Journal of Aging Science
ISSN: 2329-8847

Papanastasiou and Kalantzi, J Aging Sci 2018, 6:2
DOI: 10.4172/2329-8847.1000195

Review Article Open Access

Innovation in Formulation Development for Older People

Antigoni Papanastasiou and Lida Kalantzi*

Pharmaceutical Research Operations/Finished Formulations, Pharmathen SA, Greece

***Corresponding author**: Lida Kalantzi, Pharmaceutical Research Operations/Finished Formulations, Pharmathen SA, 44 Kifissias Ave, 15125 Marousi Attica, Greece, E-mail: lkalantzi@pharmathen.com

Received date: August 08, 2018; **Accepted date:** September 04, 2018; **Published date:** September 12, 2018

Abstract

In many cases geriatric patients constitute the main users of a medicinal product and not a special population. Even though the heterogeneity of the geriatric patient population is vast with physiological changes occurring with advanced age being diverse, the presence of multi-morbidity, disability and frailty are rather common indicating a special need for age-appropriate formulations. Dosing flexibility, swallowability and overall manageability of drug products are among the issues that have been identified as most important for this age group and thus they should drive the design of therapeutic options for the geriatric population.

Pharmaceutical industry is slowly starting to respond to these challenges with an increasing number of innovative geriatric-friendly formulations that have either reached the market or are currently under development.

The aim of this article is to discuss the adequacy of the available geriatric-friendly formulations to meet the special needs of this age group, placing particular emphasis on a couple of marketed medicinal products with innovative geriatric-friendly formulation technologies.

Keywords: Geriatric; Elderly; Seniors; Age-appropriate; Innovative; Formulation

Introduction

The demographic trend in Europe is projected to move towards a society with an increasing percentage of people above 65 years of age, from around 119 million in 2013 to an estimated number of around 210 million in 2060 [1]. As the population age structure is changing dramatically, the very elderly subset of the population (>80 years of age) is the fastest growing subset, forecasted to increase from 5% to 12% from 2013 to 2060.

Even though older people in general exhibit an increased prevalence of gradually declining organ and body functions resulting in physical, physiological, and/or cognitive impairments, multi and co-morbidities and/or frailty, impairments may start at a different chronological age, occur in different orders and worsen in different rates, introducing a vast heterogeneity within the geriatric population [2]. People of the same chronological age exhibit high inter-individual variability (healthy, facing some minor impairments, frail), making stratification of different subsets difficult. The suggested types of classifications of the elderly have been based on either chronological age (early old from 65-74 years, middle-old from 75-84 years and late-old starting from 85 years) or frailty status [3]. Frailty represents a reduction in resistance to stressors leading to increased clinical vulnerability and adverse health outcomes and is a term used to identify older adults who are at increased risk of poor clinical outcomes, such as incident disability, cognitive decline, falls, hospitalization, institutionalization, or increased mortality [4]. While there is a general agreement on the concept of frailty, lack of standardization in terms of its assessment tools may lead to the identification of groups of frail older subjects which may not be identical in composition.

Despite the high heterogeneity inherent within the geriatric population and the difficulties in the classification of older people in groups, medicinal product acceptability issues are rather common corresponding to specific special needs of this age group. Given that in many cases, geriatric patients constitute the main users of a medicinal product and not a special population, it becomes obvious that the special needs of the elderly should be taken into consideration in the pharmaceutical development of medicines intended to be used in this patient population [2]. The unavailability of age-appropriate dosage forms often leads to off-label coping practices, for example, modifications to facilitate intake or to lower the dose (e.g. opening capsules and mixing content with food, dispersions of crushed tablets, administered through feeding tubes). However, compounding practices can significantly affect the biopharmaceutical features of a drug product and its therapeutic outcome e.g. through the risk of degradation, dosing inaccuracies or altered bioavailability [5]. Alterations in the safety and efficacy profile of a product become especially serious in the case of narrow therapeutic index drugs for which, small differences in plasma concentrations may translate in large differences in pharmacodynamic effects (e.g. digoxin) [6].

An extensive list of special characteristics of the elderly subset of the population requiring particular consideration in pharmaceutical development is reported in the draft reflection paper "Quality aspects of pharmaceutical development of medicines for use in the older population", developed by the EMA CHMP Quality Working Party (QWP) (Table 1). Reduced cognition, loss of sensory functions, impaired motor functions and physiological differences in comparison with younger adults are identified as important factors influencing the overall medicinal product acceptability.

Still, the two most widely cited relevant special needs of the older age, are the need for dose adjustment without having to break or split tablets as well as the need for better swallowability properties.

Age-specific characteristics requiring particular consideration in pharmaceutical development		Consequences
Cognition	Reduced or gradually impaired cognition, mental capabilities and forgetfulness	Difficulties remembering when and how to take a medicine, swallowing oral preparations, understanding instructions
Sensory functions	a. Impaired near visual acuity and/or overall vision	a. Difficulties reading the product label or package leaflet, difficulties handling preparations or opening containers
	b. Impaired sense of smell	b. Altered patient acceptability
	c. Impaired sense of hearing	c. Missing instructions or explanations
Motor functions	a. Dysphagia	a. Increased risk of choking, off-label coping strategies
	b. Impaired tactile sense, manual and finger dexterity, grip strength, key pinch and/or loss of finger top fee	b. Difficulties in picking tablets from the container and pushing tablets through a blister
	c. Trembling hands	c. Difficulties measuring liquids without spillage
	d. Reduced suppleness/flexibility of the arms causing difficulties reaching specific parts of the bod	d. Difficulty in administering of medicines to the ear, eye, feet, back
	e. Reduced hand-eye coordination causing difficulties handling medicines	e. Difficulty in instilling eye drops
	f. Impairments in fine and gross motor skills	f. Difficulties travelling to health care providers, lying prostrate may affect gastrointestinal motility
Physiology and Pathophysiology	a. Hyposalivation, xerostomia (dry mouth) impaired mastication (chewing)	a. Swallowing problems
	b. Hyposalivation, taste bud atrophy and impaired smelling	b. Altered taste experiences
	c. Hepatic impairment, renal impairment, altered pH values in the stomach, altered gastro-intestinal motility, changes in the ratio of human body surface area to body weight and altered human composition and functions	c. Changes in the pharmacokinetic pharmacodynamics (PKPD) profile of the drug implying a need for dose adjustments

Table 1: The general characteristics of older people requiring particular consideration in the pharmaceutical development of medicines [2].

Modifications to lower the dose usually stem from pharmacokinetic differences in the elderly. Age-specific alterations affecting absorption include increased gastric pH, delayed gastric emptying, reduced splachnic blood flow, decreased absorption surface, decreased gastrointestinal motility and decreased hepatic blood flow [7]. Drug distribution can also be altered by the change in body composition and plasma protein levels (e.g. decreased serum albumin, increased α1-acid glycoprotein). With regards to liver metabolism, it has been shown to decrease with age due to the liver mass decrease of 20%-30% and a hepatic blood flow decline of 30%-50% [3]. Age-related changes in DNA methylation (e.g. increased specific methylation of *CYP* gene promoter regions resulting in gene silencing) lead to physiological decrease of *CYP* gene expression [8]. Furthermore, age-related declines in renal clearance have been attributed to kidney mass, renal blood flow, GFR decreases.

Ageing is also associated with a decline in swallowing function affecting all phases of deglutition (oral, pharyngeal and esophageal phase) [9]. Dysphagia ie difficulty in swallowing, is a determining factor in solid oral dosage form acceptability, and is reported to be of high prevalence in the geriatric population with estimates as high as 90% [10]. Dysphagia is especially common in patients affected by stroke, post-operative cognitive dysfunction or neurodegenerative diseases such as Parkinson's, Alzheimer's disease and dementia [11]. Given the direct impact of dysphagia on medication adherence, the presence of multi-morbidities and resulting polypharmacy (taking ≥ 5 medicines) can only further increase treatment regimen complexity and increase the risk of medication errors, drug-drug interactions, drug-disease interactions and rates of adverse reactions [3].

Integration of the assessment of medicines for use by older people into the general framework is the current view of the EMA [7]. A range of targeted measures are additionally implemented including the establishment of a Geriatric Expert group (GEG) to provide scientific advice to the EMA Committee for Medicinal products for Human use (CHMP), the development of targeted guidelines, the inclusion of considerations on older people in other EMA documents where appropriate, the development of a dedicated EMA webpage and the organization of workshops [7,12,13]. In line with these measures, the EMA has commented on the adequacy of available guidelines and is developing a guideline on good pharmacovigilance practices (GVP) [14]. Revision of assessment templates and guidance to assessors has taken place to increase the relevance of data to elderly patients and the content of submitted dossiers has been evaluated in terms of inclusion of geriatric data for the elderly presentation [15,16].

The European federation of Pharmaceutical industries (EFPIA) has positively responded to aforementioned initiatives and has committed to collaborate with relevant stakeholders for the implementation of the Geriatric Medicines Strategy aims [17]. As per EFPIA's recommendations within the position paper on Drug development for older and ageing patients, current gaps in the prevention/treatment of geriatric diseases should be addressed through innovative medicinal products. In parallel, there is an ongoing discussion on whether existing pediatric formulations could have a value in the treatment of geriatric patients [18]. The applicability of some products for both populations of patients would certainly be a more cost-effective approach for the industry. However, even though both groups of patients are in need of dosing flexibility and both groups present with difficulty in swallowing, treatment compliance in geriatric patients is a

greater challenge given the frequency of polypharmacy in this population. Additionally, pediatric products may be administered by a healthy caregiver whereas a geriatric patient may be independent or be supported by a caregiver who may themselves be aged or infirm. As a result, in cases where pediatric formulations are considered for the elderly, additional geriatric-friendly packaging/labeling may have to be considered to increase compliance.

It is the aim of this article to investigate whether the existing formulations are meeting the special needs of the elderly and whether unmet needs are currently translated into geriatric-friendly formulations and dosage forms. A couple of examples, where the special needs of the elderly have been met in a really innovative way will be presented and thoroughly discussed. Focus shall be placed on dosage forms administered *via* the oral route as this is the most common route of administration in elderly patients as well as across ages.

Methods

PubMed and Google scholar were used as a source. Given the similarity of dosage forms and formulations developed for both geriatric and pediatric patients, the following combination of keywords was additionally used: (Geriatric OR Elderly OR Senior OR Aged OR Elderly OR Older OR Children OR Pediatric OR Pediatric OR Infants) AND (innovation OR age appropriate OR age-friendly OR dosage forms OR formulations).

Relevance of articles was judged based on titles, abstracts or full-texts. For retrieval of further information on geriatric-friendly products identified, companies' websites were researched.

Results

A number of issues have been identified to influence the appropriateness of marketed formulations when administered in geriatric patients *via* the oral route.

Advantages associated with the use of oral tablets (and capsules) generally are well known and include unit dose accuracy, portability, convenience, stability and familiarity to patients [19]. However, larger tablets may negatively interfere with swallowability and smaller tablets with the ability to be handled. Thus, a tablet should be large enough to handle by a geriatric patient and small enough to swallow. To minimize the negative effects of a larger tablet size, certain modifications are introduced (e.g. tablets with oval, elliptical or oblong shape) to improve the perception of the ability to swallow the dosage form. Additionally, a non-functional coating may improve swallowability as uncoated tablets present with the risk of adherence on mucosal surfaces in patients with hypo salivation or xerostomia. Nonfunctional coating can also help taste-masking of bitter APIs which is an important challenge in the development of drug products. Similar swallowability issues are encountered by elderly patients when administered capsules, with size and shape playing an important role.

The need for dose adjustments often leads to off-label compounding practices (splitting and crushing) [2]. Such off-label practices can be especially dangerous in the case of extended-release tablets, leading to rapid absorption of the entire dose (intended to be release over a long period of time) and jeopardizing the safety of the patient [20,21]. Even if the presence of a breakmark on a tablet makes splitting acceptable in terms of drug product stability, bioavailability and environmental exposure to a potentially harmful active substance, the splitting of a tablet using for example tablet splitters becomes especially problematic in visually impaired elderly patients or patients with reduced motoric functions [2]. Similarly, opening hard capsules to mix their contents with food might jeopardize dose accuracy as well as the stability of the drug product.

While oral liquid formulations exhibit a number of advantages across ages such as easy swallowing, dosing flexibility and potential for administration through feeding tubes, a number of disadvantages become especially important for their administration in geriatric patients [2]. Given the risk of errors when measuring the dose, the need of high-quality and safe dosing devices arises, focusing on the ease of handling, the minimization of the dose preparation and the measurement steps, and providing legible dosing gradations and labeling [19]. Dosing accuracy becomes even more difficult without a dosing device in the case of administration of small volumes of liquid. In some cases, the administration of a liquid form poses a risk of aspiration for example in patients with neurogenic oropharyngeal dysphagia having a much smaller sip than that of healthy adults [22]. Furthermore, a universally accepted formulation in terms of palatability (taste, smell, texture, viscosity) is very hard to find. In the case of administration of multiple oral liquid medications, the total volume to be ingested maybe a problem for older people on a fluid-restricted diet, also risking excipient overload and conflicting tastes. The safety of preservatives included in multi-use oral liquid formulations and cleaning of the dose measuring device should be considered, with preservative-free single use sachets (e.g. Gaviscon®) being considered safer, more easily portable and stored [22]. With chemical stability being an additional concern, sometimes refrigeration has to be used to slow degradation but then the patient's medication routine is additionally burdened and the portability is limited. Finally, geriatric patients due to loss of manual dexterity sometimes have difficulties in opening liquid containers as well as shaking liquid suspensions, dispersions or emulsions.

Special oral dosage forms such as orodispersible tablets, chewable and effervescent tablets as well as oral films have been suggested as geriatric friendly dosage forms [22,23]. All have a number of inherent advantages but also disadvantages, with the major advantage being the easiness of swallowing with limited amount of water and the major disadvantage being the limitation in terms of the overall dose that can be delivered [24]. Furthermore, chewable tablets may challenge mastication problems in this patient population while effervescent tablets being usually overloaded with sodium may challenge low-sodium diets. Finally, oral films being small and thin might become problematic in terms of handling and manipulation for elderly patients [25]. The majority of special oral forms need protection from moisture and humidity by storage in tightly closed containers or blisters, which may also render opening by elderly patients very difficult [2]. Still several such products are currently in the market such as donepezil film, olanzapine ODT, sevelamer chewable, etc.

Overall, the existing dosage forms are struggling to meet geriatric needs, especially the two major geriatric concerns: swallowability and dose adjustment potential. Thus, the existence of a formulation that satisfies both of these needs at the same time has to be treated as an unmet need.

An example of a rather innovative formulation targeting geriatric needs is coming from the Japanese pharmaceutical company Eisai Ltd, which has recently marketed a geriatric-friendly oral jelly formulation of donepezil, claiming to improve swallowability while presented in a number of strengths, even lower than the already marketed [26,27].

Limited information is available in the literature however, as per the innovator it improves swallowability and has the right softness to be broken up with the tongue and swallowed without water. Furthermore, as the jelly comes in a cup-shaped packet, it can be divided with a spoon and administered to patients according to their ability to swallow. The development process for this product was full of trade-off problems, one of which was the usability of the container for Alzheimer's patients with dysphagia versus the size of the container, in which case priority was put on the cup being user friendly rather on the size and therefore a stable wide-mouth cup was chosen (Figure 1). The strength of the aluminum seal was adjusted appropriately in order to allow easy peeling and adequate sterilization of the product. A single-dose package, despite its associated higher cost was chosen in order to prevent overdose.

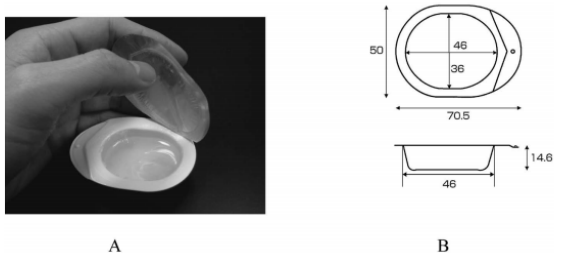

Figure 1: (A) Appearance of donepezil HCL Oral Jelly formulation. (B) Cup Shape and Size [26].

Flexilev® dispersible micro-tablets for dose dispenser

Perhaps one of the best case examples of an innovative geriatric-friendly platform technology has been developed by the Swedish pharmaceutical company Sensidose AB. Disease- and age-specific issues encountered by geriatric patients, progress into the field of Parkinson's disease and an in-depth analysis of the pharmacokinetics of already marketed formulations *via* different routes of delivery guided the development of an age-appropriate oral solid dosage form, currently marketed under the name Flexilev® (levodopa/carbidopa) [28].

The oral delivery of levodopa (L-DOPA) was a milestone for the symptomatic treatment of Parkinson's disease, with levodopa still being the most efficacious option during the entire course of the disease [29]. Levodopa, a precursor of dopamine is able to cross the blood-brain barrier and is converted into dopamine in the brain [30]. Upon oral administration, Levodopa is rapidly decarboxylated to dopamine in extra cerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa, a dopamine decarboxylase inhibitor, does not cross the blood-brain barrier and does not affect the metabolism of Levodopa within the central nervous system at therapeutic doses. Administration of Carbidopa with Levodopa enhances the amount of Levodopa available for transport to the brain. Levodopa-Carbidopa products have been registered for many years for the symptomatic treatment of Parkinson's disease.

Clinical observations of dose-related variations in symptomatology formed the starting point for research on the pharmacokinetics and pharmacodynamics of levodopa treatment at different stages of the disease [28]. Infusion and PKPD studies in Parkinson's disease patients revealed that variation in plasma levodopa concentration is the determining factor for motor fluctuations (dyskinesias and the "on-off" phenomenon) in patients on clinically optimized combination therapy with levodopa/carbidopa [31-33]. Stability of levodopa concentrations and therefore constant dopamine levels at striatal receptors are required for optimal motor performance in moderate to severe Parkinson's disease.

The finding that in rodent and primate models of Parkinson's disease, pulsatile stimulation by dopaminergic drugs has a priming effect for the development of dyskinesia implied that the shape of the plasma concentration profile i.e. constant plasma levels are of importance [34]. Thus, different technologies for sustained release formulations of levodopa tablets have been developed in the past and at present but as a general principle, slow absorption and/or incomplete bioavailability makes individualized fine-tuned dosing hard to achieve [35]. A common strategy for adapting levodopa doses to the onset of motor fluctuations is to fractionate the doses in many smaller doses. In line with basic pharmacokinetics, frequent individualized dosing of a rapidly soluble drug with short plasma half-life (for levodopa about 1.5 hr) would be the ideal strategy to obtain constant plasma concentrations [28]. However, fine-tuning of levodopa dosage with traditional tablets is limited to dose adjustments of 25 mg, which does not always provide enough granularities for adequate individualization of treatment [36]. The time spent by a patient waiting for the previous dose to take effect can occupy as much as 70% of the "off" periods (periods of no drug effect) experienced by the patient [37]. In addition, frequent levodopa administration is not without disadvantages as the increased number of doses makes it challenging for patients to adhere to medication. More refined dosage adjustment would offer potential for further reduction of adverse effects associated with levodopa. However, if the dosing interval is reduced, the dose itself must be lowered and more finely tuned. For a levodopa dose range of 5-200 mg individual oral doses with a sensitivity of 5 mg would be desirable. This could theoretically be accomplished by the patient manipulating a large number of 5 mg tablets. However, the small size of these tablets coupled with the motor dysfunction experienced by patients with Parkinson's disease suggest that the patients could require help in handling the tablets and taking the correct dose.

Considering all of the above, Sensidose AB developed fast dissolving levodopa/carbidopa micro tablets 5 mg/1.25 mg to be delivered from a dose dispenser device (MyFID®, Sensidose, Sollentuna, Sweden) in dosage steps of 5 mg that can facilitate the fine tuning and individualization of dosing both with regarding time and dose (Figure 2) [38]. The automatic dispenser delivers the correct dose for each patient who is then able to swallow them either intact or dissolved in water. To handle these small tablets with a diameter of 3 mm, an automatic dose dispenser was developed in co-operation with an advisory board of people with Parkinson's disease, and prototypes were evaluated by patients in different stages of disease [37]. The final version of the automatic dispenser, CE-classified as a medical device in 2014 and named MyFID® (My Flexible Individual Dosing), provides a number of functions (MyFID® dosing device manual). A cassette containing 750 micro tablets (3750 mg levodopa, thus roughly a week's supply) is docked into the dispenser [28]. A basal individual dosing program, with for example, at least six intakes per day is chosen by the physician. The schedule is presented on the touch screen, and the patient is reminded of dosing by an alarm. Motor and non-motor symptoms can be reported into an electronic diary and presented at the next visit to the doctor or nurse who in collaboration with the

patient can further fine-tune the levodopa delivery if needed. Information on adherence on addition to need and reason for extra dosing is also registered.

Figure 2: Automatic dose dispenser for levodopa/carbidopa micro tablets [28].

The levodopa/carbidopa microtabletwas approved by the Swedish MPA in 2014 [28]. Two pharmacokinetic studies were fundamental for the approval of this product: 1) one single-dose bioequivalence study comparing Flexilev®to a commercially available levodopa/carbidopa product and to a levodopa/benserazide product and 2) one multiple-dose study comparing the pharmacokinetics of Flexilev® to levodopa/carbidopa/entacapone [39,40]. Repeated administration of Flexilev® (initial dose of 75 mg levodopa followed by 45 mg every 2.4 hrs) was found to reduce the peak-to-trough fluctuation in plasma levodopa concentrations in comparison with levodopa/carbidopa/entacapone (100 mg every 6 hours). Steady state was reached much earlier with the new formulation.

From 2016, the levodopa/carbidopa micro tablet is reimbursed in Sweden for the treatment of patients with advanced Parkinson's disease and marketing authorization has also been granted for 14 other European countries through the mutual recognition procedure [41]. The Sensidose (Flexilev®/MyFID®) concept that is based on micro tablets, each containing a precise and sub-therapeutic amount of the active substance can offer the dosing flexibility needed in other diseases [42].

Spritam®3D printed pill (Levetiracetam)

Documented swallowing difficulties in patients suffering from epilepsy often lead to inadequate adherence to anti-epileptic drugs, with patients many times missing their regular doses. In the case of epilepsy, the consequences of non-adherence to anti-epileptic drugs can be immediate (i.e. breakthrough seizures) and devastating to an individual's quality of life [43]. Non-adherent elderly adults are at heightened risk for adverse drug effects and breakthrough seizures and in light of comorbid conditions in the elderly, seizures in this group are fraught with other consequences such as fractures, head trauma, subdural hematomas and a more prolonged postictal state [44].

Levetiracetam is an anti-epileptic drug approved worldwide for the treatment of partial onset, myoclonic and primary generalized tonic-clonic seizures [45]. Levetiracetam has a unique mechanism of action and is well tolerated, with adverse events limited primary to central nervous system such as asthenia, somnolence, dizziness and headache.

Several pharmaceutical forms of levetiracetam are currently available in the market, such as tablet formulations (immediate- and extended-release), oral solutions as well as an intravenous formulation. However, none of the available formulations are ideal for the geriatric population, as previously explained. Even though, orodispersible tablets exhibit the great advantage of fast disintegration on the tongue facilitating swallowing with a limited amount of water, they bear the disadvantage of a limited drug loading capacity (e.g. 10-30 mg) due to the high amount of disintegrants that are dominating in the tablet [2]. Thus, the 1000 mg dose of levetiracetam could not fit in a conventional ODT.

A recent breakthrough innovation based on three dimensional printing technology has been developed by pharmaceutical company Aprecia to overcome the drug loading limitations. ZipDose® technology enables the production of highly porous, rapidly disintegrating oral formulations, which can incorporate up to 1000 mg of active substance per tablet [46]. The three-dimensional printing technology approach requires each unit dose to be taken with a small volume of liquid facilitating rapid dispersion in the mouth and aiding in the subsequent swallowing of the dispersed medication [47]. ZipDose® technology resulted in the approval by the FDA of the first 3D printed medicine in 2015, under the name Spritam®. The potential of the 3D printed fast melt levetiracetam tablet was recognized by the FDA stating that "given its unique dosing and administration attributes, Spritam will provide a new option for high dosing requirements particularly in adults in whom swallowing tablets is an issue" [48]. Most subjects agreed that the mouth feel of the 3D printed fast-melt product was acceptable and easy to take and swallow [46]. The rapid oral disintegration for the 3D printed fast melt did not affect the PK profile of levetiracetam even though a delay and lower peak in the absorption were observed under fed conditions.

Facilitation of personalized dosing may prove to be an attractive potential application of 3D printing. 3D printing could ensure patient-customized dosing by taking into consideration genetic profiles, age, race, epigenetic and environmental factors [49]. High accuracy of dosing for highly potent drugs with a narrow therapeutic index (e.g. digoxin) is envisioned for the future.

Discussion

A number of age-specific characteristics are requiring particular consideration in pharmaceutical development for the special needs of the elderly to be met. However, swallowability and dose adjustment potential are two of the highest scoring geriatric concerns. Pharmaceutical industry is slowly responding to these challenges with an increasing number of special oral dosage forms (ODT, chewable tablets, films, etc.) usually addressing either of these geriatric concerns. Still, dosage forms that simultaneously permit dose adjustments and facilitate swallowability are bringing added value to products targeting the geriatric patient population. It is the authors' view that products similar to Flexilev® for example, could be of benefit for a variety of indications, in which individualization of dose is of importance and

dysphagia is highly prevalent (e.g. acenocoumarol for the treatment and prevention of thromboembolic diseases). Similarly, the manufacturers of Spritam®, have cleverly used an innovative technology to tackle an inherent problem of a well-known oral dosage form (orodispersible tablet). By increasing the drug loading to 1000 mg, they have managed to broaden the applicability of a pharmaceutical form with an already known advantage: swallowability.

Still, innovation targeting this sensitive age group should be predominately driven by therapeutic needs instead of technology itself. For example, Khaled et al. suggested using 3D printing to generate a multi-component polypill (5 APIs) [50]. But even though the polypill may reduce the total pill burden, for some patients it might compromises swallowability due to bigger tablet size (12 mm diameter).On the other hand, Otsuka developed a new product (MyCite®) that combines an existing drug (aripiprazole) with an ingestible sensor (Event Marker) embedded into the tablet, intended to track Ingestion [51]. The data gathered is communicated *via* a wearable sensor patch from the pill to a software application and upon patients' consent for information to be passed; healthcare professionals can view the data using secure web portals. This drug-device combination could revolutionize the way adherence is being tracked in elderly patients suffering from impaired cognition and have difficulty communicating information about their treatment regime.

However, to claim development of geriatric friendly pharmaceutical products, on the top of formulation attributes special attention should be placed in the proper packaging and the proper labeling of medicines. To maximize manageability and avoid administration issues as well as medication errors, medicinal products intended to be used in geriatric patients should be easily accessed (packaging) and read (labeling) [18].

Reduced motor functions in geriatric patients (e.g. reduced hand force and gripping strength, griping and pinching activities, etc.) often cause issues with handling pharmaceutical packages leading to an adoption of patterns that might alter the medicine's efficacy and safety [2,3]. These include for example asking someone else to open the container once and keeping it open from then on, removing all contents from the container and storing them differently, changing the dosing frequency in a way that fits into caregiver visits or in some cases refraining from administration at all, etc. Child-resistant packaging complicates manageability even further. Therefore, tailoring the packaging design to the needs of the elderly is crucial during medicinal product development. For example, the size of the screw cap might have to be adjusted to fit the geriatric patients' needs with larger cap sizes judged to be more suitable for this patient population, push-through blisters may also be better than bottles, etc.

Cognitive deterioration in the elderly, which is many times the consequence of neurodegenerative conditions (e.g. dementia, Parkinson's disease, etc.), might also affect the understanding of the instructions for use. As older people in general are less amenable to "modern methods" of getting information, it becomes even more essential for the patient information leaflet (PIL) to be suitable to the end-user [16]. Thus, instructions for use of a medicinal product intended for the geriatric population shall be phrased in easy-to-read language with clear legible pictorial representation in order to additionally address variable vision abilities. Testing the PIL in the targeted patient population is an EU requirement [Guideline on the readability of the labeling and package leaflet of medicinal products for human use], however, thorough testing of the PIL in the targeted geriatric group is of particular importance. Special focus should be given to the "Instructions for use", section, especially when the pharmaceutical product is a drug device combination, with the use of dummy containers and active demonstration by participants highly encouraged (i.e. human factor studies).

Conclusion

Traditionally, drug product development is guided by the physicochemical and the biopharmaceutical properties of the active pharmaceutical development with less focus on delivering a patient-centric pharmaceutical product. But the older cohort of the population may have difficulty to remember, to reach, to see, to open and to swallow medications leading to poor adherence and improper usage of drug products, resulting in lower effectiveness, poor therapeutic outcomes, and potential safety risks. The recent incentives of the European Medicines Agency towards developing geriatric friendly pharmaceutical products along with the expanding market within EU, are expected to stimulate the re-engineering of existing products to address well documented unmet geriatric medical needs. Conventional technologies used in an innovative way but also creative solutions such as drug device combinations could become highly beneficial in improving the manageability of medicines by geriatric patients. The parallel advancement of Information technology (ICT) may also allow the inclusion of instruments that will provide real-time feedback such as tracking of adherence or objective symptom quantification, which will contribute to the concept of personalized medicine, with dose adjustments stemming from objective measurements.

Conflict of Interest

No conflict of interest was reported by all authors.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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This article was originally published in a special issue, entitled: **"Aging Challenges in a Digital World"**, Edited by Dr. Fereshteh Barei, Paris Dauphine University, Paris, France.