



Review

Parameters to consider for successful medication use in older adults - An AGePOP review

Henriette Hummler^{a,b,1}, Dorota Sarwinska^{b,1}, Werner Weitschies^b, Maik Gollasch^c, Susanne Page^{a,*}^a Pharma Technical Development, F. Hoffmann-La Roche Ltd., Grenzacher Str. 124, CH-4070 Basel, Switzerland^b Center of Drug Absorption and Transport, Department of Biopharmaceutics and Pharmaceutical Technology, Institute of Pharmacy, University of Greifswald, Felix-Hausdorff-Str. 3, 17489 Greifswald, Germany^c Department of Internal Medicine and Geriatrics, University Medicine Greifswald, Ferdinand-Sauerbruch-Straße, 17475 Greifswald, Germany

ARTICLE INFO

Keywords:

Older adult
Geriatric patient
Intake condition
Medication management
Medicine acceptability
Patient-centric

ABSTRACT

Older adults are the main users of medicine and due to common multimorbidity they are often confronted with a complex medication management. This review article provides a brief overview on aspects of medication management, i.e., maintaining a stock of the required medicine, understanding and following the instructions for use, coping with the primary and secondary packaging, as well as the preparation prior to use. However, the main focus is on the drug intake itself and the review provides an overview of the current understanding of real life dosing conditions in older adults and geriatric patients. It elaborates the acceptability of dosage forms, in particular solid oral dosage forms as they represent the majority of dosage forms taken by this patient population. An improved understanding of the needs of older adults and geriatric patients, their acceptability of various dosage forms, and the circumstances under which they manage their medications will allow for the design of more patient-centric drug products.

1. Introduction

Over the last 100 years the global population has more than quadrupled (Roser 2013). An additional increase of 4.4 billion to 10.9 billion people is projected for the time frame from 2019 to the end of the century and the largest increase is observed for Asia followed by Africa (Roser 2013). This increase is mainly driven by two effects: a decline of child mortality in every country and an increase in life expectancy due to improvements in health care (Roser 2013). The latter will strongly depend on factors such as access to modern health care systems and individual or cultural preferences for traditional medicine, and will therefore lead to regional differences in life expectancy. In the developed countries, life expectancy at the age of 65 increased by 5.7 years on average between 1970 and 2019, and nowadays people in these countries can expect to reach an age of 84.9 years on average (OECD 2021).

Overall, the life expectancy is around 3.3 years higher for women than men at this age (OECD 2021). The longer life expectancy leads to a rapid increase in the number of older adults (+65 years of age) in the upcoming years (Fig. 1). On top of this, the proportion of people aged 80 years and older is projected to more than double to 12.1% by 2060 (EC 2008). Despite the fact that the life expectancy increased within OECD countries, countries being part of the Organization for Economic Cooperation and Development, it is clear that not all extra years are spent in good health (Fig. 1) (OECD 2021). Although only limited data on life expectancy are available for older adults living in non-OECD countries, the age-related needs outlined in this paper are general in nature and not specific to older adults living in a certain region.

As the aging of the population continues, health challenges, e.g. the COVID-19 pandemic, influenza, and other infectious diseases, which disproportionately affect older adults, must be anticipated (OECD

Abbreviations: API, active pharmaceutical ingredient; CAST, ClinSearch Acceptability Score Test; DRUG, Drug Regimen Unassisted Grading Scale; EMA, European Medicine Agency; FDA, U.S. Food and Drug Administration; GIT, gastrointestinal tract; HPMC, hydroxypropyl methylcellulose; IFU, instruction for use; MAQ, Medicines Acceptability Questionnaire; ODT, orodispersible tablet; OECD, Organization of Economic Cooperation and Development; SODF, solid oral dosage form; SSQ, Sydney Swallow Questionnaire.

* Corresponding author.

E-mail address: susanne.page@roche.com (S. Page).¹ Henriette Hummler and Dorota Sarwinska contributing equally to this paper.<https://doi.org/10.1016/j.ejps.2023.106453>

Received 16 January 2023; Received in revised form 27 March 2023; Accepted 24 April 2023

Available online 4 May 2023

0928-0987/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2021). Furthermore, with the decline in organ and body functions, older adults commonly suffer from multiple diseases and are therefore the main user of medicines. Multimorbidity is defined as the presence of two or more chronic medical conditions. A successful pharmacotherapy in multimorbid patients can improve the quality of life, reduce caregiver burden, avoid hospitalization, and can thus contribute to a reduction of the overall health care costs (Riet-Nales et al., 2022). Despite the benefits of a successful pharmacotherapy, it was shown that only 50% of people suffering from long-term illnesses use pharmaceuticals in the prescribed manner (Asola and Hautala 2022). In order to better understand the reasons for this medication non-adherence, a better understanding of the patient characteristics, their abilities, and impairments is needed. Older patients deserve particular attention because they are a very heterogeneous group. Focusing solely on their chronological age is not helpful as some of them are healthy and physically active, others are coping well with good quality of life despite illness, co- or multimorbidity, and some of them are seriously ill, frail, and care dependent (Roller-Wirnsberger et al., 2020). It is therefore helpful to focus on the biological, rather than the chronological age (EMA 2020). This is also reflected in the different terms, i.e., older adults and geriatric patients. The term older adult (alternatively older people or older population) refers to the chronological age of a person, and is used for adults 65 years of age and older. Contrary, the term geriatric patient is used for either older adults that need medical care or for younger individuals diagnosed with geriatric syndromes (Carlson et al., 2015), also requiring medical care and treatment.

On a biological level, aging is characterized by a continuous accumulation of molecular and cellular damage, which over time leads to a decrease in body functions, an increased vulnerability, a growing risk of disease, and ultimately death (Roller-Wirnsberger et al., 2020). Therefore, one primary aim in the care of older patients is maintenance of functional capacity in order to prevent disability and frailty (Roller-Wirnsberger et al., 2020). With increasing age, many older adults suffer from co- or multimorbidity and geriatric syndromes, i.e., recurrent falls, syncope, frailty, dementia, delirium, and incontinence (Roller-Wirnsberger et al., 2020). Patients with multimorbidity often face difficulties due to fragmentation of care and associated issues in daily prescribing practice (Roller-Wirnsberger et al., 2020). However, the therapeutic complexity in those patients can be reduced by

developing patient-centric drug products (Stegemann et al., 2020) including ease in medication management and improved medication adherence.

This review therefore highlights the current knowledge with respect to handling of medicines in the daily routine of older adults (medication management), administration under real-life dosing conditions (e.g. timing of drug intake, extent of assistance), and strategies used in order to cope with challenges during administration (e.g. dosage form modifications). Finally, it will provide an overview about the acceptability of solid oral dosage forms, SODFs, in this patient population and identify existing knowledge gaps. A better understanding of patient needs will contribute towards the design of patient-centric medicines for older adults. However, the article will not discuss topics such as access to the health care systems or use of traditional versus conventional medicine in different regions of the world, as this goes beyond the use of medication in older adults.

2. Medication management of older adults and geriatric patients – a challenging task

The safe, effective, and appropriate use of prescribed medication for a patient is defined as medication management (EMA 2020). Contrary to the usability of medicine, the medication management takes patients' entire medication regime into account. Therefore, adequate medication management can only be achieved by addressing a variety of practical problems, i.e., the use of multiple medications and polypharmacy, medication recognition, switching medications, and stability (EMA 2020).

Barnett et al. showed that 65% of those being 65 years or older and even more than 80% of those being 80 years or older are affected by multimorbidity (Barnett et al., 2012). Hence, they are frequently facing the burden of polypharmacy implying an intake of five or more medications a day (39% to 47.4% of people 65+ years) (Gnjidic et al., 2018). Even hyperpolypharmacy, the intake of ten or more medications a day, is not unusual (4.5% to 8.6% of people 65+ years) (Gnjidic et al., 2018). The intake of multiple medications a day implies complexity in the medication management of patients. This leads to a higher risk of prescription cascades, drug-drug and drug-food interactions, overload of salts and/or potentially inadequate excipients, as well as to increased

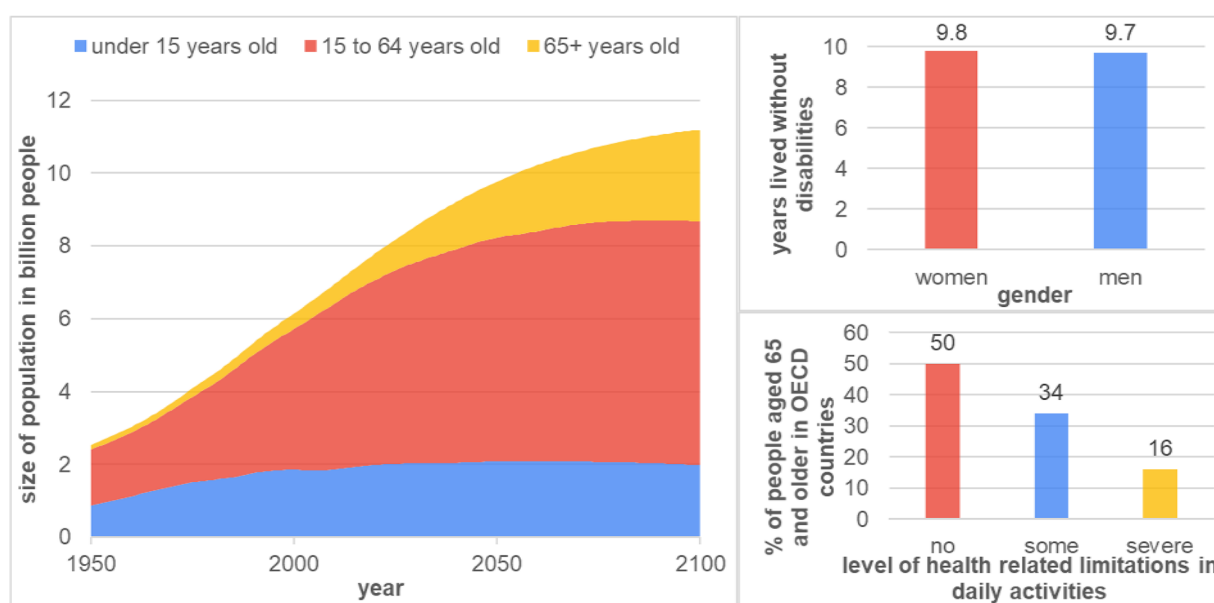


Fig. 1. Population size of young, working-age, and older people in the world from 1950 to 2100 (based on historic estimates from 1950 to 2015 and projected to 2100 based on the United Nations medium scenario) (Rosier 2013). Further, years lived without disabilities after an age of 65 years and level of health related limitations in people aged 65 and older are shown (NA OECD 2021).

non-adherence (EMA 2020).

Non-adherence has been reported to occur in up to 29% of patients (Messina et al., 2015). As a consequence of poor medication adherence, often caused by complex medication regimes and medication errors, worsening of the disease, unplanned hospitalizations, adverse drug events, increased health care costs, and a deterioration in quality of life may occur (Jamerson et al., 2016; Rantanen et al., 2017; Wurmbach et al., 2022). Zed et al. report that 12% of emergency department visits were drug-related and of those 68% were considered preventable (Zed et al., 2008). A study conducted in care homes showed that nearly half of the studied administration errors were due to forgotten administration and 21.6% were caused by wrong dosing (Barber et al., 2009). Additionally, Barat et al. demonstrated that people taking 3 or more medications, receiving prescriptions from different doctors, living alone, and showing symptoms of pre-dementia are at particular risk of non-adherence (Barat et al., 2001). As the necessity of medication increases, the functional abilities decrease (due to age), and coping with complex medication management becomes more difficult (Messina et al., 2015).

A number of different studies have investigated medication management in older adults and geriatric patients (Notenboom et al., 2014; Alsaeed et al., 2016; Schenk et al., 2020). In particular, older and multimorbid patients with polypharmacy overestimate their own medication management skills. They use daily routines and coping strategies that are not in accordance with their medication plan and/or the instructions for use, IFU (Schenk et al., 2020). Complexity is even increased in patients who can no longer take care of their own medication management and to whom family caregivers provide assistance (Alsaeed et al., 2016). With the increasing number of older adults living alone (Supplementary Material Figure S1) (Ortiz-Ospina 2019), it gets more important that medication management is eased and feasible for themselves. Despite the fact that a number of studies have been performed in recent years in order to investigate the ease of opening blister (Braun-Münker and Ecker 2016), the impact of different user instructions for opening bottles (Braun-Münker et al., 2020), the acceptability of different oral dosage forms (Liu et al., 2016; Belissa et al., 2019; Vallet et al., 2020), to understand the link between the drug product design and medication incidents (Karapinar-Çarkit et al., 2020), and so on, scientific evidence of patient acceptability in the older population is still considered scarce and fragmented (EMA 2020). Thus, the different steps of medication management (Fig. 2) are viewed from the perspective of older adults who are often showing different impairments exacerbating to independently cope with these steps.

2.1. Maintenance of medicine stock at home

The medication management starts with the prescription of one or more drugs by one or multiple physicians. During the process of prescribing, physicians have to pay attention to the pharmacological aspect of a drug but also to the ease of administration of the individual drug product by the patient. According to Wurmbach et al., there is a constant risk that patients are overcharged by the management of their drug treatment as the complexity of the latter is neglected in routine care (Wurmbach et al., 2022). Therefore, the significance of medication reviews, aiming for the reduction in the number of prescribed medications, as well as assessing the possibility of alternative dosage forms to ease medication intake, should be considered (Topinková et al., 2012; Yetzer et al., 2015; EMA 2020). The overall goal should always be to secure the administration of the safest and most effective medication to the patient allowing for the maximum benefit. While doing so, patients' personal health priorities should serve as a guide (Hughes et al., 2016; Wahlich et al., 2019; Eidam et al., 2022).

After one or more drugs are prescribed to patients, they need to order and collect the respective drugs in order to maintain a medicine stock at home. Not only purchasing the right drug, but also timing and arranging the medication schedule is crucial for correct drug administration. The

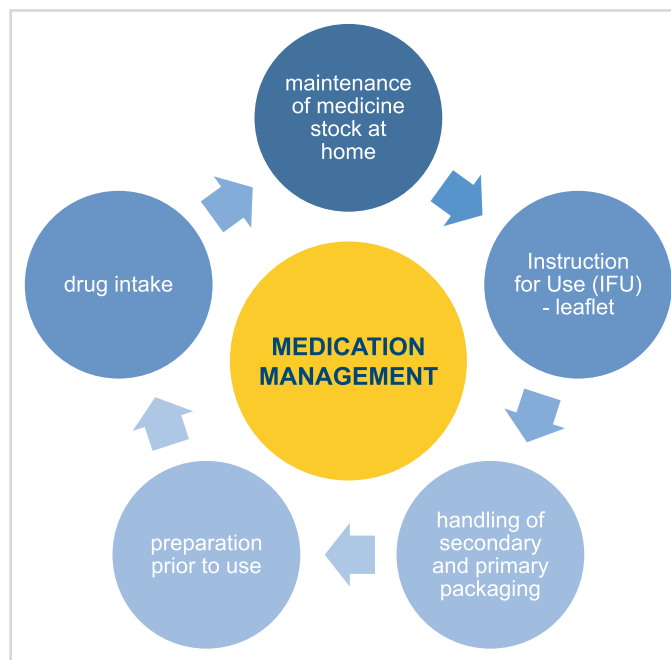


Fig. 2. Steps in medication management (Notenboom et al., 2014; Alsaeed et al., 2016; Schenk et al., 2020).

timing of medications can be a challenge. Often not only the time of the day but also whether the medication should be taken before, with, or after food intake needs to be considered. Decreased adherence was related to an increasing number of drugs to be taken at once, number of daily intakes, and necessity of intake at a specific time (Mehuys et al., 2012; Schmidt et al., 2020).

The implementation of new technologies, i.e., an integrated advanced robotic device and telecare system to remind patients of their medication schedule, could improve medication adherence (Rantanen et al., 2017). In implementing such new technologies, it has to be ensured that older adults, possibly lacking intuition towards such technologies, are sufficiently trained in their use to obtain a benefit (EMA 2020). It is obvious that for these first steps of medication management, i.e., purchasing and arranging medication schedules, the patient needs to have sufficient cognitive and functional abilities (Sino et al., 2014). For the cognitively challenging adherence to the medication schedule, often multi-compartment compliance aids and multi-dose dispensing systems are used by patients. To this end, product stability is of great importance. Pharmaceutical companies are asked to study those open dish conditions and to provide sufficient information to the patient and all healthcare professionals to ensure adequate and safe use of the drug products. If sufficient stability outside the primary packaging is not given, other strategies such as unit dose blisters or day to day indication on the packaging are recommended to be used (EMA 2020).

Cognitive impairments in the old patient population might not only impact on obtaining and scheduling, but also on dealing with changes of medication, e.g. use of a different generic drug. The need to contact healthcare professionals in case of problems with medication use or what to do in case of deviations from the planned medication schedule are further challenges for older adults (Sino et al., 2014). Loss of mobility is impeding the process of purchasing needed drug products (Yetzer et al., 2015).

2.2. Reading and understanding the instructions for use

When a new drug is prescribed to a patient, the IFU leaflet has to be read in order to allow for correct medicine intake. Besides cognitive impairments, those of visual characteristics can make this step of

medication management a challenging one. The leaflet might be written in too small letters impeding the process of reading and/or the written content might be too complex to understand. A study performed by Nathan et al. investigated the comprehensibility and readability of information leaflets of medications being new or refilled for patients aged 17 to 90 years (mean age: 49 years). The detailed results of their study are depicted in Fig. 3. While approximately half of the patients (49.2%) read at least the information leaflet for newly prescribed drugs, for refilled medication this only held true for 21.6% of the patients. The percentage of patients 65 years and older reading the information leaflet was lower compared to the younger patients (63% vs. 72%). Thus, older adults might often give up on the IFU leaflet and rely on their own use assumptions as well as on information received from health care professionals (Nathan et al., 2007). Information about adverse events included in the leaflet can be alarming and distressing, possibly resulting in reducing or skipping dose intake (Notenboom et al., 2014; Schenk et al., 2020). Dexterity issues can impede the process of getting the leaflet out of the secondary packaging, folding it up again, and putting it back into the secondary packaging. Often the leaflet rather gets discarded than being put back into the secondary packaging, making a later reading of the instructions impossible (Schenk et al., 2020). Thus, information leaflets need to be adjusted to patients' impairments and requirements, especially to the needs of older patients.

2.3. Handling of the primary and secondary packaging

Prior to the administration of the medicine, the patient needs to identify the medicine or medicinal product and be able to open the secondary as well as the primary packaging. Due to the frequent presence of reduced eyesight within older adults, the identification of specific medications and their packaging can be challenging in particular when a switch between medications is necessary. The implementation of color coding of medication, appropriate font size in instruction leaflets and on devices, as well as the use of visuals on packaging to enhance intuitive use are possible strategies to overcome the hurdles of visual impairment (Hughes et al., 2016).

Impairments concerning hand and grip strength as well as dexterity were found to be associated with difficulties in opening secondary packaging and container closure systems to access medication (Yetzer et al., 2015). Older female patients as well as those being affected by physical restrictions, e.g. with rheumatoid arthritis, were more likely to experience such difficulties with packaging (Lorenzini et al., 2022). Often occurring difficulties in opening secondary or primary packaging account for tight closing of the side-flap in the carton box or that the side-flap is not adapted to the right-hand user patterns. The blister design might lead to difficulties by having the cavities too close together

or exhibiting too small cavities. Additionally, the back-foil might be of too high tensile strength or be liable to crumble and this might lead to tablets retaining in the blister or to loss of tablets as they are e.g. falling on the ground (Schenk et al., 2020). Patients show different strategies to cope with the above mentioned difficulties. They might stop the medication intake, get frustrated which might bring along non-adherence, or ask others to open the container and leave it open (Notenboom et al., 2014). The latter needs to be accounted for in drug product development by providing a sufficient stability of the product not being stored as intended in the original packaging (EMA 2020).

2.4. Preparation prior use

Wurmbach et al. showed that the use of inhalers, splitting of tablets, and liquid oral dosage forms should be considered relevant complexity factors (Wurmbach et al., 2022). To assess the abilities of older adults to deal with medications, the Drug Regimen Unassisted Grading Scale, DRUG, was developed. This tool focuses on four assignments: identification of a medication, access to the package, selection of the correct dose, and timing of the dosing (Edelberg et al., 1999). It allows the identification of the tasks that are especially difficult for certain patients. A study by Kripalani et al., which utilized the DRUG tool, showed that 46% of study participants aged ≥ 65 years were unable to identify all medications. Problems with drug identification affected not only people with visual impairments, but also those with cognitive impairment (Kripalani et al., 2006).

Dose adjustment of solid and liquid medications can be a hurdle older adults and geriatric patients may experience prior to medication use. The most common problems in tablet splitting are difficulties in breaking the tablet, obtaining unequal parts, and loss of mass (Santen et al., 2002). A study by Rodenhuis et al. investigated patients experience with dividing tablets (Rodenhuis et al., 2004). The majority of negative evaluations were obtained from study participants aged 60 – 75 years. The most common complaints were: unequal halves, crumbs, and difficulties to break. Breaking a tablet was further seen as a challenge for study participants aged 65 - 99 years (mean age: 81.8 ± 6.2 years) in a study by Atkin et al. In this study, 72.5% and 64.3% of participants were unable to break any tablet or their own tablets, respectively (Atkin et al., 1994). Regarding liquid medications, there are several challenges for older adults. Different dosing devices for liquid preparations were investigated by Ryu and Lee (Ryu and Lee 2012). Despite the fact that the study was performed among people younger than 65 years of age, it showed that inaccurate dosing appeared, when dosing was performed with the dosing spoon, the regular dosing cup, and the printed dosing cup. Furthermore, Pelletier et al. compared the usage of a teaspoon and cup to deliver the liquid to patients with

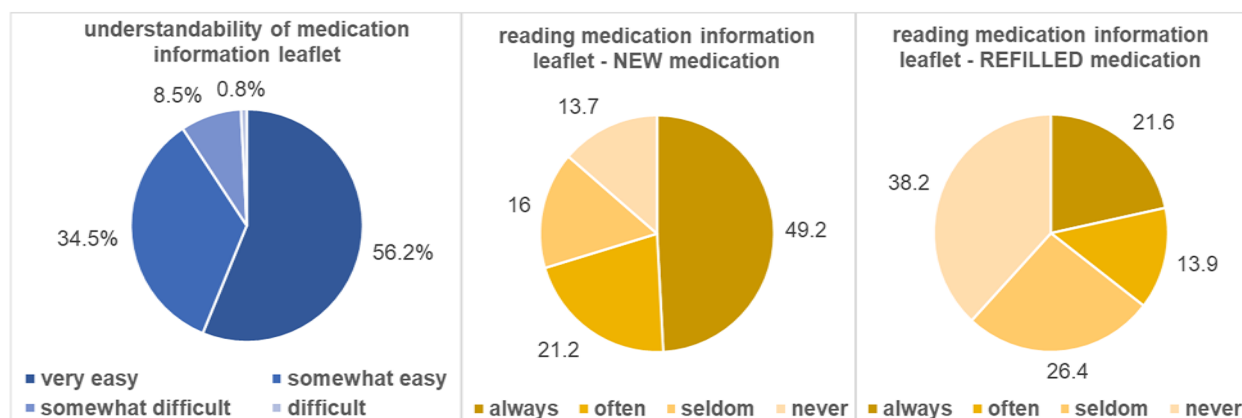


Fig. 3. Detailed results of the study: Patients' Use and Perception of Medication Information Leaflets (Nathan et al., 2007).

dysphagia. A teaspoon caused less aspiration than a cup and seemed to be safer (Pelletier and Lawless 2003).

2.5. Drug intake

Drug intake via the oral route of administration seems to be a simple process that does not require any special abilities. However, a number of studies showed that problems occur when taking medications orally, i.e., placing a drug form in the mouth, swallowing difficulties, sticking of the medication in the mouth or throat, and unpleasant taste and/or odor of the medication. Detailed information about swallowability of dosage forms and swallowing difficulties will be provided in Section 4.3. Placing a drug in the mouth requires strength of the tongue, which with advanced age and especially among dysphagic patients is reduced (Perrie et al., 2012). The medicine might stick to the mouth or throat as reported by about 29% of participants being 70 years or older in a study by Notenboom et al. (Notenboom et al., 2014). Another study showed that 79.4% of participants with swallowing difficulties (mean age about 62 years) experienced lodging of the medicine in the throat (Schiele et al., 2013). For liquid formulations it is often the unpleasant taste of the medicine that prevents patients from taking it. 17% of participants reported an unpleasant taste of the medication as a problem in a study by Notenboom et al. (Notenboom et al., 2014). Liquid oral formulations that contain a flavoring agent were better accepted by older patients, especially by women, contrary to the formulations without a flavoring agent (Belissa et al., 2019). It indicates the need to focus on the palatability of liquid oral formulations for older adults in order to enhance patients' adherence (Muramatsu et al., 2010).

The setting in which older adults live among others determines the extent of help they are offered with their medication (self-)management (Wahlich et al., 2019). The extent of needed help is likely to be associated with age-related changes such as cognitive function, presence of medical conditions and related medications, as well as activities of daily living (Jamerson et al., 2016). It is important that all parties do their best to support the patient in the process of medication management. If support is needed from different parties, the communication between those different parties as well as the communication with the affected patient is of paramount importance (Page et al., 2016). The necessity of communication between the different parties gets even more pronounced in case of the transition of older adults from one setting to another, e.g. from their home to a nursing home. These transitions often come along with a change in responsibilities within the process of medication management (Stegemann et al., 2012).

3. Intake conditions – real-life or extreme-case scenario?

The behavior of a drug in the gastrointestinal tract, GIT, is influenced by the dosing conditions, e.g. the fluid and food intake of the person, the drug intake in relation to the food intake, and potential dosage form modifications.

3.1. Clinical trial conditions

During the clinical development of a new oral medication, a number of different clinical studies need to be performed. In order to assess the safety of the molecule and its pharmacokinetic profile, the dosing conditions in the initial phase 1 clinical studies are well defined and dosing often occurs after an overnight fasting. Later on, the bioavailability of the drug, with or without food, is tested in a food effect study using standardized conditions (Table 1) as presented by the U.S. Food and Drug Administration, FDA (FDA 2002).

However, it is generally known that those standardized conditions present an extreme-case scenario allowing to investigate medicines under conditions that affect the gastrointestinal physiology and drug absorption to the greatest extent (FDA 2002; Wagner et al., 2012).

Table 1

U.S. Food and Drug Administration procedure, food effect study (FDA 2002).

	Fasted state	Fed state
Overnight fasting time	at least 10 h	at least 10 h
Type of meal	–	high-caloric (800 – 1000 kcal), high-fat meal: <ul style="list-style-type: none"> • two eggs fried in butter • two strips of bacon • two slices of toast with butter • four ounces of hash brown potatoes • eight ounces of whole milk
Meal ingestion time	–	30 min before medicine administration, should be eaten in max. 30 min.
Type and amount of fluid co-administered with medicine	240 mL water	240 mL water
No fluid before and after ingestion of medicine (time)	1 h before and 1 h after	1 h before and 1 h after
No food after ingestion of medicine (time)	at least 4h	at least 4h

3.2. Real-life dosing conditions

In contrast to the highly standardized dosing conditions in food effect studies, real-life dosing conditions are highly variable (Fig. 4). In addition, these real-life conditions may also differ from the intended intake conditions. These differences lead to increased variability in the pharmacokinetics of the drug and may affect the efficacy and/or safety of the drug.

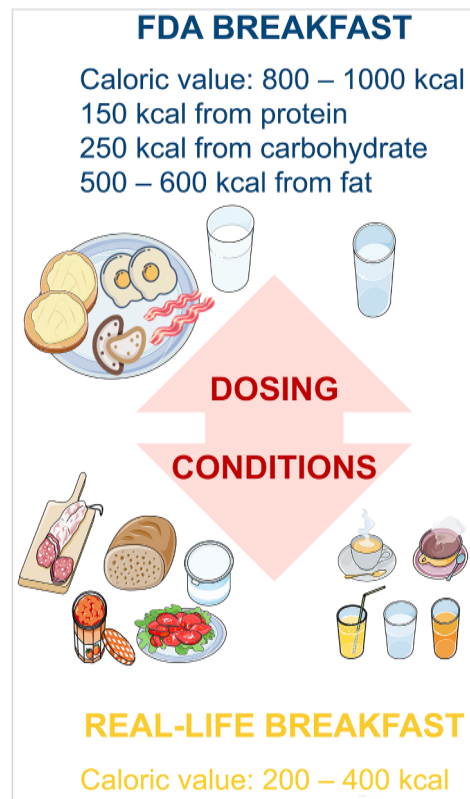


Fig. 4. Comparison of the FDA standardized breakfast as described by U.S. Food and Drug Administration (FDA 2002) and people's presumed breakfast (Yazio 2022).

3.2.1. Volume and type of fluid co-administered with medications

While FDA guidelines for food effect studies require the ingestion of 240 mL of water with the drug product (FDA 2002), the European Medicine Agency, EMA, recommends the intake of at least 150 mL of water for bioequivalence studies (EMA 2010). A number of studies demonstrated that the volume of water co-administered with a drug influences the drug behavior in the GIT. The ingested fluid defines the volume being available for medication's dissolution. The volume and caloric content of the ingested fluid determines gastric emptying time. Thus, it is especially important for poorly water-soluble compounds (Koziolek et al., 2019). Nader et al. demonstrated that a larger volume of water (50 vs. 250 mL) co-administered with nifedipine IR lowered the variability in C_{max} (Nader et al., 2016). Similarly, Sunesen et al. showed an increased absolute bioavailability of danazol if taken with a large volume of fluid (200 vs. 1000 mL) (Sunesen et al., 2005). Matsumoto et al. found a higher absorption of cefteram-pivoxil if co-administered with a larger volume of water (30 vs. 150 mL). However, for the pro-drug ceftizoxime alapivoxil (AS-924) no effect of the water volume was observed (Matsumoto et al., 2001). Similarly, the amount of water (30 vs. 240 mL) did not affect digoxin absorption (Bustrack et al., 1984).

The amount of fluid co-administered with the medication is further important in respect to drug-induced esophageal disorders, e.g. for antibiotics such as doxycycline and tetracycline, potassium chloride, alendronate, or non-steroidal anti-inflammatory drugs (Jaspersen 2000; Organon 2015). The more fluid is taken with medication, the lower the risk of dosage form's adhesion to the esophagus during transit. Thus, some authors recommend to take medications possibly causing drug-induced esophageal disorders with at least 100 mL of fluid (Jaspersen 2000). In addition, people encountering swallowing difficulties may use more fluid in order to ease swallowing of SODFs (Schiele et al., 2013).

Patient education should include the importance of the amount of fluid co-administered with medication as studies reported about different amounts of fluid being used in real life. In one study, 64% of patients (mean 55 years (15–83)) were using 101 – 150 mL (Fuchs 2009), which is in line with a recommendation to use at least 100 mL of water (Jaspersen 2000). In another study by Hens et al. (Hens et al., 2017), the majority of adult participants (16 years and older) swallowed their medication with half a glass of water, second most often they only used one sip, and least often they drank a full glass of water (240 mL). When taking bisphosphonates, in which case the importance of water intake is clearly emphasized in the IFU, more people used a full glass of water rather than only half of a glass (Hens et al., 2017). Interestingly, some patients enrolled in the study swallowed their medication without any fluid (Hens et al., 2017).

Not only the amount, but also the type of fluid may affect drug absorption. Despite the general recommendation to administer oral medications with water, patients sometimes use tea, coffee, soda, fruit juices, or even alcoholic beverages, e.g. whiskey (Hens et al., 2017; Haighton et al., 2018). Several studies showed that co-administered fluids may enhance or reduce the bioavailability of the active pharmaceutical ingredient, API. Grapefruit juice has been found to increase the bioavailability of sildenafil and to delay its absorption. This might be due to a delay in gastric emptying or an alteration in gastric pH value (Jetter et al., 2002). Green tea decreased the plasma concentration of nadolol probably due to inhibition of OATP1A2-mediated intestinal absorption (Misaka et al., 2014) and milk reduces the absorption of levothyroxine likely due to an interference of calcium with the drug absorption (Chon et al., 2018). A recent study (Abeele et al., 2017) showed that sparkling water might accelerate and lower the variability of paracetamol absorption.

3.2.2. Food intake and its influence on drug absorption

As food products are complex mixtures of various constituents, food-drug-interactions may appear and affect drug absorption. Additionally, the food itself alters the GIT conditions (Welling 1996; Koziolek et al.,

2019; Vinarov et al., 2021).

In general, food may change the bioavailability of an orally administered drug by delaying gastric emptying, stimulating bile flow, altering the pH in the GIT, increasing splanchnic blood flow, changing luminal metabolism of a drug substance, or by physical or chemical interactions with a drug (FDA 2002). Drugs showing a negative food effect include e.g. alendronate (Porras et al., 1999) and furosemide (Beermann and Midskov 1986). Intake of these drugs with food reduces its bioavailability possibly resulting in ineffective pharmacotherapy. Thus, these types of drugs should be taken in fasted state. For alendronate, it is particularly important to refrain from eating for at least 30 minutes after taking the drug (Organon 2015). A positive food effect is seen for danazol (Sunesen et al., 2005) as food intake enhances its bioavailability. Thus, danazol is recommended to be administered during or directly after food intake. An undesired outcome of a positive food effect was reported for fampridine as the C_{max} was increased when taken with food, which was related to adverse reactions (Biogen 2011). No food effect was seen for ozanimod. Neither a low-fat meal nor a high-fat meal influenced ozanimod's systemic exposure (Tran et al., 2018). Drugs showing no food effect may be taken regardless of food intake.

As an alternative to food effect studies in humans, attempts are being made to predict food effects through biorelevant *in vitro* dissolution tests (Havenaar et al., 2013; Martir et al., 2020b). In recent years, *in silico* tools have gained increasing importance and are used as additional tool to predict food effects on pharmacokinetics (Kuepfer et al., 2016). The models can be adjusted to special patient populations (Cheng and Wong 2020; Riedmaier et al., 2020).

3.2.3. Food vehicles

The usage of food vehicles for medication administration is another aspect of drug intake with food. Food vehicles are especially common among pediatric and geriatric patients. Medications can be added to or sprinkled on food, e.g. applesauce or mashed potatoes, either directly or after dosage form modification, i.e., crushing tablets or opening capsules (see Section 3.3). Only limited information about drug intake with food among older adults is available in literature. However, some studies addressed the medication administration with food in hospitals, including hiding of medication in food and beverages (Kirkeveld and Engedal 2005; Haw and Stubbs 2010). Covert drug administration is often applied in nursing homes and hospitals in case of mental impairments, non-adherence, and swallowing difficulties. Commonly used food vehicles for medication administration in hospitals are: jam, squash, high protein nutritional supplements, cooked meals, water, compote, enriched cream, honey, thickened fluid, juice, custard, or yogurt (Nissen et al., 2009; Haw and Stubbs 2010).

Martir et al. investigated the impact of frequently used food vehicles in pediatric patients for treatment with montelukast sodium and mesalazine. Food vehicles, i.e., formula, milk, yogurt, juice, Coca-Cola, squash, apple sauce, honey, and jam, altered the solubility of the tested drugs and thus might impact their bioavailability. The interaction between medication and food vehicles depends on the physicochemical properties, e.g. pH value, surface tension, buffer capacity, osmolality, and viscosity, and/or macronutrient composition of the vehicle, as well as on solubility of the drug (Martir et al., 2020a). Thus, the appropriateness of the used food vehicles is crucial for drug administration (FDA 2002). Dissolution tests including food vehicles, that are commonly used in pediatrics, are utilized to characterize the influence of the food vehicles on drug solubility (Martir et al., 2020b; Freerks et al., 2022). Application of similar approaches might advance drug development targeted to the geriatric patient population.

3.2.4. Drug intake in relation to food – timing of drug intake

Appropriate timing of dosing in relation to food intake is crucial for drug effectiveness as well as in respect to side effects. In the following paragraph, we illustrate these cases with a couple of examples. Only if clodronate is taken at least 30 minutes before breakfast or during the day

with at least four hours prior fasting time, proper bioavailability is reached (Laitinen et al., 2000). Semaglutide should also be taken 30 minutes prior to breakfast and no food intake should take place within the following 30 minutes (NA Novo 2022). For a proper absorption of risedronate, it has to be taken first thing in the morning. If this is not the case, it can be taken during the day with an at least two hours long preceding fasting period (NHS 2022a). Tamsulosin is another drug that should be taken in the morning, as highest drug levels within the body are reached after six hours. However, it is a drug that should be taken after breakfast or the first meal of the day (NHS 2023). In order to avoid or reduce side effects, some drugs should be taken together or after food intake, i.e., metformin (NHS 2022b) and betamethasone (NHS 2022c).

3.2.5. Nutritional practice in older adults

Different physiological and anatomical changes in older adults affect eating habits, i.e., loss of teeth, xerostomia, dysphagia, diminished appetite and thirst sensation, as well as changes in taste and smell perception (Rémond et al., 2015). Based on alterations appearing in humans due to aging, the nutritional practice of older adults changes and may influence drug absorption. Those changes include limited fluid intake, decreased food consumption, extended intake of fiber products, use of thickening agents, and a monotonous diet (Stillhart et al., 2020). Furthermore, the diet may be modified if the patient suffers from chronic diseases such as diabetes, obesity, or hypertension.

3.3. Dosage form modifications – potentially harmful simplifications?

Drug manipulation means physical alteration of a dosage form to derive the required dose or to ease administration (Richey et al., 2012). Modifications of SODFs are most commonly performed in case of swallowing difficulties with the respective dosage form or if other psycho-behavioral problems are present (Strachan and Greener 2005; Bourdenet et al., 2015). The most frequent modifications observed among patients include: splitting tablets, opening capsules, mixing with food, crushing, dissolving in water, or chewing (Haw and Stubbs 2010; Vallet et al., 2020). In addition to the patients, caregivers perform dosage form modifications. They most often crush and divide medicines, mix modified medicines with food, i.e., jam or yogurt, or mix them together (Nissen et al., 2009; Bourdenet et al., 2015; Fodil et al., 2017; Solberg et al., 2021). Studies showed that dosage form modifications were carried out for up to 32% of residents in institutionalized geriatric units and 25.5% of SODFs administered to older mentally ill patients in a psychiatric hospital were modified. In both cases, around 40% of the dosage form modifications were not authorized (Stubbs et al., 2007; Carvajal et al., 2016) and therefore these modifications are often considered as off-label use which implies a transfer in responsibility to the person performing the modification (Wahlich et al., 2019). Bourdenet et al. found an increased prevalence of dosage form modifications within nursing homes and long-term care units. The lower autonomy and the high prevalence of swallowing difficulties of the residents might be a reason for this observation (Bourdenet et al., 2015). Quinzler et al. reported that nearly one quarter of tablets within primary care in Germany were split. 8.7% of these split tablets did not have any break-mark and in 3.8% of the cases tablets were actually not allowed to be split (Quinzler et al., 2006).

Kirkevoid and Engedal (Kirkevoid and Engedal 2005) investigated the use of concealment of drugs in food and beverages in nursing homes. They showed that often drugs such as antiepileptics, antipsychotic, and anxiolytics were covertly administered to patients suffering from dementia, aggression, and to those having a reduced ability to perform daily activities. Among ward characteristics, the authors reported about a reduced risk for drugs to be given covertly in teaching nursing homes or in wards with a high staff-to-patient ratio (Kirkevoid and Engedal, 2005). Thus, time constraints due to manpower shortage, avoidance of long discussions with refusing patients, and lack of knowledge might explain the frequent occurrence of dosage form modifications within

nursing homes and hospitals.

Dosage form modifications affect the safety and efficacy of medication administration, possibly increase the risk for side-effects, and can lead to a contamination of the caregiver (Bourdenet et al., 2015; Forough et al., 2020). This is particularly important if physical barriers of drugs containing highly active APIs are destroyed during the dosage form modification. Allergenic, carcinogenic, or teratogenic drug characteristics can lead to toxic and hazardous exposure of caregivers. The extent of potentially hazardous exposure can be decreased by using protective equipment, i.e., gloves, masks, special tools, or by performing the modifications in a protective environment such as an insulator (Fodil et al., 2017).

Dosage form modifications can also be critical if formulation's taste masking barrier gets destroyed and consequently the risk for non-adherence of the patient is increased (Kelly et al., 2008; Gill et al., 2012). Bisoprolol, donepezil, fluoxetine, and mirtazapine are APIs profiting from a taste-masking formulation (Fodil et al., 2017). For modified release formulations intended to show extended release or to release the drug only within the intestine due to gastro-resistant coating, dosage form modifications can be critical (Gill et al., 2012; Carvajal et al., 2016). By destroying coatings or matrices as well as by enlarging the surface area through modifications, drugs' bioavailability might be altered potentially resulting in adverse drug events (Cleary et al., 1999; Schier et al., 2003; Cornish 2005; Paparella 2010). For drugs with a narrow therapeutic index, an altered bioavailability depending on the state of the dosage form is especially important to be considered (Yamamoto 2003; EMA 2020).

An incomplete intake due to spillage, imprecise splitting of dosage forms, or if modified dosage forms are mixed with food and this mixture is not entirely ingested by the patient can affect dose accuracy and can result in under- or overdosing (Gerber et al., 2008; Verrue et al., 2011; Lau et al., 2018). Use of shared equipment for dosage form modifications for different patients, having been observed in health-care units, can result in cross-contamination and has to be respected in terms of safety (Forough et al., 2020).

Depending on the tools being used to perform splitting of dosage forms, differences in accuracy have been reported. However, some patients might not even be able to split tablets for their intake of the correct dose (Verrue et al., 2011; Bourdenet et al., 2015; Wurmbach et al., 2022).

The high prevalence of dosage form modifications within older adults highlights the necessity of alternative dosage forms to monolithic SODFs. Those alternatives need to be studied in terms of their acceptability and suitability for the targeted patient population (Stegemann et al., 2012). Further insights into the acceptability of SODFs can be found in Section 4.3.2.

4. Putting the patient at the centre of dosage form design

4.1. Solid oral dosage forms – widely used and accepted?

Patients' adherence to their pharmacotherapy is an important requirement for a successful treatment. Medicines' acceptability plays a key role for patients' adherence, especially in vulnerable patients (Vallet et al., 2018a). If patients and caregivers are able and willing to use a medicinal product as intended by the manufacturer, this product can be considered acceptable (EMA 2020). The acceptability is according to EMA based on a multi-dimensional concept. It is influenced by characteristics of the medicinal product itself as well as by its user, the patient (Fig. 5) (EMA 2020). Product characteristics influencing medicines' acceptability are for instance the route of administration, the appearance, and for SODFs swallowability is of major importance (Brotherman et al., 2004; EMA 2020). The aspect of SODFs' swallowability is further important in terms of safety, especially for older adults (Liu et al., 2014). Besides causing discomfort and pain, SODFs can get stuck in the esophagus and might cause severe damage to the mucosa due to

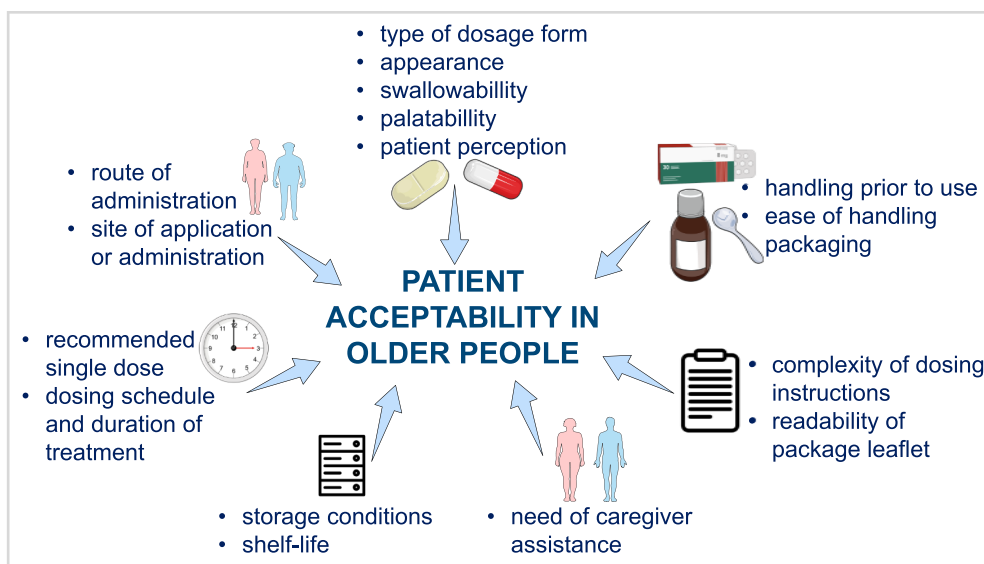


Fig. 5. Product characteristics influencing patient acceptability in older adults according to the European Medicine Agency Reflection Paper (EMA 2020).

cauterization. Any handling that might be required prior to administration to achieve the right dose or to mix it with food or drink needs to be thought of when choosing an appropriate type of dosage form for a patient population. Further, the need and the availability for assistance by caregivers has to be considered. In the context of polypharmacy, not only the appropriateness of the specific medication on its own, but rather its use in combination with any other medication needed by the patient needs to be respected (Hughes et al., 2016; EMA 2020). Besides, it was shown that dosage forms' acceptability can depend on the setting. Even if SODFs are positively accepted in patients without swallowing difficulties independent of the setting, for patients with swallowing difficulties, SODFs are only positively accepted by those being at the hospital but not by those at a nursing home (Jani et al., 2021).

SODFs are the most prescribed medicines due to their numerous advantages, i.e., relatively easy and inexpensive manufacturing, stability, dose accuracy, and ease of use (Vallet et al., 2020). But despite all these advantages, the swallowability of SODFs is a prerequisite for adequate efficacy (Schiele et al., 2013).

When developing the intended future commercial formulations for new APIs some unalterable facts are given, i.e., the efficacious dose, the indication, and herewith the target patient group. Further, the route of administration and the target organ are known. Right from the beginning, the target patients' conditions as well as all medical and therapeutic conditions have to be put at the center of the drug product design process. Additionally, drug characteristics such as drug profile, clinical efficacy, and drug safety have to be respected. Combining those with product characteristics, namely product and manufacturing requirements, supply chain requisites, market access, and regulatory requirements, one can build up the Quality Target Product Profile. By building the aforementioned profile, the consequence and the area of impact of the different attributes need to be assessed and the respective attributes need to be prioritized. This approach is following the proposed roadmap by Stegemann et al. for a patient-centric drug product development (Stegemann et al., 2022). By designing patient-centric dosage forms for older adults, the high prevalence of polypharmacy within this patient population needs to be considered. Polypharmacy comes with a high potential for interactions between APIs. Safety issues can additionally arise when the patient is exposed to different types and amounts of pharmaceutical inactive ingredients at the same time. Omidian et al. suggest that special attention should be paid to polymeric excipients and their impurities as they might build up in an ill-performing body (Omidian et al., 2022). Further, common

co-medication within the target patient population should be respected during the development process. For example, proton pump inhibitors are widely used in older adults and at the same time it is known that they are influencing the bioavailability of multiple APIs (Ogawa and Echizen 2010; Rotman and Bishop 2013). By adjusting the formulation composition, the effect of increased pH due to co-administered proton pump inhibitors can be reduced. Other formulation approaches, e.g. modified release formulations, avoid multiple dosing per day by decreasing the dosing frequency (Reflection Paper EMA, 2020). The combination of multiple APIs in one drug product can additionally reduce the pill burden for patients. Thus, the choice of formulation can impact the dosing schedule and therefore help to simplify medication management.

Usability or human factor studies are not required from pharmaceutical companies for the approval of drug products without any type of device. Still, the target patient group would benefit if usability engineering principles would be applied in the drug product design process.

To apply the patient-centric approach in drug development, fundamental knowledge about the target patient group and its preferences in terms of medicines' acceptability is needed. To test this acceptability different approaches have been used in the past.

4.2. Acceptability as prerequisite for patients' adherence – how to assess it?

As mentioned, medicines' acceptability is influenced by different factors resulting in many different approaches to test it. Even though there exists an increasing interest in studying acceptability, no clear limit of acceptability is given (Ranmal et al., 2018). While EMA guidelines are not stating a clear threshold for acceptability, one of 80% appears to be commonly used when studying patient acceptability (Ruiz et al., 2019). It is important to explicitly distinguish between acceptability and preference. Preference only represents a relative comparison, but it does not represent the actual acceptability of the individual medicine (Ranmal et al., 2018). Thus, preference studies are limited to provide an indirect indication of patient acceptability (Walsh et al., 2018). In general, the transferability of results of acceptability studies has to be questioned critically as they are always strongly influenced by characteristics of the studied population and the study setting. Focusing on the heterogeneous older population, this means that results of studies including patients being in hospitals or living in nursing homes cannot simply be extrapolated to e.g. the older home dwelling population (Ruiz et al., 2019).

There exist different approaches to study medicines' acceptability. ClinSearch Acceptability Score Test, CAST, is a tool to measure medicines' acceptability (Vallet et al., 2018a). It combines multiple observational measures to an acceptability reference framework which can be used to discriminate between positively and negatively accepted medicines in specific sub-populations of patients (Vallet et al., 2018b). CAST can be used to identify individual characteristics of sub-populations and of the product, respectively, having a positive or negative influence on medicines' acceptability (Vallet et al., 2020). A limit of CAST is that only observational measures are considered and these observations are based on specific experiences of a patient with one single product without him or her knowing alternatives to this specific product. CAST is further limited to the acceptability evaluations of already existing formulations or indications, as the tool always needs objects of comparison. Besides CAST, further attempts have been made to study medicines' acceptability e.g. by using the Medicines Acceptability Questionnaire, MAQ (Liu et al., 2016). MAQ was used by Liu et al. for the assessment of SODF acceptability in older ambulatory patients with and without dysphagia. In addition to the MAQ, Liu et al. used the Sydney Swallow Questionnaire, SSQ, to assess oral and pharyngeal swallowing function. However, the SSQ usage in this context has to be scrutinized as it focuses on swallowing difficulties during intake of food and might not be simply transferable to swallowing difficulties of SODFs. Using, e.g. 3D-printed models of differently sized and shaped dosage forms within questionnaire based studies can strengthen the results by giving the study subject a point of reference (Yoder 2014; Liu et al., 2016). A third method to assess patient's acceptability of medicines and to identify design features causing problems is to conduct semi-structured interviews (Noteboom et al., 2017; Shariff et al., 2020). Semi-structured interviews are meant to collect qualitative data. Following an underlying interview schedule, it still allows to ask follow up questions depending on participants' responses. However, participants' convenience during the interview, e.g. depending on the location, have to be considered in respect to the study outcome (Shariff et al., 2020).

In order to assess medicines' acceptability in a standardized way and thus be able to compare results of different studies approved procedures are needed. On top of this, a clear definition and limits for the acceptability evaluation are needed.

4.3. Swallowability and handling of solid oral dosage forms – key aspects for acceptability

There exists a larger number of studies focusing on the broader aspect of medicines' acceptability, while only fewer studies specifically focus on swallowability of SODFs. Swallowability is influenced by many different factors of the tested product as well as of the patient. As already mentioned for acceptability, the result-transferability of swallowability studies has to be critically scrutinized. Within swallowability studies, the clinical term of dysphagia is often not clearly delimited from swallowing difficulties with SODFs (Kelly et al., 2010); sometimes it is even used synonymously. This makes comparison and transfer of study results hard and sometimes even impossible. Dysphagia, being clinically diagnosed and most likely requiring the adaptation of food and drink viscosities to some degree, needs to be distinguished from patients' self-reported swallowing difficulties with medication. Latter is often not caused by physiological and/or neurological abnormalities but is rather due to psychogenic reasons (Franko et al., 1997).

Studies mainly focusing on swallowability of SODFs are often of observational and retro-perspective character. Hereby, previous experiences of the study participants with their regular medicines are taken into account (Schiele et al., 2013). Only a few reported studies investigate the swallowability of SODFs by actually asking the study participants to swallow different test objects and to evaluate their swallowability (Overgaard et al., 2001; Oshima et al., 2006; Miura and Kariyasu 2007; Hofmanová et al., 2019; Bogdahn et al., 2021). Even fewer studies use objective measurements, i.e., surface

electromyography and video fluorography, instead of subjective observations to evaluate swallowability (Yamamoto et al., 2014). While participants can subjectively evaluate the oral as well as pharyngeal swallowability, objective measurements are needed to evaluate dosage forms' esophageal transit.

Besides swallowability, handling and picking of dosage forms are of great importance for medicines' acceptability especially when focusing on older adults often affected by dexterity issues. To test the process of picking up SODFs from a table and putting them into the mouth, study subjects can be asked to pick up SODFs from a table and to put them into a box being approximately 30 centimeters above table height mimicking the distance to the mouth (Goyanes et al., 2017).

4.3.1. The influence factor – older adult and geriatric patient

Swallowing difficulties occur more often with increasing age (Vallet et al., 2020) and reasons include age-related neuromuscular decline and reduction in masticatory strength (Liu et al., 2014). Difficulties in swallowing are often a concomitant of several diseases, i.e., stroke, cancer, Parkinson's or Alzheimer's disease (Schiele et al., 2013; Liu et al., 2014), or can occur as a side effect of several drugs (Walsh et al., 2018). According to literature, the prevalence of swallowing difficulties varies between the community-dwelling older population and older adults living in nursing homes, affecting 2 - 16% of the former and 30 - 60% of the latter (Liu et al., 2016; Belissa et al., 2019; Vallet et al., 2020). Even though most publications refer to a higher prevalence of swallowing difficulties with growing age, Schiele et al. report about young women being frequently affected by swallowing difficulties with SODFs (Schiele et al., 2013). These findings might be due to the restriction of study participants attending the general practitioner, excluding nursing home residents, but may also allude to the psychological impact on swallowing (Shariff et al., 2020). Schiele et al.'s findings are supported by Andersen et al. and Hofmanová et al., both reporting difficulties in swallowing tablets with a high prevalence in younger age (Andersen et al., 1995; Hofmanová et al., 2019). This phenomenon can be seen as non-physiological related swallowing difficulties (McCloskey et al., 2022). Even if many patients do not show clinically diagnosed dysphagia, they are still affected by swallowing difficulties of SODFs. This is why one has to bear in mind phagophobia, the impact of an aversion to swallow medicine (Shariff et al., 2020; McCloskey et al., 2022).

Within the older population swallowing difficulties are often caused by hyposalivation (Gerdin et al., 2005; Sasegbon and Hamdy 2017). The unstimulated as well as the stimulated saliva flow rates are reduced in older adults compared to younger ones (Affoo et al., 2015; Vandenberghe-Descamps et al., 2016). Hyposalivation is among others provoked by physiological changes due to aging. These changes include a decreased reflex activity caused by less available olfactory and taste receptors, widening of the neuro-glandular junction, declined concentrations of transmitters and their activity on receptors, reduced gland perfusion with blood, as well as reduced sex steroid blood levels (Ekström et al., 2017). In contrast to the mostly preserved functionality of existing salivary glands in terms of saliva volume, the composition of excreted saliva changes with age. Mucin secretion was shown to be changed in (sero-)mucous glands as well as the secretion of immunoglobulin A in labial glands, while no change was observed in the composition of parotid saliva (Ekström et al., 2017). The mucin of xerostomia patients shows reduced sulfation which might have an impact on saliva's lubricating properties (Xu et al., 2019). The missing lubricating saliva effect might make swallowing SODFs more cumbersome for older adults compared to younger ones. Besides physiological causes, hyposalivation can further be provoked by dehydration, several diseases, and different APIs. There exists a large number of drugs showing xerogenic potential. Among others those include antidepressants, anticholinergics, antispasmodics, antihistamines, antihypertensives, sedatives, and bronchodilators (Liu et al., 2012). Besides the type of medicine being taken, the number of the latter was shown to influence

the prevalence of oral dryness. The prevalence of oral dryness increases with an increasing number of used medicines (Gilbert et al., 1993; Nederfors et al., 1997).

Even within healthy older adults swallowing difficulties are more often observed when compared to young adults. This age-related symptom is called presbyphagia. Changes within physiological and neural mechanisms as well as changes in head, neck, and spine anatomy, e.g. scoliosis, related to swallowing occur due to aging (Ney et al., 2009). It is well known that sarcopenia, a general loss of muscle mass and strength, occurs within the process of aging. This loss of muscle mass also applies to the tongue and consequently results in reduced tongue pressure (Robbins et al., 1995; Ogino et al., 2021). Furthermore, the tongue thickness was observed to be decreased within the process of aging, possibly caused by an often observed malnutrition within older adults (Tamura et al., 2012). A slowdown of the oral phase and in general a decrease in the velocity over the whole swallowing process can be observed. Causes might be of central and peripheral nature (Nicosia et al., 2000). A diminished upper esophageal sphincter opening in older adults contributes to a delay in bolus transport. Muscle weakness is causing a narrower opening of the latter (Shaw et al., 1995). As smooth bolus passage through the pharynx and esophagus is impaired, older adults are more prone to aspiration (Yokoyama et al., 2000). Adequate clearance of the esophagus is not guaranteed due to an increasing esophageal dysmotility (Britton 2016). Thus, the risk of esophageal residues, which potentially travel retrograde into the pharynx and might end up in the trachea, rises (Ney et al., 2009). Parkinson's disease patients often suffer from severe drooling. One could think that this is in contrast to the above-mentioned often-occurring hyposalivation in older adults, but usually the drooling is not caused by an increased production of saliva. It is rather caused by a reduced spontaneous swallowing rate (48/h vs. 71/h). The reduced ability to swallow saliva can arise from oropharyngeal dysphagia (Warnecke et al., 2022).

Besides swallowability, an easy and acceptable handling is important for patients' adherence to their pharmacotherapy. As a first step prior to administration, the patient needs to remove the SODF from the primary packaging or from any other aid such as e.g. a multi compartment compliance aid. Classic monolithic SODFs, i.e., capsules and tablets, need to be picked from a container or pushed through a blister before administration. This can be a challenging task for older adults with

impairment in manual and finger dexterity, if their grip strength is decreased or they suffer from a loss in finger top feel (Isaac et al., 1993; Wilson et al., 2001; Vasylenko et al., 2018; EMA 2020). Sometimes monolithic SODFs need to be divided to achieve the right dose strength, which might be difficult or not possible to perform by the older adults and geriatric patients due to the aforementioned impairments (Santen et al., 2002). Other SODFs, i.e., multiparticulates, orodispersible tablets, ODTs, oral films, or effervescent tablets, often being referred to as alternative SODFs, are on the one hand beneficial for older patients in terms of swallowability but on the other hand they have their own handling challenges. ODTs and oral films are moisture sensitive dosage forms and therefore need to be well sealed during storage. For the administration the patient first of all needs to know whether the individual dosage form can be pushed through the blister or whether the sealing needs to be torn off. Secondly, the dispensation needs to be achieved by the patient in order to administer the medicine which can cause difficulties for the old patient population (Philbert et al., 2014). In turn, multiparticulates might be presented to the patient in stick packs, sprinkle capsules, or as bulk in bottles. Their administration with e.g. a dosing spoon or by sprinkling over food might be challenging for older patients with dexterity issues. Thus, not only the dosage form itself but together with its packaging needs to be thought through during the patient-centric drug product design process in order to be well accepted by the target patient group (Lorenzini and Olsson 2022).

All of the above-mentioned characteristics and age-related changes are summarized in Fig. 6. To allow for the design of patient-centric dosage forms for the individual patient population, all of these aspects need to be considered. Innovative solutions have to be found and applied to overcome the above-mentioned hurdles.

4.3.2. The influence factor – dosage form

The impact on medicines' acceptability of various design aspects of SODFs, i.e., size, shape, thickness, color, surface, taste, and density vary. Size, shape, and surface roughness seem to be of major importance for swallowability while for example thickness is crucial for the handling of SODFs (Andersen et al., 1995; Notenboom et al., 2017; Shariff et al., 2020). The swallowability as one aspect of SODFs' acceptability is further influenced by manufacturing-related characteristics, i.e., disintegration time and propensity for swelling (Drumond and Stegemann

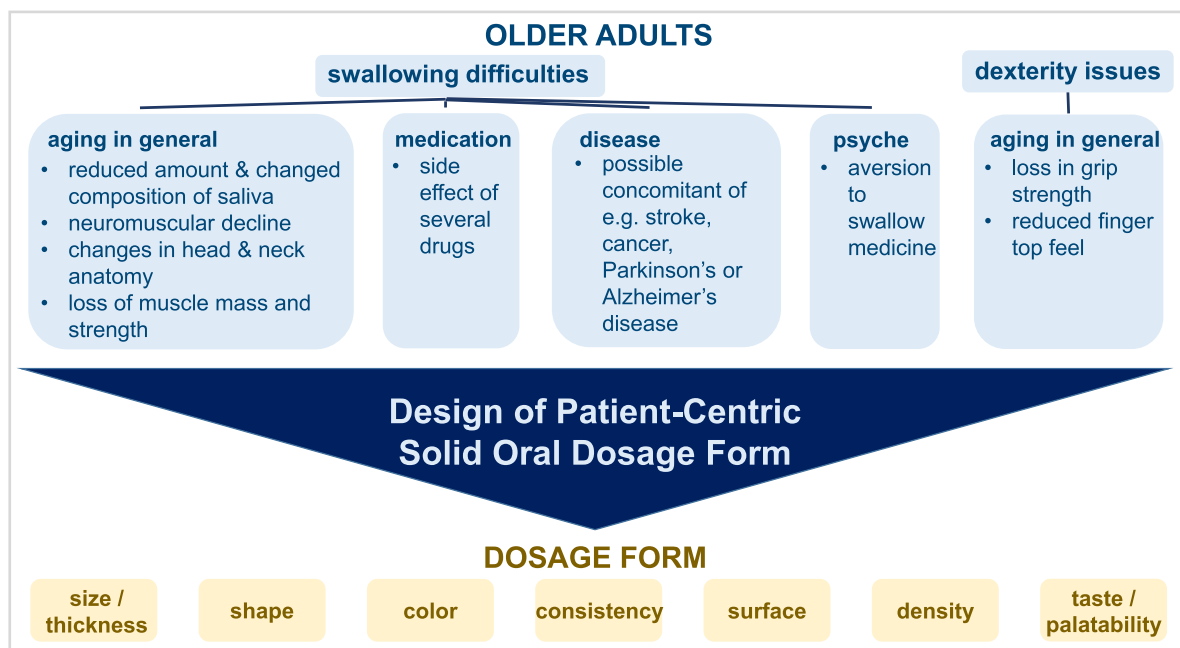


Fig. 6. Development of patient-centric solid oral dosage forms - characteristics of older adults needed to be respected for the right choice of dosage form attributes.

2020). Color is found to be important for the identification and memorability of different medicines, while having minor influence on patients' adherence (Overgaard et al., 2001). Individual colors are associated with different indications. In this context and in the one of palatability, a strong influence of age, sex, and ethnicity has to be considered (Drumond and Stegemann 2020). The shape of SODFs can positively affect the identification process and any handling that needs to be conducted prior to administration (Shariff et al., 2020). As mentioned the aspect of size and thus weight has a strong influence on swallowability, but also on the handling process. A tablet weight of 300 - 450 mg was identified as a good balance between swallowability and handling for the working age population (Yoder 2014). For old frail Japanese patients, tablets of 7 - 8 mm are preferred in respect to swallowability and handling (Miura and Kariyasu 2007). A CAST study focusing on SODF design specifically for the older population included 938 evaluations, mostly collected in hospitals (70%) in France (81.3%). All patients were 65 years or older and the mean age was 86 years. Tablets were classified as accepted for older patients without swallowing disorders while this was not always the case for those showing swallowing disorders (15.6% of study population). In these patients, only tablets with a size of <6.5 mm were considered acceptable (Vallet et al., 2020). The size of dosage forms was described as the largest dimension of the tablet and it varied between 4.7 - 21.54 mm. For oblong and oval tablets, the largest dimension is represented by the length and for round tablets by the diameter (Vallet et al., 2020). MAC was used by Liu et al. for the assessment of SODF acceptability in older ambulatory patients with and without dysphagia. The study showed that participants with dysphagia estimate SODFs of larger size, 11 - 13 mm and 00-sized capsules, as critical to swallow. While this was not the case for their counterparts, older adults without dysphagia (Liu et al., 2016). Most publications conclude that patients prefer a round tablet shape for smaller sized tablets. With increasing tablet size, the oval or oblong shape is preferred (Overgaard et al., 2001; Schiele et al., 2013). However, Shariff et al. describe round tablets depicting a diameter <7 mm as least accepted with respect to swallowing and handling by older adults (Shariff et al., 2020). One has to be careful by generalizing findings of this study, as it is based on a limited number of interviews. Schiele et al. report that hard and soft gelatin capsules as well as oblong tablets are most commonly associated with swallowing difficulties. Round tablets caused the least swallowing difficulties (Schiele et al., 2013). The participants in the study of Overgaard et al. reported increasing difficulties in swallowing tablets as their size increased. But it was not shown whether there exist significant differences between the younger and older (≥ 65 years) study participants (Overgaard et al., 2001). There are several studies on the influence of size and shape of SODFs on swallowability. However, it is often not considered that differently shaped tablets exhibiting the same largest dimension cannot simply be compared to each other. Schiele et al. suggest that the minimum cross-sectional area should be considered rather than the largest dimension of SODFs to allow smooth esophageal passage (Schiele et al., 2013). This is explained by the rotation of tablets and capsules during the process of deglutition to pass the esophageal sphincter with least resistance (Schiele et al., 2013). Kabeya et al. propose to use the sum of the major and minor axis as well as the thickness for the comparison of different tablet shapes, while neglecting the ratio between these three parameters. Tablets' swallowability was related to this sum while it was not related with the major axis as such. Tablets exceeding a sum threshold of 20 - 22 mm were more difficult to swallow for adults visiting a Japanese pharmacy (Kabeya et al., 2021). Thus, the largest dimension of dosage forms might not be appropriate for the comparison between tablets of different shapes.

Besides size and shape of the SODFs, formulations' density impacts esophageal transit times and has to be considered when comparing different dosage forms, i.e., tablets and capsules (Perkins et al., 1994). The coating is another manufacturing-related aspect that can enhance the swallowability of SODFs (Notenboom et al., 2017; Shariff et al.,

2020). For dysphagic patients, coatings can show a positive effect on the number of swallows and on the esophageal contraction force needed (Carnaby-Mann and Cray 2005). Coatings can have a positive effect on transit times and decrease the risk of tablet lodging in the esophagus and further can decrease surface roughness (Perkins et al., 1999; Yamamoto et al., 2014; FDA 2015; Drumond and Stegemann 2020). The mechanisms behind the potentially swallowability enhancing effects depend on the chemical properties of the used materials. An overview of underlying principles behind different materials has been provided by Drumond et al. in their review article (Drumond and Stegemann 2020). Drumond et al. state a large discrepancy between the availability of scientific articles about the evidence of swallowability enhancing coatings and the large number of patents aiming to retain intellectual property and to reduce competitiveness. Most of these patented coatings are made of well-known polymers that have been on the market for decades (Drumond and Stegemann 2020). One of the few studies on the evidence of the swallowability enhancing effect of different coatings was performed by Hofmanová et al. (Hofmanová et al., 2019). In a randomized double-blinded study, 84 adults, whereof 51% were 55 years or older, assessed ease of swallowing and palatability using visual analogue scales. None of the healthy study participants showed self-reported swallowing difficulties with tablets. The four tested dosage forms were white oblong placebo tablets being $19 \times 9 \times 7$ mm in size. One of them remained uncoated while the others were coated either with Opadry white, Opadry EZ white, or Opadry EZ clear (Colorcon, USA), all being hydroxypropyl methylcellulose, HPMC, based film coatings (Hofmanová et al., 2019). The results show that the most slippery and smooth coating was rated as the best. While a differentiation of the three coated tablets in terms of ease of swallowing was not possible, they were all preferred compared to the uncoated tablet. In addition, more time and amount of water was needed to swallow the uncoated tablet compared to the three coated versions. With regard to age, participants being 54 years or younger more often reported difficulties in swallowing these tablets compared to the study participants being 55 years or older. The latter needed more time but used less water to swallow the different tablets tested in the study (Hofmanová et al., 2019). The different performance of the uncoated tablet vs. the coated versions might be explained by the exposure of the insoluble excipients of the tablet core leading to rough interactions when coming in contact with wet surfaces and thus resulting in greater friction. In case of the coated version, maintained lubrication and reduced friction is achieved by the layer of polymer coating leading to reduced amounts of water being absorbed. The polymers form a slippery layer under hydration which further reduces friction (Hofmanová et al., 2019). One limitation of this study is that participants only once assessed the acceptability and palatability of the investigated objects. Thus, no statement on intraindividual variability can be made. The inability of differentiating the three different coatings in terms of swallowability might be due to their common HPMC basis. One could question whether it might be the simple fact of coating application that allows for the swallowability enhancing effect downgrading the importance of the effective coating composition.

Instead of enhancing swallowability by applying different coatings to tablets, swallowability difficulties can further be overcome by using alternative dosage forms, i.e., ODTs, effervescent tablets, chewable tablets, or multiparticulates, e.g. mini tablets. In respect to acceptability of oral liquid drug products a study using CAST accounts for a *positively accepted* profile cluster for liquid pharmaceutical products (Belissa et al., 2019). However, when the focus is exclusively on older patients with swallowing disorders this is not the case (Belissa et al., 2019). Liquid pharmaceutical products are classified as *negatively accepted* in this population group (Belissa et al., 2019). This shows that liquid pharmaceutical products seem not to be suitable alternatives to SODFs for older patients with swallowing disorders (Belissa et al., 2019). CAST was used to compare the acceptability of different paracetamol products in the older population (Ruiz et al., 2019). Hereby, ODTs occurred as potential alternatives to conventional SODFs for patients showing swallowing

difficulties (Ruiz et al., 2019). Additionally, ODTs are besides dispersible/effervescent tablets revealed as most accepted by participants showing dysphagia in a study conducted by Liu et al. (Liu et al., 2016). However, unpleasant taste is often reported as a hurdle for ODTs as it might reduce patients' adherence (Slavkova and Breikreutz 2015). Chewable tablets and granules were the least favored dosage forms in the study conducted by Liu et al. There were concerns about the handling of mini tablets due to their small size (Liu et al., 2016). Participants without dysphagia were less in favor of alternative dosage forms compared to conventional SODFs (Liu et al., 2016). This strengthens the convenient, simple, and easy application of tablets and capsules as long as their swallowability is given. Further, it highlights the impact of familiarity with different dosage forms on patients' acceptability (Liu et al., 2016).

Swallowing in general is an extremely complex process comprising an oral, pharyngeal, and esophageal part and it is influenced by many different factors. *In vitro* and *in silico* experiments depict attractive complements to *in vivo* investigations. The variation of parameter in the swallowability assessments, enables a better understanding of the impact of different properties of the swallowed dosage form on swallowability, and allows their adaptation to the different patient needs (Marconati et al., 2019). There exist different approaches for *in vitro* assays addressing the process of swallowing. Complex models simulating the oral, pharyngeal, and/or esophageal circumstances as realistically as possible were developed in the past (Marconati et al., 2019). In contrast to those models mimicking the deglutition process as such, other types of *in vitro* assays are used to investigate physical and chemical interactions of swallowed materials and the oral cavity. Drummond et al. proposed methods to study particle interactions and mechanical forces in order to predict mucoadhesive strength properties of different polymers (Drummond and Stegemann 2018a, b). Rheological and turbidimetric measurements seem to be most appropriate to measure the amount of polymer adhering to mucus (Drummond and Stegemann 2018a). Furthermore, tribology was proposed as a tool to study texture and mouthfeel in the pharmaceutical field after already being implemented in the food industry (Hofmanová et al., 2021). Hofmanová et al. showed the feasibility of discrimination between tablets with different coatings using surface and thin film tribology (Hofmanová et al., 2021). The *in vitro* measurements of Hofmanová et al. are supported by *in vivo* data. Smart et al. suggested an apparatus incorporating a section of porcine esophageal mucosa to test esophageal adhesion of different materials commonly used in pharmaceutical coatings (Smart et al., 2013). Recently, a multi-analytical framework including measurements to mimic the oral transition of SODFs in a static as well as dynamic stage was proposed by Ershad et al. (Ershad et al., 2021). They calculated a quantitative swallowability index putting critical physical forces which govern the process of swallowability into a mathematical relationship (Ershad et al., 2021).

In order to get meaningful predictions from *in vitro* and *in silico* tools, these tools need to be verified by *in vivo* data and adaptations to the characteristics of individual target patient groups need to be possible. For older adults and geriatric patients, the change in viscoelastic properties of saliva due to altered composition should be considered as one example (Zussman et al., 2007).

The ease of handling monolithic SODFs was shown to be influenced by their size and shape. A study conducted by Goyanes et al. shows that within differently shaped 3D printed medicines the torus shape was rated highest in swallowability but also in handling by 50 young adults (average age 24.6 years) (Goyanes et al., 2017). Besides its influence on handling, the shape of tablets can further be used to enhance breaking of the latter if such is needed, e.g. to allow for correct dosing. The "Snap-Tab" tablets are one example for such a tablet design (Santen et al., 2002).

Despite the fact that there already exists knowledge about the preference and acceptability of different SODFs, a gap in respect to older adults, as one of the main drug product end users often confronted with

use difficulties and problems, still exists. Filling those knowledge gaps would allow for validation and adoption of the above mentioned *in vitro* and *in silico* tools. These adaptable tools can subsequently be used for easier screening of adequate SODFs for the individual target patient group reducing the burden for the latter. This is of major importance when focusing on vulnerable patient groups such as older adults and geriatric patients.

5. Conclusion

Despite the fact that older adults and geriatric patients are the main users of medicine, their needs are often neglected during the development of new medicinal products. This is at least partially related to the fact that systematic studies investigating the different aspects of medication management, i.e., real-life dosing conditions or appropriate tablet sizes and shapes, are scarce in this heterogeneous group of adults ranging from very fit to multimorbid, and even frail patients. However, the existing studies indicate that real-life dosing conditions are often far away from the intended use of the medications. Dosage form modifications and wrong timing of drug intake in relation to other drugs or food can lead to reduced efficacy or even safety concerns. An improved understanding of real-life dosing conditions would not only help to better educate patients on the correct use of their medicine but also in the development of more patient-centric products. In contrast to the pediatric population, little is known on the acceptability of dosage forms in older adults. The existing literature is quite diverse in terms of methods used to investigate the acceptability of dosage forms in general as well as aspects such as swallowability or handling. This highlights the importance of creating a better understanding of this patient population and the need for patient-centric dosage form design. Assessing the acceptability of innovative new approaches in a multi-dimensional way, i.e., swallowability, palatability, and handling of the dosage form, the packaging material, and instructions for use, will finally prove the applicability in the selected patient population. Considering the older patients with their often complex medication management would allow for appropriate pharmacological treatment. If this can be achieved, the quality of life of the multimorbid patients will be improved, caregiver burden reduced, and hospitalization avoided. A successful pharmacotherapy can thus contribute to a reduction of the overall health care costs.

Funding

This research has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 956146.

CRediT authorship contribution statement

Henriette Hummler: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Dorota Sarwinska:** Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Werner Weitschies:** Funding acquisition, Conceptualization, Writing – review & editing. **Maik Gollasch:** Writing – review & editing. **Susanne Page:** Funding acquisition, Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

All references that were used for the review article are cited and listed under references.

Acknowledgements

The authors acknowledge the use of Servier Medical Art as the Graphical Abstract and Figs. 4 and 5 were partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported licence. Further, icons from Roche Media Library have been used for the before mentioned illustrations. Icons integrated in the Graphical Abstract as well as in Figs. 4 and 5 are used from <https://icons8.com/> (<https://icons8.com/icons/set/fried-egg>, <https://icons8.com/icons/set/bacon>, <https://icons8.com/icons/set/roast-potatoes>).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ejps.2023.106453](https://doi.org/10.1016/j.ejps.2023.106453).

References

- Abeele, J.V.D., Brouwers, J., Deloose, E., et al., 2017. The effect of sparkling water on intraluminal formulation behavior and systemic drug performance. *J. Pharm. Sci.* 106, 2472–2482. <https://doi.org/10.1016/j.xphs.2017.03.039>.
- Affoo, R.H., Foley, N., Garrick, R., et al., 2015. Meta-Analysis of Salivary Flow Rates in Young and Older Adults. *J. Am. Geriatr. Soc.* 63, 2142–2151. <https://doi.org/10.1111/jgs.13652>.
- Alsaeed, D., Jamieson, E., Gul, M.O., Smith, F.J., 2016. Challenges to optimal medicines use in people living with dementia and their caregivers: a literature review. *Int J Pharmaceut* 512, 396–404. <https://doi.org/10.1016/j.ijpharm.2015.12.050>.
- Andersen, O., Zweidorff, O., Hjelde, T., Rødland, E., 1995. Problems when swallowing tablets. A questionnaire study from general practice. *Tidsskrift for den Norske Laegeforening : Tidsskrift for Praktisk Medicin*.
- Asola E., Hautala A. (2022) Value chain for pharmacotherapy. <https://stm.fi/en/value-chain-for-pharmacotherapy>. Accessed 23 Jul 2022.
- Atkin, P.A., Finnegan, T.P., Ogle, S.J., Shenfield, G.M., 1994. Functional Ability of Patients to manage Medication Packaging: a Survey of Geriatric Inpatients. *Age Ageing* 23, 113–116. <https://doi.org/10.1093/ageing/23.2.113>.
- Barat, I., Andreasen, F., Damsgaard, E.M.S., 2001. Drug therapy in the elderly: what doctors believe and patients actually do. *Brit J Clin Pharmacol* 51, 615–622. <https://doi.org/10.1046/j.0306-5251.2001.01401.x>.
- Barber, N.D., Alldred, D.P., Raynor, D.K., et al., 2009. Care homes' use of medicines study: prevalence, causes and potential harm of medication errors in care homes for older people. *Qual Saf Heal Care* 18, 341. <https://doi.org/10.1136/qshc.2009.034231>.
- Barnett, K., Mercer, S.W., Norbury, M., et al., 2012. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 380, 37–43. [https://doi.org/10.1016/s0140-6736\(12\)60240-2](https://doi.org/10.1016/s0140-6736(12)60240-2).
- Beermann, B., Midskov, C., 1986. Reduced bioavailability and effect of furosemide given with food. *Eur. J. Clin. Pharmacol.* 29, 725–727. <https://doi.org/10.1007/bf00615967>.
- Belissa, E., Vallet, T., Laribe-Caget, S., et al., 2019. Acceptability of oral liquid pharmaceutical products in older adults: palatability and swallowability issues. *Bmc Geriatr* 19, 344. <https://doi.org/10.1186/s12877-019-1337-2>.
- Biogen N.B.V. (2011) Fampyra 10 mg - ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS. https://www.ema.europa.eu/en/documents/product-information/fampyra-epar-product-information_en.pdf. Accessed 26 Sep 2022.
- Bogdahn, M., Torner, J., Krause, J., et al., 2021. Influence of the geometry of 3D printed solid oral dosage forms on their swallowability. *Eur. J. Pharm. Biopharm.* 167, 65–72. <https://doi.org/10.1016/j.ejpb.2021.07.009>.
- Bourdenet, G., Giraud, S., Artur, M., et al., 2015. Impact of recommendations on crushing medications in geriatrics: from prescription to administration. *Fundam Clin Pharm* 29, 316–320. <https://doi.org/10.1111/fcp.12116>.
- Braun-Münker, M., Ecker, F., 2016. Ease of opening of blistered solid dosage forms in a senior citizens target group. *Int J Pharmaceut* 512, 412–415. <https://doi.org/10.1016/j.ijpharm.2015.10.063>.
- Braun-Münker, M., Kahrman, B., Ecker, F., 2020. The package barrier to user adherence: comparative analysis of various types of opening instructions on the ease of opening comprising effectiveness, efficiency and user satisfaction. *Brit J Clin Pharmacol* 86, 1982–1988. <https://doi.org/10.1111/bcp.14060>.
- Britton, D., 2016. The Impact of Aging and Progressive Neurological Disease on Swallowing: a Concise Overview. *J. Texture Stud.* 47, 257–265. <https://doi.org/10.1111/jtxs.12189>.
- Brotherman, D.P., Bayraktaroglu, T.O., Garofalo, R.J., 2004. Comparison of Ease of Swallowing of Dietary Supplement Products for Age-Related Eye Disease. *J Am Pharm Assoc* 44, 587–593. <https://doi.org/10.1331/1544-3191.44.5.583>. brotherman.
- Bustrack, J.A., Katz, J.D., Hull, J.H., et al., 1984. Bioavailability of digoxin capsules and tablets: effect of coadministered fluid volume. *J. Pharm. Sci.* 73, 1397–1400. <https://doi.org/10.1002/jps.2600731018>.
- Carlson, C., Merel, S.E., Yukawa, M., 2015. Geriatric Syndromes and Geriatric Assessment for the Generalist. *Med Clin N Am* 99, 263–279. <https://doi.org/10.1016/j.mcna.2014.11.003>.
- Carnaby-Mann, G., Crary, M., 2005. Pill Swallowing by Adults With Dysphagia. *Archives Otolaryngology Head Neck Surg* 131, 970–975. <https://doi.org/10.1001/archotol.131.11.970>.
- Carvajal, F.A., Martínez, M.G., Santamaría, E.C., et al., 2016. Adaptation of oral medication in people institutionalized in nursing homes for whom medication is crushed: the ADECUA Study. *Farmacia Hosp Organo Oficial De Expresion Cientifica De La Sociedad Espanola De Farmacia Hosp* 40, 514–528. <https://doi.org/10.7399/fh.2016.40.6.10467>.
- Cheng, L., Wong, H., 2020. Food Effects on Oral Drug Absorption: application of Physiologically-Based Pharmacokinetic Modeling as a Predictive Tool. *pharm.* 12, 672. <https://doi.org/10.3390/pharmaceutics12070672>.
- Chon, D.A., Reisman, T., Weinreb, J.E., et al., 2018. Concurrent Milk Ingestion Decreases Absorption of Levothyroxine. *Thyroid* 28, 454–457. <https://doi.org/10.1089/thy.2017.0428>.
- Cleary, J.D., Evans, P.C., Hikal, A.H., Chapman, S.W., 1999. Administration of crushed extended-release pentoxifylline tablets: bioavailability and adverse effects. *Am J Health-syst Ph* 56, 1529–1534. <https://doi.org/10.1093/ajhp/56.15.1529>.
- Cornish, P., 2005. Avoid the crush: hazards of medication administration in patients with dysphagia or a feeding tube. *Can. Med. Assoc. J.* 172, 871–872. <https://doi.org/10.1503/cmaj.050176>.
- Drumond, N., Stegemann, S., 2020. Better Medicines for Older Patients: considerations between Patient Characteristics and Solid Oral Dosage Form Designs to Improve Swallowing Experience. *pharm.* 13, 32. <https://doi.org/10.3390/pharmaceutics13010032>.
- Drumond, N., Stegemann, S., 2018a. Polymer adhesion predictions for oral dosage forms to enhance drug administration safety. Part 1: in vitro approach using particle interaction methods. *Colloids Surfaces B Biointerfaces* 165, 9–17. <https://doi.org/10.1016/j.colsurfb.2018.02.012>.
- Drumond, N., Stegemann, S., 2018b. Polymer adhesion predictions for oral dosage forms to enhance drug administration safety. Part 2: in vitro approach using mechanical force methods. *Colloids Surfaces B Biointerfaces* 166, 17–23. <https://doi.org/10.1016/j.colsurfb.2018.03.006>.
- EC (2008) Population projections 2008-2060. https://ec.europa.eu/commission/press-corner/detail/en/STAT_08_119. Accessed 17 Sep 2022.
- Edelberg, H.K., Shallenberger, E., Wei, J.Y., 1999. Medication Management Capacity in Highly Functioning Community-Living Older Adults: detection of Early Deficits. *J. Am. Geriatr. Soc.* 47, 592–596. <https://doi.org/10.1111/j.1532-5415.1999.tb02574.x>.
- Eidam, A., Roth, A., Frick, E., et al., 2022. Development of an electronic tool to assess patient preferences in geriatric polypharmacy (PolyPref). *Patient Prefer Adher* 16, 1733–1747. <https://doi.org/10.2147/ppa.s364681>.
- Ekström, J., Khosravani, N., Castagnola, M., Messana, L., 2017. Saliva and the control of its secretion. In: Ekberg, O (Ed.), *Dysphagia, Diagnosis and Treatment*.
- EMA (2020) Reflection paper on the pharmaceutical development of medicines for use in the older population. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-pharmaceutical-development-medicines-use-older-population-first-version_en.pdf. Accessed 2 Oct 2021.
- EMA (2010) Guideline on the investigation of bioequivalence. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Accessed 20 Sep 2022.
- Ershad A.L., Rajabi-Siahboomi A., Missaghi S., et al., (2021) Multi-analytical framework to assess the in vitro swallowability of solid oral dosage forms targeting patient acceptability and adherence. <file:///C:/Users/hummlh1/Downloads/pharmaceutics-13-00411-v2.pdf>. Accessed 31 May 2021.
- FDA (2002) Guidance for industry - food-effect bioavailability and fed bioequivalence studies. <https://www.fda.gov/files/drugs/published/Food-Effect-Bioavailability-and-Fed-Bioequivalence-Studies.pdf>. Accessed 20 Sep 2022.
- FDA (2015) Size, shape, and other physical attributes of generic tablets and capsules. <https://www.fda.gov/files/drugs/published/Size-Shape-and-Other-Physical-Attributes-of-Generic-Tablets-and-Capsules.pdf?next=/answers/six-tips-to-avoid-getting-pill-stuck-in-your-throat/avoid-pill-getting-stuck-in-throat/>. Accessed 20 Sep 2022.
- Fodil, M., Nghiem, D., Colas, M., et al., 2017. Assessment of clinical practices for crushing medication in geriatric units. *J. Nutrition Heal Aging* 21, 904–908. <https://doi.org/10.1007/s12603-017-0886-3>.
- Forough, A.S., Lau, E.T.L., Steadman, K.J., et al., 2020. Appropriateness of oral dosage form modification for aged care residents: a video-recorded observational study. *Int. J. Clin. Pharm-net* 42, 938–947. <https://doi.org/10.1007/s11096-020-01036-x>.
- Franko, D.L., Shapiro, J., Gagne, A., 1997. Phagophobia: a form of psychogenic dysphagia a new entity. *Ann. Otol. Rhinol. Laryngol.* 106, 286–290. <https://doi.org/10.1177/000348949710600404>.
- Freerks, L., Zielke, C., Tarnow, M.-J., et al., 2022. A toolbox for mimicking gastrointestinal conditions in children: simulated paediatric breakfast media (SPBM) for addressing the variability of gastric contents after typical paediatric breakfasts. *J. Pharm. Sci.* 111, 51–61. <https://doi.org/10.1016/j.xphs.2021.05.003>.
- Fuchs, J., 2009. The amount of liquid patients use to take tablets or capsules. *Pharm. Pract. Granada* 7, 170–174. <https://doi.org/10.4321/s1886-36552009000300007>.
- Gerber, A., Kohaupt, I., Lauterbach, K.W., et al., 2008. Quantification and classification of errors associated with hand-repackaging of medications in long-term care facilities in Germany. *Am. J. Geriatric Pharmacother.* 6, 212–219. <https://doi.org/10.1016/j.amjpharm.2008.10.005>.
- Gerdin, E.W., Einarsson, S., Jonsson, M., et al., 2005. Impact of dry mouth conditions on oral health-related quality of life in older people. *Gerodontology/Gerodontology* 22, 219–226. <https://doi.org/10.1111/j.1741-2358.2005.00087.x>.

- Gilbert, G.H., Heft, M.W., Duncan, R.P., 1993. Mouth dryness as reported by older Floridians. *Community Dent. Oral Epidemiol.* 21, 390–397. <https://doi.org/10.1111/j.1600-0528.1993.tb01105.x>.
- Gill, D., Spain, M., Edlund, B.J., 2012. Crushing or splitting medications: unrecognized hazards. *J. Gerontol. Nurs.* 38, 8–12. <https://doi.org/10.3928/00989134-20111213-01>.
- Gnjidic, D., Husband, A., Todd, A., 2018. Challenges and innovations of delivering medicines to older adults. *Adv. Drug Deliver. Rev.* 135, 97–105. <https://doi.org/10.1016/j.addr.2018.08.003>.
- Goyanes, A., Scarpa, M., Kamlow, M., et al., 2017. Patient acceptability of 3D printed medicines. *Int. J. Pharmaceut.* 530, 71–78. <https://doi.org/10.1016/j.ijpharm.2017.07.064>.
- Haighton, C., Kidd, J., O'Donnell, A., et al., 2018. I take my tablets with the whiskey': a qualitative study of alcohol and medication use in mid to later life. *PLoS ONE* 13, e0205956. <https://doi.org/10.1371/journal.pone.0205956>.
- Havenaar, R., Anneveld, B., Hanff, L.M., et al., 2013. In vitro gastrointestinal model (TIM) with predictive power, even for infants and children? *Int. J. Pharmaceut.* 457, 327–332. <https://doi.org/10.1016/j.ijpharm.2013.07.053>.
- Haw, C., Stubbs, J., 2010. Administration of medicines in food and drink: a study of older inpatients with severe mental illness. *Int. Psychogeriatr.* 22, 409–416. <https://doi.org/10.1017/s1041610209991669>.
- Hens, B., Abeele, J.V.D., Rubbens, J., et al., 2017. Evaluation of real-life dosing of oral medicines with respect to fluid and food intake in a Dutch-speaking population. *J. Clin. Pharm. Ther.* 42, 467–474. <https://doi.org/10.1111/jcpt.12535>.
- Hofmanová, J.K., Mason, J., Batchelor, H.K., 2021. Tribology provides an in vitro tool that correlated to in vivo sensory data on the mouthfeel of coated tablets. *Int. J. Pharmaceut.* 597, 120323. <https://doi.org/10.1016/j.ijpharm.2021.120323>.
- Hofmanová, J.K., Rajabi-Siahboomi, A., Haque, S., et al., 2019. Developing methodology to evaluate the oral sensory features of pharmaceutical tablet coatings. *Int. J. Pharmaceut.* 562, 212–217. <https://doi.org/10.1016/j.ijpharm.2019.03.046>.
- Hughes, C.M., Cadogan, C.A., Patton, D., Ryan, C.A., 2016. Pharmaceutical strategies towards optimising polypharmacy in older people. *Int. J. Pharmaceut.* 512, 360–365. <https://doi.org/10.1016/j.ijpharm.2016.02.035>.
- Isaac L.M., Tambllyn R.M., Team M.-C.D.R. (1993) Compliance and cognitive function: a methodological approach to measuring unintentional errors in medication compliance in the elderly. 1. 33:772–781. <https://doi.org/10.1093/geront/33.6.772>.
- Jamerson, B.D., Fillenbaum, G.G., Sloane, R., Morey, M.C., 2016. A new method of identifying characteristics of needing help to take medications in an older representative community-dwelling population: the older adults medication assist scale. *J. Am. Geriatr. Soc.* 64, 1195–1202. <https://doi.org/10.1111/jgs.14166>.
- Jani, Y.H., Liu, F., Orlu, M., et al., 2021. Medicine acceptability for older people in hospital and care home: the influence of setting. *Int J Pharm Pract* 30, riab077. <https://doi.org/10.1093/ijpp/riab077>.
- Jaspersen, D., 2000. Drug-induced oesophageal disorders. *Drug Saf* 22, 237–249. <https://doi.org/10.2165/00002018-200022030-00007>.
- Jetter, A., Kinzig-Schippers, M., Walchner-Bonjean, M., et al., 2002. Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin. Pharmacol. Amp. Ther.* 71, 21–29. <https://doi.org/10.1067/mcp.2002.121236>.
- Kabeya, K., Satoh, H., Hori, S., Sawada, Y., 2021. Experimental study on patient preferences regarding the shape and size of medical tablets and capsules using three-dimensionally printed plastic model formulations. *Patient Prefer. Adher.* 15, 863–870. <https://doi.org/10.2147/ppa.s306582>.
- Karapinar-Çarkit, F., Bemt, P.M.L.A., Sadik, M., et al., 2020. Opportunities for changes in the drug product design to enhance medication safety in older people: evaluation of a national public portal for medication incidents. *Brit. J. Clin. Pharmacol.* 86, 1946–1957. <https://doi.org/10.1111/bcp.14392>.
- Kelly, J., D'Cruz, G., Wright, D., 2008. A qualitative study of the problems surrounding medicine administration to patients with dysphagia. *Dysphagia* 24, 49. <https://doi.org/10.1007/s00455-008-9170-3>.
- Kelly, J., D'Cruz, G., Wright, D., 2010. Patients with dysphagia: experiences of taking medication. *J. Adv. Nurs.* 66, 82–91. <https://doi.org/10.1111/j.1365-2648.2009.05145.x>.
- Kirkevold, Øyvind, Engedal, K., 2005. Concealment of drugs in food and beverages in nursing homes: cross sectional study. *BMJ* 330, 20. <https://doi.org/10.1136/bmj.38268.579097.55>.
- Koziolek, M., Alcaro, S., Augustijns, P., et al., 2019. The mechanisms of pharmacokinetic food-drug interactions – a perspective from the UNGAP group. *Eur. J. Pharm. Sci.* 134, 31–59. <https://doi.org/10.1016/j.ejps.2019.04.003>.
- Kripalani, S., Henderson, L.E., Chiu, E.Y., et al., 2006. Predictors of medication self-management skill in a low-literacy population. *J. Gen. Intern. Med.* 21, 852–856. <https://doi.org/10.1111/j.1525-1497.2006.00536.x>.
- Kuepfer, L., Niederalt, C., Wendt, T., et al., 2016. Applied concepts in PBPK modeling: how to build a PBPK/PD model. *Cpt. Pharmacometrics. Syst. Pharmacol.* 5, 516–531. <https://doi.org/10.1002/psp4.12134>.
- Laitinen, K., Patronen, A., Harju, P., et al., 2000. Timing of food intake has a marked effect on the bioavailability of clodronate. *Bone* 27, 293–296. [https://doi.org/10.1016/s8756-3282\(00\)00321-5](https://doi.org/10.1016/s8756-3282(00)00321-5).
- Lau, E.T.L., Steadman, K.J., Cichero, J.A.Y., Nissen, L.M., 2018. Dosage form modification and oral drug delivery in older people. *Adv. Drug Deliver. Rev.* 135, 75–84. <https://doi.org/10.1016/j.addr.2018.04.012>.
- Liu, B., Dion, M.R., Jurasic, M.M., et al., 2012. Xerostomia and salivary hypofunction in vulnerable elders: prevalence and etiology. *Oral. Surg. Oral Medicine Oral Pathol. Oral Radiol.* 114, 52–60. <https://doi.org/10.1016/j.oooo.2011.11.014>.
- Liu, F., Ghaffar, A., Bains, J., Hamdy, S., 2016. Acceptability of oral solid medicines in older adults with and without dysphagia: a nested pilot validation questionnaire based observational study. *Int. J. Pharmaceut.* 512, 374–381. <https://doi.org/10.1016/j.ijpharm.2016.03.007>.
- Liu, F., Rannal, S., Batchelor, H.K., et al., 2014. Patient-centered pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. *Drugs* 74, 1871–1889. <https://doi.org/10.1007/s40265-014-0297-2>.
- Lorenzini, G.C., Bell, A., Olsson, A., 2022a. You need to be healthy to be sick': exploring older people's experiences with medication packaging at home. *Age Ageing* 51, afac050. <https://doi.org/10.1093/ageing/afac050>.
- Lorenzini, G.C., Olsson, A., 2022b. Exploring how and why to develop patient-centered packaging: a multiple-case study with pharmaceutical companies. *Ther. Innov. Regul. Sci.* 56, 117–129. <https://doi.org/10.1007/s43441-021-00338-0>.
- Marconati, M., Engmann, J., Burbidge, A., et al., 2019. A review of the approaches to predict the ease of swallowing and post-swallow residues. *Trends Food Sci Tech* 86, 281–297. <https://doi.org/10.1016/j.tifs.2019.02.045>.
- Martir, J., Flanagan, T., Mann, J., Fotaki, N., 2020. Impact of food and drink administration vehicles on paediatric formulation performance: part 1—effects on solubility of poorly soluble drugs. *AAPS PharmSciTech* 21, 177. <https://doi.org/10.1208/s12249-020-01722-z>.
- Martir, J., Flanagan, T., Mann, J., Fotaki, N., 2020b. Impact of food and drink administration vehicles on paediatric formulation performance part 2: dissolution of montelukast sodium and mesalazine formulations. *AAPS PharmSciTech* 21, 287. <https://doi.org/10.1208/s12249-020-01815-9>.
- Matsumoto, F., Sakurai, I., Morita, M., et al., 2001. Effects of the quantity of water and milk ingested concomitantly with AS-924, a novel ester-type cephem antibiotic, on its pharmacokinetics. *Int. J. Antimicrob. Ag* 18, 471–476. [https://doi.org/10.1016/s0924-8579\(01\)00447-2](https://doi.org/10.1016/s0924-8579(01)00447-2).
- McCloskey, A.P., Penson, P.E., Tse, Y., et al., 2022. Identifying and addressing pill aversion in adults without physiological-related dysphagia: a narrative review. *Brit. J. Clin. Pharmacol.* <https://doi.org/10.1111/bcp.15463>.
- Melhuys, E., Dupond, L., Petrovic, M., et al., 2012. Medication management among home-dwelling older patients with chronic diseases: possible roles for community pharmacists. *J. Nutrition Heal Aging* 16, 721–726. <https://doi.org/10.1007/s12603-012-0028-x>.
- Messina, R., Becker, R., van, Riet-Nales DA, Stegemann, S., 2015. Results from a preliminary review of scientific evidence for appropriateness of preparations, dosage forms and other product design elements for older adult patients. *Int. J. Pharmaceut.* 478, 822–828. <https://doi.org/10.1016/j.ijpharm.2014.10.052>.
- Misaka, S., Yatabe, J., Müller, F., et al., 2014. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. *Clin. Pharmacol. Ther.* 95, 432–438. <https://doi.org/10.1038/clpt.2013.241>.
- Miura, H., Kariyasu, M., 2007. Effect of size of tablets on easiness of swallowing and handling among the frail elderly. *Nippon Ronen Igakkai Zasshi Jpn J. Geriatrics* 44, 627–633. <https://doi.org/10.3143/geriatrics.44.627>.
- Muramatsu, R.S., Litzinger, M.H.J., Fisher, E., Takeshita, J., 2010. Alternative formulations, delivery methods, and administration options for psychotropic medications in elderly patients with behavioral and psychological symptoms of dementia. *Am. J. Geriatric Pharmacother.* 8, 98–114. <https://doi.org/10.1016/j.amjopharm.2010.03.003>.
- Nader, A.M., Quinney, S.K., Fadda, H.M., Foster, D.R., 2016. Effect of gastric fluid volume on the in vitro dissolution and in vivo absorption of bcs class ii drugs: a case study with nifedipine. *AAPS J.* 18, 981–988. <https://doi.org/10.1208/s12248-016-9918-x>.
- Nathan, J.P., Zerilli, T., Cicero, L.A., Rosenberg, J.M., 2007. Patients' use and perception of medication information leaflets. *Ann. Pharmacother.* 41, 777–782. <https://doi.org/10.1345/aph.1h686>.
- Nederfors, T., Isaksson, R., Mörnstad, H., Dahlöf, C., 1997. Prevalence of perceived symptoms of dry mouth in an adult Swedish population - relation to age, sex and pharmacotherapy. *Community Dent Oral Epidemiol.* 25, 211–216. <https://doi.org/10.1111/j.1600-0528.1997.tb00928.x>.
- Ney, D.M., Weiss, J.M., Kind, A.J.H., Robbins, J., 2009. Senescent swallowing: impact, strategies, and interventions. *Nutr. Clin. Pract.* 24, 395–413. <https://doi.org/10.1177/0884533609332005>.
- NHS (2022a) How and when to take risedronate. <https://www.nhs.uk/medicines/risedronate/how-and-when-to-take-risedronate/>. Accessed 17 Mar 2023.
- NHS (2023) How and when to take tamsulosin. <https://www.nhs.uk/medicines/tamsulosin/how-and-when-to-take-tamsulosin/>. Accessed 17 Mar 2023.
- NHS (2022b) How and when to take metformin. <https://www.nhs.uk/medicines/metformin/how-and-when-to-take-metformin/>. Accessed 17 Mar 2023.
- NHS (2022c) How and when to take betamethasone tablets. <https://www.nhs.uk/medicines/betamethasone-tablets/how-and-when-to-take-betamethasone-tablets/>. Accessed 17 Mar 2023.
- Nicosia, M.A., Hind, J.A., Roecker, E.B., et al., 2000. Age effects on the temporal evolution of isometric and swallowing pressure. *J. Gerontol. Ser* 55, M634–M640. <https://doi.org/10.1093/gerona/55.11.m634>.
- Nissen, L.M., Haywood, A., Steadman, K.J., 2009. Solid medication dosage form modification at the bedside and in the pharmacy of queensland hospitals. *J. Pharm. Pract. Res.* 39, 129–134. <https://doi.org/10.1002/j.2055-2335.2009.tb00436.x>.
- Notenboom, K., Beers, E., Riet-Nales, D.A., et al., 2014. Practical problems with medication use that older people experience: a qualitative study. *J. Am. Geriatr. Soc.* 62, 2339–2344. <https://doi.org/10.1111/jgs.13126>.
- Notenboom, K., Leufkens, H.G., Vromans, H., Bouvy, M.L., 2017. Learning from patients: identifying design features of medicines that cause medication use problems. *Int. J. Pharmaceut.* 517, 128–134. <https://doi.org/10.1016/j.ijpharm.2016.12.004>.
- Novo N.A. (2022) How to Start RYBELSUS®. <https://www.rybelsus.com/taking-rybelsus/how-to-start-rybelsus.html>. Accessed 17 Mar 2023.

- OECD, 2021. Life expectancy and healthy life expectancy at age 65. Health At a Glance 2021. OECD Indicators. <https://www.oecd-ilibrary.org/sites/ae3016b9-en/1/3/10/2/index.html?itemId=/content/publication/ae3016b9-en&csp=ca413da5d44587bc56446341952c275e&itmiGO=oe&itemContentype=book#>. Accessed 6 Aug 2022.
- Ogawa, R., Echizen, H., 2010. Drug-drug interaction profiles of proton pump inhibitors. *Clin. Pharmacokinet.* 49, 509–533. <https://doi.org/10.2165/11531320-000000000-00000>.
- Ogino, Y., Suzuki, H., Ayukawa, Y., et al., 2021. Analyses of swallowing function and its related factors in community-dwelling elderly patients: a case-control study. *J. Clin. Med.* 10, 3437. <https://doi.org/10.3390/jcm10153437>.
- Omidian, H., Babanejad, N., Mfoafo, K., et al., 2022. Toxicity of the polymeric excipients in geriatric polypharmacy. *Int. J. Pharmaceut.* 622, 121901. <https://doi.org/10.1016/j.ijpharm.2022.121901>.
- Organon N.V. (2015) FOSAVANCE 70mg - ANNEX I summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/fosavance-epar-product-information_en.pdf. Accessed 20 Sep 2022.
- Ortiz-Ospina E. (2019) The rise of living alone: how one-person households are becoming increasingly common around the world. <https://ourworldindata.org/living-alone>. Accessed 12 Mar 2023.
- Oshima, T., Hori, S., Maida, C., Miyamoto, E., 2006. Effect of size and shape of tablets and capsules on ease of grasping and swallowing (1) : comparison between elderly and students. *Iryo Yakugaku Jpn J. Pharm. Heal Care Sci.* 32, 842–848. <https://doi.org/10.5649/ijphcs.32.842>.
- Overgaard, A.B.A., Møller-Sonnergaard, J., Christrup, L.L., et al., 2001. Patients' evaluation of shape, size and colour of solid dosage forms. *Pharm. World Sci.* 23, 185–188. <https://doi.org/10.1023/a:1012050931018>.
- Page, S., Coupe, A., Barrett, A., 2016. An industrial perspective on the design and development of medicines for older patients. *Int. J. Pharmaceut.* 512, 352–354. <https://doi.org/10.1016/j.ijpharm.2016.03.008>.
- Paparella, S., 2010. Identified safety risks with splitting and crushing oral medications. *J. Emerg. Nurs.* 36, 156–158. <https://doi.org/10.1016/j.jen.2009.11.019>.
- Pelletier, C.A., Lawless, H.T., 2003. Effect of citric acid and citric acid–sucrose mixtures on swallowing in neurogenic oropharyngeal dysphagia. *Dysphagia* 18, 231–241. <https://doi.org/10.1007/s00455-003-0013-y>.
- Perkins, A.C., Wilson, C.G., Blackshaw, P.E., et al., 1994. Impaired oesophageal transit of capsule versus tablet formulations in the elderly. *Gut* 35, 1363. <https://doi.org/10.1136/gut.35.10.1363>.
- Perkins, A.C., Wilson, C.G., Frier, M., et al., 1999. Esophageal transit of risedronate cellulose-coated tablet and gelatin capsule formulations. *Int. J. Pharmaceut.* 186, 169–175. [https://doi.org/10.1016/s0378-5173\(99\)00172-6](https://doi.org/10.1016/s0378-5173(99)00172-6).
- Perrie, Y., Badhan, R.K.S., Kirby, D.J., et al., 2012. The impact of ageing on the barriers to drug delivery. *J. Control Release* 161, 389–398. <https://doi.org/10.1016/j.jconrel.2012.01.020>.
- Philbert, D., Notenboom, K., Bouvy, M.L., Geffen, E.C.G., 2014. Problems experienced by older people when opening medicine packaging. *Int. J. Pharm. Pract.* 22, 200–204. <https://doi.org/10.1111/ijpp.12070>.
- Porras, A.G., Holland, S.D., Gertz, B.J., 1999. Pharmacokinetics of alendronate. *Clin. Pharmacokinet.* 36, 315–328. <https://doi.org/10.2165/00003088-199936050-00002>.
- Quinzler, R., Gasse, C., Schneider, A., et al., 2006. The frequency of inappropriate tablet splitting in primary care. *Eur. J. Clin. Pharmacol.* 62, 1065–1073. <https://doi.org/10.1007/s00228-006-0202-3>.
- Ranmal, S.R., O'Brien, F., Lopez, F., et al., 2018. Methodologies for assessing the acceptability of oral formulations among children and older adults: a systematic review. *Drug Discov. Today* 23, 830–847. <https://doi.org/10.1016/j.drudis.2018.01.038>.
- Rantanen, P., Parkkari, T., Leikola, S., et al., 2017. An in-home advanced robotic system to manage elderly home-care patients' medications: a pilot safety and usability study. *Clin. Ther.* 39, 1054–1061. <https://doi.org/10.1016/j.clinthera.2017.03.020>.
- Rémond, D., Shahar, D.R., Gille, D., et al., 2015. Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition. *Oncotarget* 6, 13858–13898. <https://doi.org/10.18632/oncotarget.4030>.
- Richey, R.H., Craig, J.V., Shah, U.U., et al., 2012. The manipulation of drugs to obtain the required dose: systematic review. *J. Adv. Nurs.* 68, 2103–2112. <https://doi.org/10.1111/j.1365-2648.2011.05916.x>.
- Riedmaier, A.E., DeMent, K., Huckle, J., et al., 2020. Use of physiologically based pharmacokinetic (PBPK) modeling for predicting drug-food interactions: an industry perspective. *AAPS J.* 22, 123. <https://doi.org/10.1208/s12248-020-00508-2>.
- Riet-Nales, D.A., Bemt, B., Bodegom, D., et al., 2022. Commentary on the EMA reflection paper on the pharmaceutical development of medicines for use in the older population. *Brit. J. Clin. Pharmacol.* 88, 1500–1514. <https://doi.org/10.1111/bcp.15207>.
- Robbins, J.A., Levine, R., Wood, J., et al., 1995. Age effects on lingual pressure generation as a risk factor for dysphagia. *J. Gerontol. Ser. Biol. Sci. Med. Sci.* 50A, M257–M262. <https://doi.org/10.1093/gerona/50a.5.m257>.
- Rodenhuis, N., Smet, P.A.G.M.D., Barends, D.M., 2004. The rationale of scored tablets as dosage form. *Eur. J. Pharm. Sci.* 21, 305–308. <https://doi.org/10.1016/j.ejps.2003.10.018>.
- Roller-Wirnsberger, R., Thurner, B., Pucher, C., et al., 2020. The clinical and therapeutic challenge of treating older patients in clinical practice. *Brit J Clin Pharmacol* 86, 1904–1911. <https://doi.org/10.1111/bcp.14074>.
- Roser M. (2013) Future Population Growth. <https://ourworldindata.org/future-populati-on-growth>. Accessed 23 Jul 2022.
- Rotman, S.R., Bishop, T.F., 2013. Proton Pump Inhibitor Use in the U.S. Ambulatory Setting, 2002–2009. *PLoS ONE* 8, e56060. <https://doi.org/10.1371/journal.pone.0056060>.
- Ruiz, F., Vallet, T., Wojcicki, A.D., et al., 2019. Dosage form suitability in vulnerable populations: a focus on paracetamol acceptability from infants to centenarians. *PLoS ONE* 14, e0221261. <https://doi.org/10.1371/journal.pone.0221261>.
- Ryu, G.S., Lee, Y.J., 2012. Analysis of liquid medication dose errors made by patients and caregivers using alternative measuring devices. *J. Manag. Care Pharm.* 18, 439–445. <https://doi.org/10.18553/jmcp.2012.18.6.439>.
- Santen, E van, Barends, D.M., Frijlink, H.W., 2002. Breaking of scored tablets: a review. *Eur. J. Pharm. Biopharm.* 53, 139–145. [https://doi.org/10.1016/s0939-6411\(01\)00228-4](https://doi.org/10.1016/s0939-6411(01)00228-4).
- Sasegbon, A., Hamdy, S., 2017. The anatomy and physiology of normal and abnormal swallowing in oropharyngeal dysphagia. *Neurogastroenterol. Motil.* 29, e13100. <https://doi.org/10.1111/nmo.13100>.
- Schenk, A., Eckardt-Felmlberg, R., Steinhagen-Thiessen, E., Stegemann, S., 2020. Patient behaviour in medication management: findings from a patient usability study that may impact clinical outcomes. *Brit. J. Clin. Pharmacol.* 86, 1958–1968. <https://doi.org/10.1111/bcp.13946>.
- Schiele, J.T., Quinzler, R., Klimm, H.-D., et al., 2013. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. *Eur. J. Clin. Pharmacol.* 69, 937–948. <https://doi.org/10.1007/s00228-012-1417-0>.
- Schier, J.G., Howland, M.A., Hoffman, R.S., Nelson, L.S., 2003. Fatality from administration of labetalol and crushed extended-release nifedipine. *Ann. Pharmacother.* 37, 1420–1423. <https://doi.org/10.1345/aph.1d091>.
- Schmidt, S.J., Wurmbach, V.S., Lampert, A., et al., 2020. Individual factors increasing complexity of drug treatment—a narrative review. *Eur. J. Clin. Pharmacol.* 76, 745–754. <https://doi.org/10.1007/s00228-019-02818-7>.
- Shariff, Z., Kirby, D., Missaghi, S., et al., 2020. Patient-centric medicine design: key characteristics of oral solid dosage forms that improve adherence and acceptance in older people. *Pharm.* 12, 905. <https://doi.org/10.3390/pharmaceutics12100905>.
- Shaw, D.W., Cook, I.J., Gabb, M., et al., 1995. Influence of normal aging on oral-pharyngeal and upper esophageal sphincter function during swallowing. *Am J Physiol-gastr L* 268, G389–G396. <https://doi.org/10.1152/ajpgi.1995.268.3.g389>.
- Sino, C.G.M., Sietzema, M., Egberts, T.C.G., Schuurmans, M.J., 2014. Medication management capacity in relation to cognition and self-management skills in older people on polypharmacy. *J. Nutrition Heal Aging* 18, 44–49. <https://doi.org/10.1007/s12603-013-0359-2>.
- Slavkova, M., Breitkreutz, J., 2015. Orodispersible drug formulations for children and elderly. *Eur. J. Pharm. Sci.* 75, 2–9. <https://doi.org/10.1016/j.ejps.2015.02.015>.
- Smart, J.D., Dunkley, S., Tsibouklis, J., Young, S., 2013. An in vitro model for the evaluation of the adhesion of solid oral dosage forms to the oesophagus. *Int. J. Pharmaceut.* 447, 199–203. <https://doi.org/10.1016/j.ijpharm.2013.02.017>.
- Solberg, H., Devik, S.A., Bell, H.T., et al., 2021. Drug modification by nurses in Norwegian nursing homes: a cross-sectional study. *Geriatr. Nurs.* 42, 351–357. <https://doi.org/10.1016/j.gerinurse.2021.01.005>.
- Stegemann, S., Gosch, M., Breitkreutz, J., 2012. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. *Int. J. Pharmaceut.* 430, 197–206. <https://doi.org/10.1016/j.ijpharm.2012.04.022>.
- Stegemann, S., Riet-Nales, D van, Boer, A de, 2020. Demographics in the 2020s—Longevity as a challenge for pharmaceutical drug development, prescribing, dispensing, patient care and quality of life. *Brit. J. Clin. Pharmacol.* 86, 1899–1903. <https://doi.org/10.1111/bcp.14511>.
- Stegemann, S., Sheehan, L., Rossi, A., et al., 2022. Rational and practical considerations to guide a Target Product Profile for patient-centric drug product development with measurable patient outcomes – a proposed roadmap. *Eur. J. Pharm. Biopharm.* 177, 81–88. <https://doi.org/10.1016/j.ejpb.2022.06.006>.
- Stillhart, C., Vučićević, K., Augustijns, P., et al., 2020. Impact of gastrointestinal physiology on drug absorption in special populations – An UNGAP review. *Eur. J. Pharm. Sci.* 147, 105280. <https://doi.org/10.1016/j.ejps.2020.105280>.
- Strachan, I., Greener, M., 2005. Medication-related swallowing difficulties may be more common than we realise. *Pharmacy Practice* 15, 411–414.
- Stubbs, J., Haw, C., Dickens, G., 2007. Dose form modification – a common but potentially hazardous practice. A literature review and study of medication administration to older psychiatric inpatients. *Int. Psychogeriatr.* 20, 616–627. <https://doi.org/10.1017/s1041610207006047>.
- Sunesen, V.H., Vedelsdal, R., Kristensen, H.G., et al., 2005. Effect of liquid volume and food intake on the absolute bioavailability of danazol, a poorly soluble drug. *Eur. J. Pharm. Sci.* 24, 297–303. <https://doi.org/10.1016/j.ejps.2004.11.005>.
- Tamura, F., Kikutani, T., Tohara, T., et al., 2012. Tongue thickness relates to nutritional status in the elderly. *Dysphagia* 27, 556–561. <https://doi.org/10.1007/s00455-012-9407-z>.
- Topinková, E., Baeyens, J.P., Michel, J.-P., Lang, P.-O., 2012. Evidence-based strategies for the optimization of pharmacotherapy in older people. *Drug Aging* 29, 477–494. <https://doi.org/10.2165/11632400-000000000-00000>.
- Tran, J.Q., Hartung, J.P., Tompkins, C., Frohna, P.A., 2018. Effects of high- and low-fat meals on the pharmacokinetics of ozanimod, a novel sphingosine-1-phosphate receptor modulator. *Clin. Pharm. Drug Dev.* 7, 634–640. <https://doi.org/10.1002/cpdd.409>.
- Vallet, T., Bellissa, E., Laribe-Caget, S., et al., 2018a. A decision support tool facilitating medicine design for optimal acceptability in the older population. *Pharmaceut. Res.* 35, 136. <https://doi.org/10.1007/s11095-018-2424-3>.
- Vallet, T., Michelon, H., Orlu, M., et al., 2020. Acceptability in the older population: the importance of an appropriate tablet size. *Pharm.* 12, 746. <https://doi.org/10.3390/pharmaceutics12080746>.

- Vallet, T., Ruiz, F., Lavarde, M., et al., 2018b. Standardised evaluation of medicine acceptability in paediatric population: reliability of a model. *J. Pharm. Pharmacol.* 70, 42–50. <https://doi.org/10.1111/jphp.12829>.
- Vandenbergh-Descamps, M., Labouré, H., Prot, A., et al., 2016. Salivary flow decreases in healthy elderly people independently of dental status and drug intake. *J. Texture Stud.* 47, 353–360. <https://doi.org/10.1111/jtxs.12191>.
- Vasylenko, O., Gorecka, M.M., Rodríguez-Aranda, C., 2018. Manual dexterity in young and healthy older adults. 1. Age- and gender-related differences in unimanual and bimanual performance. *Dev. Psychobiol.* 60, 407–427. <https://doi.org/10.1002/dev.21619>.
- Verrue, C., Mehuys, E., Boussery, K., et al., 2011. Tablet-splitting: a common yet not so innocent practice. *J. Adv. Nurs.* 67, 26–32. <https://doi.org/10.1111/j.1365-2648.2010.05477.x>.
- Vinarov, Z., Abdallah, M., Agundez, J.A.G., et al., 2021. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: an UNGAP review. *Eur. J. Pharm. Sci.* 162, 105812 <https://doi.org/10.1016/j.ejps.2021.105812>.
- Wagner, C., Jantratid, E., Kesisoglou, F., et al., 2012. Predicting the oral absorption of a poorly soluble, poorly permeable weak base using biorelevant dissolution and transfer model tests coupled with a physiologically based pharmacokinetic model. *Eur. J. Pharm. Biopharm.* 82, 127–138. <https://doi.org/10.1016/j.ejpb.2012.05.008>.
- Wahlich, J., Orlu, M., Mair, A., et al., 2019. Age-related medicine. *pharm.* 11, 172. <https://doi.org/10.3390/pharmaceutics11040172>.
- Walsh, J., Ranmal, S.R., Ernest, T.B., Liu, F., 2018. Patient acceptability, safety and access: a balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations. *Int. J. Pharmaceut.* 536, 547–562. <https://doi.org/10.1016/j.ijpharm.2017.07.017>.
- Warnecke, T., Schäfer, K.-H., Claus, I., et al., 2022. Gastrointestinal involvement in Parkinson's disease: pathophysiology, diagnosis, and management. *Npj Park Dis* 8, 31. <https://doi.org/10.1038/s41531-022-00295-x>.
- Welling, P.G., 1996. Effects of Food on Drug Absorption. *Annu. Rev. Nutr.* 16, 383–415. <https://doi.org/10.1146/annurev.nu.16.070196.002123>.
- Wilson, M.-M.G., Kaiser, F.E., Morley, J.E., 2001. Tablet-breaking ability of older persons with type 2 diabetes mellitus. *Diabetes Educ.* 27, 530–540. <https://doi.org/10.1177/014572170102700408>.
- Wurmbach, V.S., Schmidt, S.J., Lampert, A., et al., 2022. Prevalence and patient-rated relevance of complexity factors in medication regimens of community-dwelling patients with polypharmacy. *Eur. J. Clin. Pharmacol.* 78, 1127–1136. <https://doi.org/10.1007/s00228-022-03314-1>.
- Xu, F., Laguna, L., Sarkar, A., 2019. Aging-related changes in quantity and quality of saliva: where do we stand in our understanding? *J. Texture Stud.* 50, 27–35. <https://doi.org/10.1111/jtxs.12356>.
- Yamamoto, S., Taniguchi, H., Hayashi, H., et al., 2014. How do tablet properties influence swallowing behaviours? *J. Pharm. Pharmacol.* 66, 32–39. <https://doi.org/10.1111/jphp.12155>.
- Yamamoto, T., 2003. Tablet formulation of levothyroxine is absorbed less well than powdered levothyroxine. *Thyroid* 13, 1177–1181. <https://doi.org/10.1089/10507250360731596>.
- Yazio G. (2022) Calories in food: calorie chart database. <https://www.calories.info/>. Accessed 17 Mar 2023.
- Yetzer, E., Blake, K., Goetsch, N., et al., 2015. SAFE medication management for patients with physical impairments of stroke, part one. *Rehabil. Nurs.* 40, 260–266. <https://doi.org/10.1002/rmj.194>.
- Yoder S. (2014) Physical appearance preferences for oral solid dosage formulations.
- Yokoyama, M., Mitomi, N., Tetsuka, K., et al., 2000. Role of laryngeal movement and effect of aging on swallowing pressure in the pharynx and upper esophageal sphincter. *Laryngoscope* 110, 434–439. <https://doi.org/10.1097/00005537-200003000-00021>.
- Zed, P.J., Abu-Laban, R.B., Balen, R.M., et al., 2008. Incidence, severity and preventability of medication-related visits to the emergency department: a prospective study. *Can. Med. Assoc. J.* 178, 1563–1569. <https://doi.org/10.1503/cmaj.071594>.
- Zussman, E., Yarin, A.L., Nagler, R.M., 2007. Age- and flow-dependency of salivary viscoelasticity. *J. Dent. Res.* 86, 281–285. <https://doi.org/10.1177/154405910708600316>.