 y	Norgine/tesa Labtec Galena Biopharm
Migraine	Zolmitripan	Zolmitriptan Renantos	≥ 18 y	Renantos
Schizophrenia	Risperidone	Risperidon HEXAL SF	≥ 4 y	Hexal/Sandoz
Alzheimer's disease	Donezepil Hydrochloride	Donezepil-HCl HEXAL SF	≥ 18 y	Hexal/Sandoz
Erectile dysfunction	Sildenafil citrate	Sildenafil Sandoz Sedera	≥ 18 y	Sandoz C.L. Pharm



Table 7. Summary of published buccal and sublingual drug delivery systems

Drug	Formulation / Reference
Paracetamol, indomethacin	Film <sup>45</sup>
Rizatriptan benzoate	Film <sup>46</sup>
Insulin	Film <sup>47</sup>
Insulin	Film <sup>48</sup>
Nicotine	Film <sup>49</sup>
Zolmitriptan	Film <sup>50</sup>
Lidocaine	Patch <sup>51</sup>
Omeprazole	Film <sup>52</sup>
BSA	Wafer <sup>53</sup>
BSA	Xerogels <sup>54</sup>
BSA	Wafer <sup>55</sup>
BSA	Wafer <sup>56</sup>
BSA	Wafer <sup>57</sup>
Insulin	Xerogels <sup>58</sup>
Ibuprofen, paracetamol	Wafer <sup>59</sup>
Nicotine	Films / wafers <sup>60</sup>
Nicotine	Films / wafers <sup>61</sup>
Omeprazole	Films <sup>62</sup>
Ondansetron	Films <sup>63</sup>
Lidocaine hydrochloride	Films <sup>64</sup>

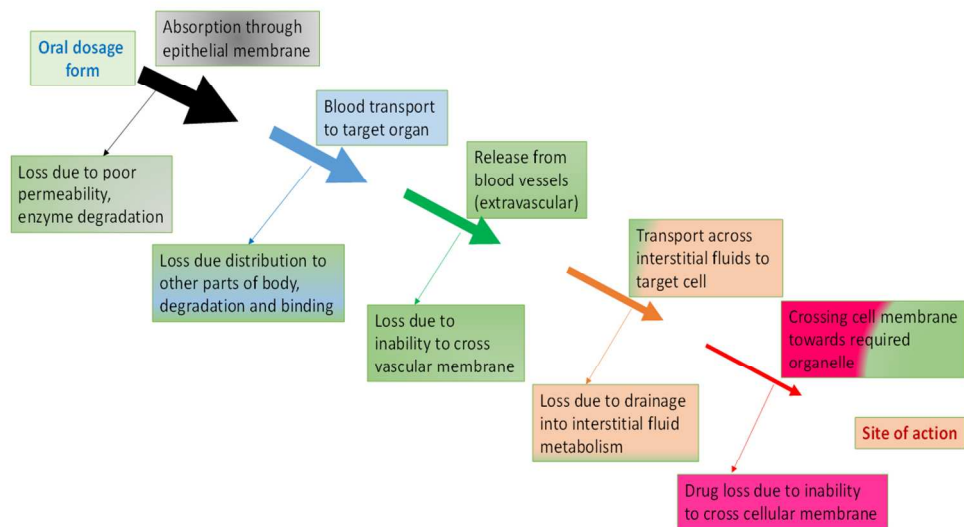


Figure 1

338x190mm (96 x 96 DPI)

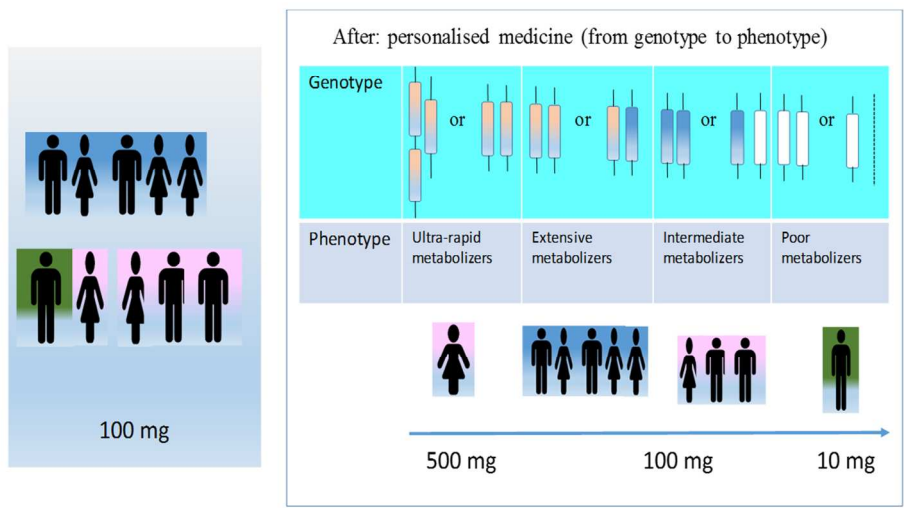


Figure 2

338x190mm (96 x 96 DPI)

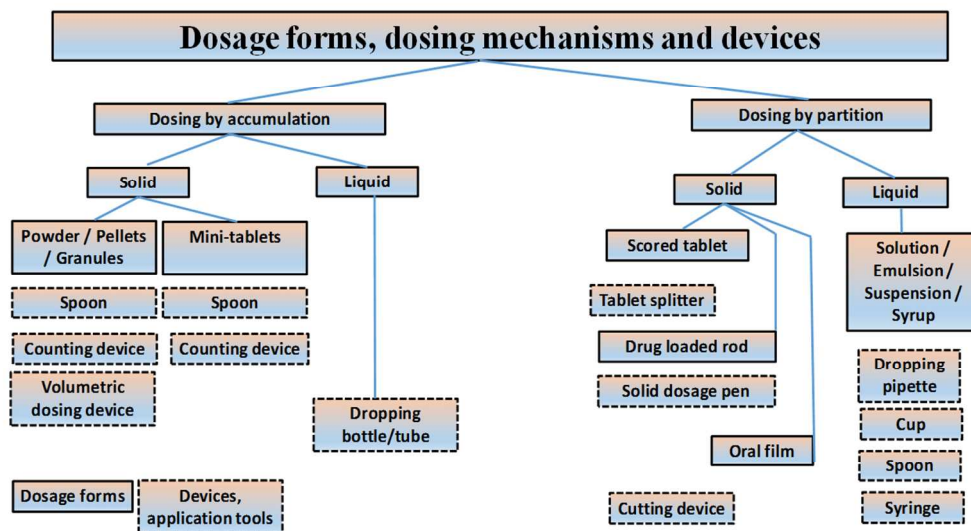


Figure 3

338x190mm (96 x 96 DPI)