

Patient centric formulations for paediatrics and geriatrics: Similarities and differences

Sara M Hanning^{a*}, Felipe L Lopez^a, Ian C K Wong^a, Terry B Ernest^b, Catherine Tuleu^a, Mine Orlu Gul^a

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- a. UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom
- b. GlaxoSmithKline Pharmaceuticals, Harlow, Essex CM19 5AW, United Kingdom

10 *Corresponding author:

Sara Hanning

Department of Pharmaceutics

UCL School of Pharmacy

29-39 Brunswick Square

15 London, WC1N 1AX

United Kingdom

Phone 0044 20 7753 5968

Email s.hanning@ucl.ac.uk

20 Abstract

Paediatrics and geriatrics both represent highly heterogenous populations and require special consideration when developing appropriate dosage forms. This paper discusses similarities, differences and considerations with respect to the development of appropriate medicine formulations for paediatrics and geriatrics. Arguably the most significant compliance challenge in older people is polypharmacy, whereas for children the largest barrier is taste. Pharmaceutical technology has progressed rapidly and technologies including FDCs, multi-particulates and orodispersible dosage forms provide unprecedented opportunities to develop novel and appropriate formulations for both old and new drugs. However, it is important for the formulation scientists to work closely with patients, carers and clinicians to develop such formulations for both the paediatric and geriatric population.

Key words

Paediatric, geriatric, medicine, excipients, dosage form, patient-centric

35 Paediatric and geriatric patients do not fall into the category of ‘standard patient’ due
to altered pharmacokinetics, different acceptable dosage forms, formulation
composition and route of administration. In the paediatric population, there are
distinct physiological differences between neonates, infants, children and adolescents.
However, relating this information to adult data when determining an appropriate
40 dosing regimen is complicated (Bartelink et al., 2006). In neonates and infants,
immaturity of enzymes, volume of distribution and clearance may result in differences
in pharmacokinetics. In older people, these differences cannot be defined by age
alone. Pharmacokinetics are strongly influenced by morbidity, co-morbidity, multiple
drug use or reduced organ function. The ICH Harmonised Tripartite Guideline:
45 Studies in Support of Special Populations: Geriatrics E7 highlights the need to
conduct pharmacokinetic studies in healthy geriatric subjects or volunteers with the
disease to be treated by the drug of interest. It is not uncommon for clinical trials to
exclude older patients, for reasons such as concomitant conditions, polypharmacy or
frailty, yet this data is essential to maintain safety and optimise medication for the
50 older population (Ford, 2000; Mangoni and Jackson, 2004). If age-related differences
are found that could be of medical importance, a larger, multiple-dose PK study may
be necessary to permit statistical comparisons between different patient cohorts at
steady state (International Conference on Harmonisation, 1993). Similarly, the
Paediatric Regulation was introduced in 2007 to ensure that medicines for use in
55 children are of high quality, ethically researched and appropriately authorised.

In both paediatric and geriatric population groups, challenges exist in the development
of formulations that will offer a predictable and safe drug release in the patient, whilst
also being presented in an acceptable dosage form to ensure safety and compliance.

60 Manufacturing complexity and cost are also important considerations. From an
industry perspective, the paediatric population represent a small market, with many
illnesses short term. Adopting a patient centric approach for such a small target group
can be difficult financially, requiring significant labour and resources. The geriatric
population, on the other hand, are a wider group with a broad range of therapeutic,
65 hence pharmaceutical, needs. By considering the similarities between the paediatric
and geriatric population, labour and resource costs may be minimised whilst
maintaining this patient focus. This paper outlines some of the paediatric and geriatric
formulation needs from a patient centric perspective, with a focus on novel

oral systems such as fixed-dose combinations, multi-particulates and orodispersible
70 dosage forms. Patient centric formulation development refers to considering the
end user from the beginning of the formulation process and right through the
development to an end product.

Excipient and other formulation issues

75 Excipients of medications that may be acceptable in adult formulations may not be
suitable for special populations such as paediatrics and geriatrics. For example, high
sodium intake disturbs electrolyte balance, causing water retention and increasing the
risk of cardiovascular conditions including stroke, hypertension and heart failure,
particularly in older adults (George et al., 2013). Despite this, a recent review of
80 cardiovascular formulations listed in the British National Formulary (BNF) found
instances where effervescent, dispersible and soluble tablets prescribed for
cardiovascular disorders contained sodium levels higher than the recommended daily
intake of sodium in adults (2.4g or 104mmol) (Hanning et al., 2015; Joint Formulary
Committee, 2013). In addition, only 40% of medicines listed in the BNF for
85 cardiovascular disorders specified dose recommendations that could be adjusted for
older patients, taking into consideration factors such as comorbidity, polypharmacy
and vulnerability to adverse effects (Hanning et al., 2015).

For children the situation is even more critical, as the vast majority of medicines
90 prescribed for children with cardiovascular problems are unlicensed and often
manipulated at the point of administration or only available as extemporaneous
formulations (Standing and Tuleu, 2005). Implications of this include dosing
accuracy, unknown bioavailability of extemporaneously prepared formulations, use of
excipients that may be toxic and a lack of access to modified release preparations for
95 children. Although the introduction of the European Union regulation on medicinal
products for paediatric use in 2007 has endeavoured to improve rational, evidence-
based prescribing and age-appropriate formulations for children, a significant number
of products still lack paediatric information (Breitkreutz; Frattarelli et al., 2014; Sachs
et al., 2012).

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Oral drug delivery is the most popular route of medicine administration. Advantages
include ease of ingestion, avoidance of administration discomfort/pain, low

manufacture cost, versatility and expected better patient compliance (Sastry et al., 2000). Many individuals find it difficult to swallow tablets and hard gelatin capsules
105 and this difficulty is especially prevalent in paediatric and geriatric patients (Lindgren and Janzon, 1991; Patel et al., 2015). Co-administration with food is often recommended to ease ingestion of medication, although this practice might have an impact on the oral bioavailability of the drug. Depending on the active moiety and the type of food this can result in an increased or decreased exposure (Martinez and
110 Amidon, 2002). Therefore, recommendations need to be made in a case-by-case basis. Critically, food preferences may vary between paediatric and geriatric individuals, so a variety of food types need to be considered. Not only food, but also oral vehicles (syrups and gels) and thickening agents (which can be added to a drink to increase its consistency) have been investigated and proposed. These administration aids could be
115 supplied along with the drug product, could be commercially available as a separate product, or could be extemporaneously prepared in community pharmacies as required (Kluk and Sznitowska, 2014). Caution must be taken with recommending these products until sufficient scientific evidence with regards to the safety of this practice is generated. In fact, preliminary data suggest that thickening agents could
120 hinder release of drugs from crushed tablets (Manrique et al., 2014). Further research in this topic is required to enable safe administration of medication with food and thickening agents.

Fixed-dose combinations

125 Fixed-dose combinations (FDCs) are a way of administering multiple medications in a single dosage form. Their primary advantage is to reduce complexity of therapy and improve medication compliance by reducing pill burden in patients with co-morbidities. Therefore, FDCs address two key determinants of poor medication compliance – polypharmacy and the complexity of treatment regimen. FDCs have
130 been shown to decrease the risk of medication non-compliance in patients with chronic conditions (Bangalore et al., 2007). In addition, the combination of drugs with different mechanism of action can achieve greater efficacy (synergistic effect) with a lower occurrence of adverse events compared to increasing the dose of the monotherapy (Garber et al., 2002; Panaccione et al., 2014). Other advantages include
135 the simplification of drug handling and lower packing and shipping costs. FDCs are primarily advantageous for geriatric patients with polypharmacy, however, can also

be helpful for paediatrics in conditions requiring combined medication, such as tuberculosis and HIV. Although some commercial FDC preparations exist, such as Rifater® and Rifanah® (Sanofi-Aventis) for the treatment of tuberculosis, these are not
140 licenced for use in children. However, these preparations could be considered in older children provided that the dose of each drug is appropriate given the weight of the child (BMJ Group, 2011).

FDCs also have some potential limitations. FDCs restrict individual dose titration of
145 each active ingredient which, indeed, discourages adjustment of doses to the individual patient's need (Blomberg et al., 2001; World Health Organisation, 2003). This is of critical importance when the combined drugs exhibit different pharmacokinetics and/or pharmacodynamics. Unless each active ingredient is available as a separate drug product, FDCs encourage polypharmacy irrespective of
150 the appropriateness of drug combination for a particular patient (World Health Organisation, 2003). The incorporation of various drugs in single dosage forms pose unprecedented technical challenges which arise from incompatibilities of the combined drugs (Singh et al., 2001). Furthermore, the final dosage form may become significantly larger, obstructing oral administration (Desai et al., 2013). This is of
155 particular importance if an individual suffers from dysphagia or struggles to swallow tablets, which are common features in the geriatric and paediatric population. Some of these challenges might be overcome via the preparation of multi-particulate formulations or oral fast dissolving dosage forms.

160 **Multi-particulate formulations**

Compared to single dose units, which usually take the form of a tablet, multi-particulate formulations are smaller, multiple unit systems of mini-tablets or pellets that are either filled into capsules or compressed into tablets that disintegrate into the original pellet size on administration (Newton, 2010). In some cases, the dose may be
165 adapted to meet patient requirements, for example the administration of a quantity of pellets based on body weight. The utilisation of specialised counting and dosing devices may be necessary in these instances (Wening and Breitzkreutz, 2011) and new research is on-going in this area.

170 Commercial examples of multiparticulate formulations include Depakote[®] capsules
(divalproex sodium) and Creon[®] capsules (pankrelipase), whereby the capsules can be
swallowed whole, or if swallowing is an issue the capsule contents may be sprinkled
onto soft food. As discussed previously, the type of food that is used as the vehicle in
these instances is important, although often little instruction is given.

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Multi-particulate formulations are a good choice for the development of FDC
products since individual dosage units containing different entities can be combined
in the final dosage form (e.g. filled into capsules). This approach clearly presents
fewer limitations from a pharmaceutical development perspective than the
180 combination of drugs in the same dosage unit, particularly in the case of drugs with
physical or chemical incompatibilities (Desai et al., 2013). Thus, multi-particulate
formulations offer great design flexibility by combining particles with different drugs
and/or with different release profiles. This type of formulation is also a great
candidate for the preparation of controlled release products with minimal risk of dose
185 dumping. Due to their reduced size, multi-particulates are expected to exhibit a
shorter and more reproducible gastric emptying than single-unit dosage forms, which
is desirable in the design of controlled release products. However, evidence in this
area is limited in the young and the old, as studies have focused in the adult
population only (Newton, 2010; Varum et al., 2010). Paediatric and, in particular,
190 geriatric patients with chronic conditions may benefit from controlled release products
to reduce the frequency of administration and ultimately the pill burden.

Many barriers and unknowns arise at the point of administration of pellets and mini-
tablets. The maximum number of dosage units that can be administered in a single
195 dose has not yet been investigated for any targeted patient group. This is important as
it defines the maximum dose that can be delivered, which could hinder the preparation
of FDC if the dose required exceeds the maximum delivery dose.

In spite of the acclaimed advantages of this type of formulation, the number of
200 products in the market is still limited. The development of multi-particulate systems
may require advanced pharmaceutical technology, multiple step processes and
diligent control of processing variables. This can entail a time-consuming and costly
production with respect to conventional solid dosage forms (Roy and Shahiwala,

2009), although in practice multi-particulates could be manufactured in the same way
205 as conventional tablets but down to 1mm diameter (Tissen et al., 2011), using an
established and well-controlled process. It is important that the combination of multi-
particulate technology with the selected drug substance and packaging system is
prosperous to achieve patient acceptance and smooth the path for other medicines to
take the form of multi-particulate products. Oral fast-dissolving dosage forms are a
210 more established platform that have already come a long way, with many patients
already benefiting from this novel approach to drug delivery in various therapeutics
areas.

Orodispersible dosage forms

215 Orodispersible dosage forms are those that disintegrate or dissolve rapidly in the oral
cavity, resulting in a solution or suspension without the need for water. Examples of
commercially manufactured orodispersible dosage forms are highlighted in Table 1.
In terms of specific use for paediatric and geriatric population groups, their primary
advantage is their ability to be administered to those with difficulties swallowing solid
220 dosage forms (Sastry et al., 2000). However, disadvantages include limited drug
loading and the requirement for taste masking.

Orodispersible tablets (ODTs) and oral lyophilisates dominate the market of oral fast-
dissolving dosage forms (Slavkova and Breitzkreutz, 2015). Similar in appearance to
225 conventional tablets, these solid formulations disintegrate quickly in the oral cavity
thanks to a rational selection of excipients (e.g. superdisintegrants) and/or
manufacturing processes which confer higher tablet porosity (Al-khattawi and
Mohammed, 2014; Badgujar and Mundada, 2011). Orodispersible films (ODFs) are
thin strips of film that undergo rapid disintegration in the oral cavity when placed on
230 the tongue (Hoffmann and Breitenbach, 2011). Alternative fast-dissolving dosage
forms are being introduced including orodispersible granules and orally disintegrating
mini-tablets (Krause et al., 2009; Stoltenberg and Breitzkreutz, 2011).

Table 1 Examples of marketed orodispersible tablets, oral lyophilisates and
235 orodispersible films. Adapted from Slavkova and Breitzkreutz (2015).

Dosage form

Examples of marketed products

Orodispersible tablets	Prevacid solutab (lansoprazole), Allegra (fexofenadine hydrochloride), Orapred ODT (prednisolone), Parcopa (levodopa/carbidopa), Zomig-ZMT (zolmitriptan)
Oral lyophilisates	Zofran Zydis (ondansetron), Imodium akut lingual (loperamide), Zyprexa Velotab (olanzapine), Clarinex Reditabs (loratadine), Zelapar (selegiline), Maxalt-lingua (Rizatriptan benzoate)
Orodispersible films	Setofilm (ondansetron), Zuplenz (ondansetron), Risperidone Hexal SF (risperidone), Donezepil-HCl Hexal SF (Donezepil hydrochloride)

240 A fundamental gap in the development of fast-dissolving dosage forms is the lack of officially recognised characterisation methods. According to the European Pharmacopoeia 7.4, orodispersible preparations should be produced in a way that they possess suitable mechanical strength to withstand handling without being damaged, but the only specific test mentioned is dissolution. Despite this, there is no clear indication of how long an orodispersible preparation should take to disintegrate and there is no clearly defined endpoint for disintegration in the European Pharmacopoeia. This is particularly important as the disintegration time is a vital property that affects

 245 drug administration and drug release (Pein et al., 2014). Compendial disintegration testing has shown very poor correlation with *in vivo* disintegration time in the mouth, while novel testing techniques can attain much better correlation (Brniak et al., 2012; Hoashi et al., 2013; Szakonyi and Zelkó, 2013). In addition to fast disintegration other ideal properties include flexibility (in the case of films), physical stability, good

 250 handling and suitable mechanical strength (Visser et al., 2015).

Palatability and in particular taste are key attributes of oral fast-dissolving dosage forms as the formulation is intended to disintegrate in the oral cavity. The utilisation of taste-masking technologies in combination with oral fast-dissolving dosage forms

 255 is often required (Douroumis, 2011). Several techniques might be considered, either alone or in combination, to attain taste masking. The addition of sweeteners and flavouring agents are often the first approach investigated since special

manufacturing technologies or equipment are not required and the pharmacokinetic properties of the drug product are not likely to be affected (Walsh et al., 2014). The use of complexation (e.g. ion exchange resins) or coating (e.g. sugar, polymeric or lipidic coating) to apply a molecular or physical barrier between drug and palate is considered to be more effective than the sole addition of sweeteners and flavours; however, this approach could have an impact on the bioavailability of the product and is also more technically challenging (Walsh et al., 2014). Selection of the most appropriate taste-masking technique needs to be rationalised based on the physicochemical and organoleptic properties of the drug.

The evaluation of taste and overall palatability is becoming common practice. Taste assessment can be performed by means of dissolution testing in bio-relevant conditions (Tan et al., 2013), *in vitro* techniques such as electronic tongues (Preis et al., 2012), *in vivo* animal models (Noorjahan et al., 2014), or with a panel of human volunteers (Pein et al., 2014). Studies using human taste panels are typically conducted in adults, which can be problematic when the target population is paediatrics and geriatrics, who have different taste sensations (Krause and Breitzkreutz, 2008). Appropriate palatability is particularly important in the case of medicines for children. The current European guidelines urge the assurance of appropriate palatability in paediatric products (European Medicines Agency, 2013).

The future direction of pharmaceutical development of medicines for paediatric and geriatric use

Both geriatric and paediatric patients, particularly of extreme age, sometimes find it difficult to swallow; therefore, flexible dosing and appropriate strengths of formulations are needed. In terms of difference in disease incidence and distribution in neurological disorders, pharmaceutical research in older patients should focus on neurodegenerative diseases and disorder due to neuro-insult such as Parkinson's disease, Alzheimer's, stroke and epilepsy, all these illnesses still require appropriate formulation to assist the carers to administer and patient to swallow. Similarly, neurodevelopmental disorders in children also create significant challenges. Illnesses such as Autism Spectrum Disorder, cerebral palsy and epilepsy all require careful formulation research to develop appropriate medicines that assist the ease of administration for the carers and also make it easy for the patient to swallow.

Another important clinical area for formulation research is palliative care for both older people and children. As the population ages, there is clearly an increased need
295 for palliative care. Palliative care patients require medications to be administered within their homecare settings to allow them to stay in a familiar environment; however, many medicines for fast symptom relief require injection. This route could be potentially replaced by non-invasive dosage forms, such as orodispersible and oromucosal formulations and current research is working towards addressing this.

300 The above-mentioned issues are also applied to paediatric palliative care, but with the added complexity due to the small dose requirement that the appropriate formulation is very important to avoid accidental overdose.

The most appropriate dosage form and manufacturing technology need to be selected
305 considering the physicochemical properties of the drug, but also the target population. Novel technologies including inkjet and 3D printing bring unparalleled opportunities for the preparation of personalised medicines, either in industrial settings or in hospitals and community pharmacies. Investment and development of infrastructure are required for this to be feasible and adaptations of regulatory framework are
310 already underway to support this (Food and Drug Administration, 2013). In August 2015, a 3D-printed drug became the first of its type to be approved by the FDA, which reinforces promise for this direction. Spritam (levetiracetam), developed by Aprelia Pharmaceuticals (Langhorne, Pennsylvania), uses the company's ZipDose Technology platform, which applies powder-liquid 3D printing to produce a porous
315 formulation that rapidly disintegrates with a small volume of liquid (Voelker, 2015).

Pharmaceutical technology has progressed rapidly and many of the above-mentioned technologies provide unprecedented opportunities to develop novel and appropriate formulations for both old and new drugs. However, it is important for the formulation
320 scientists to work closely with patients, carers and clinicians to develop such formulations for both older people and children.

Conclusions

Paediatric and geriatric populations deviate from the standard patient with respect to
325 both pharmacokinetics and pharmacodynamics. These changes require dose

adaptations and careful selection of excipients when developing a dosage form. Although there is considerable overlap when it comes to ‘ideal’ formulations and dosage forms for these two population groups, there are also key differences that require consideration.. The development of novel drug delivery systems including FDCs and multi-particulates may help to address some of these problems in both population groups. In addition, regulatory expectations are being established to help facilitate the development of dosage forms that are suitable for paediatric and geriatric populations. The release of further regulatory guidance documents and academic research articles as well as success stories in the form of licensed patient centric products will drive the future of paediatric and geriatric appropriate formulations.

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