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Review

Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy

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ABSTRACT

There is evidence that swallowing issues and dysphagia are an increasing problem of the aging population in the coming decades that is affecting oral medication administration. There is a variety of clinical expressions of swallowing dysfunction caused by aging, acute or chronic disease conditions, decline in physiological functions and adverse drug reactions. About one third of patients in long term care facilities experience serious difficulties with swallowing solid oral dosage forms (SODF). Manipulations of the solid oral drug products occur frequently in nursery homes leading to medication errors and potential changes in drug product performance. The alteration of the drug products is performed with the best intention of the care giver to help the patients but bears concerns about safety and lawfulness. Alternative SODF and drug delivery technologies should be considered in the development of new and generic products and their prescription to overcome medication administration problems in patients with swallowing difficulties of SODF.

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1. Introduction

Increasing life expectancy and the aging "baby-boomer" generation are leading to a challenging demographic shift in our society over the next decades. While the onset of chronic diseases seem to occur earlier in life of the younger generations (Maas et al., 2010; Marengoni et al., 2008) the other age-related functional declines and the decreasing reserve becomes more dominant at higher age. Overall the increasing life expectancy and higher age are correlated with a higher probability of functional declines and potential

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disabilities that have consequences across the various domains of independent life and care giving (Mort, 2009; Stegemann et al., 2010). For the treatment and management of the age related chronic diseases and functional declines several new drugs have been developed over the past decades or are in the development stages. With this growing number of effective and available drugs and drug products, drug therapy is and will continue to be an integral part of older age.

There is no doubt that the oral route is the most preferred route in the administration of medicinal products and drug therapy. The active moieties are formulated and processed into solid oral dosage forms (SODF) like tablets and capsules that are swallowed as such to release its content by disintegration and dissolution of the drug in gastrointestinal fluids for absorption (Weitschies and Wilson, 2011). There are several advantages related to SODF like dose accuracy, various opportunities to provide different release profiles, facilitated drug distribution, non-invasiveness and ease of use by the patients.

Oral drug application follows the assumption that safe swallowing is a stable function in life and swallowing SODF is a given capability of every human older than 12 years (EMEA/CHMP/PEG/194810/2005). Swallowing is a complex function involving several nerves and muscles acting in a synchronized reflex mode upon the voluntary swallowing initiation. Swallowing functions underlay a normal aging process and can be seriously impacted by diseases and disease progression as well as by drug substances. Latest research has identified swallowing issues as a silent and concealed problem and health burden in older adults leading to dehydration, malnutrition and pneumonia. The intention of this article is to review the impact of declining swallowing capabilities of older adults on the oral drug therapy.

2. Dysphagia

2.1. Pathophysiology of dysphagia

The oropharyngeal system is an important physiological functionality regulating breathing and alimentation of the body. The decline and loss of the oro-gastric swallowing functions is caused to a certain extent by the natural process of aging, but can progress significantly by pathophysiological conditions that lead to a broad spectrum of individual expressions of perceived and real deterioration (Ney et al., 2009; Humbert and Robbins, 2008). The age-related functional changes in the swallowing process are referred to as *presbyphagia*. When the swallowing functions are affected beyond the normal aging by pathological conditions, as co-morbidities or by drug therapies, the swallowing disorder is referred to as *dysphagia* with its major symptoms of food sticking in the oropharyngeal tract, aspiration, coughing and choking.

The process of swallowing is divided into 3 major phases: the oral phase, the pharyngeal phase and the esophageal phase.

In the oral phase, the food is chewed and mixed with saliva to form a bolus. During the voluntary swallowing initiation the tongue pushes the bolus posterior towards the pharynx stimulating several receptors to start and trigger the swallowing response in a concerted muscle activity sequence. The pharyngeal phase starts the swallowing response by stopping the breathing and raising the larynx to prepare for the bolus to pass. The bolus is transported by peristaltic muscle movements across the closed vocal folds and epiglottis into the esophagus through the cricopharyngeal sphincter. The swallowing reflex is coordinated by several sensory and motor activity controlling cranial nerves in the 'swallowing center' of the medulla oblongata (Castell and Castell, 1996). In the esophageal phase peristaltic movements continue to drive the bolus downwards through the lower esophageal sphincter into the stomach. The swallowing process is controlled by sensory receptors that analyze the bolus volume, viscosity, temperature and taste for the required motoric response to the stimulus. The duration of the swallow response in 40 years old healthy volunteers is <740 ms with the laryngeal vestibule closure in <160 ms and the esophageal sphincter opening within <220 ms (Clavé et al., 2006). The maximal vertical hyoid motion is around 310 ms and tongue propulsion forces are 22 mN (Rofes et al., 2010). The sequenced swallowing response generally assures that the bolus swallow is complete and no residues are remaining that could move retrograde or enter into the airways upon breathing.

Swallowing issues can occur at single stages (oral stage, pharyngeal stage of esophageal stage dysphagias) or at various stages simultaneously with different disability levels determining its severity (Chadwick and Jolliffe, 2009). The onset of swallowing issues has been experienced by patients as a sudden event or a gradual process. It may occur as an acute event of short duration or a chronic event persisting for months (Roy et al., 2007). The development of dysphagia was reported by older patients as an acute event in 79% of the cases while 21% reported a gradual onset. In two third of the cases dysphagia remained a chronic problem and only for one third the swallowing issues persisted for less than 4 weeks (Roy et al., 2007).

2.1.1. Age-related swallowing alteration

The theory of differential aging by Smith and Gerstorf suggests that there is a time dimension within the aging process but also diversity in the level and direction of distinct changes (Smith and Gerstorf, 2004), which may also explain the heterogeneity of the age related swallowing issues. While the individual swallowing capacity might differ significantly in older adults, the overall swallowing capability is declining with increasing age (Nilsson et al., 1996). These changes in the swallowing function remain asymptomatic and do usually not lead to any clinical relevant problems until they get dominant or are associated with other pathological conditions like cancer, neurogenic or myogenic malfunctions.

Age-related changes in swallowing functions are attributed to physiological, anatomical, motoric and sensory alterations. Declining muscle strength, receptor density and sensory receptor responsiveness are associated with a reduced tongue and lingual pressure leading to slow bolus velocity (Nicosia et al., 2000), a smaller amount of pressure 'reserve' (Robbins et al., 1995), delayed laryngeal vestibule closure and upper esophageal sphincter (UES) opening time (Rofes et al., 2010), increased oral and pharyngeal transit time and increased laryngeal clearance and exposure time (Cook et al., 1994), a delayed maximal vertical hyoid motion (Rofes et al., 2010), higher periventricular white matter lesions and cerebral atrophy leading to longer swallowing duration (Robbins et al., 1995), a prolonged swallowing reflex time and promotor time in the submental muscles (Nagaya and Sumi, 2002), a loss in synchronization of the temporal events of the swallowing response between the glossopalatal junction, the velopharyngeal junction, laryngeal vestibule and the UES (Clavé et al., 2006, 2008), higher frequency of intra-esophageal stasis (bolus retention) and reflux (Jou et al., 2009) and a lower pharyngo-UES contractile reflex due to an age-related decline in the afferent signaling of the reflex (Kawamura et al., 2004). Effortful swallowing has shown to impact the swallowing response in young and older adults. While effortful swallowing can increase the oral pressure and the swallow response durations at various levels in both age groups, there were significant differences between young and older volunteers whereby the older achieved a lower maximum pressure and higher residues in the pyriform sinuses upon effortful swallowing (Hind et al., 2001).

Swallowing might also be impacted by a decline in saliva production and Xerostomia, which affects bolus formation and smooth deglutination. Even so the saliva secretion, which is triggered by

Table 1
Pathological conditions causing dysphagia.

Etiology	Diseases known to cause dysphagia
Central-nervous	Stroke
	Alzheimer's disease
	Parkinson's disease
	Dementia syndrome
	Intellectual disability
	Motor Neuron disease
	Amyotrophic lateral sclerosis
	Multiple sclerosis
	Schizophrenia
	Depression
	Infectious brain diseases
	Polyneuropathy
	Down's syndrome
Musculoskeletal	Spinal muscular atrophy
	Oculopharyngeal dystrophy
	Myasthenia gravis
	Zenker diverticulum
	Osteoarthritis
	Disseminated idiopathic skeletal hyperostosis
	Polymyositis
	Inflammatory myophathies
Metabolic	Diabetes
	Hyper- and hypothyroidism
	Cushing syndrome
Oncological	Brain tumors
	Neck tumors
	Oropharyngeal tumors

cholinergic stimulation of the muscarinic receptors within the saliva glands, remains stable over the live span the decreasing number of saliva producing acinar cells might decrease the salivary reserve (Ney et al., 2009). The saliva is composed of water, mucin, and various bactericidal components like proteolytic enzymes, antibodies, amylases and lipases. The composition of the saliva is changing with age which leads to a saliva of higher density and viscosity (Astor et al., 1999) affecting the swallowing functions (Shay and Ship, 1995).

Sarcopenia is a loss of muscle tissue and strength which occurs frequently in older adults' as a consequence of biological aging and other factors like reduced exercise and altered nutrition (Doherty, 2003). Sarcopenia also seems to affect the muscles of the upper aerodigestive tract involved in the swallowing process reducing the strength and function of the swallowing response (Ney et al., 2009).

2.1.2. Disease related swallowing issue

The incidence of chronic and age-related diseases increases over the life-time causing swallowing issues and dysphagia as a co-morbidity. Common chronic diseases and medical conditions impact the swallowing process beyond the natural aging process triggering the development of dysphagia with clinical relevance. Older patients with osteoarthritis or hypertension show a prolonged pharyngeal and oropharyngeal transit time of a bolus compared to healthy older people. But also other health conditions like hypothyroidism, hypercholesterolemia, gastroesophageal reflux, thyroid disease and depression lead to prolonged pharyngeal and oropharyngeal transit times (Kendall et al., 2004).

Dysphagia is a common co-morbidity of several diseases that directly or indirectly impact the swallowing process or swallowing response. Despite direct head and neck injuries dysphagia has been shown to be caused by diseases of the central-nervous system, musculoskeletal system, metabolic disorders and oncological diseases related to the tongue, palate, tonsil, glottis and pharynx (Table 1).

Dysphagia develops in these health conditions due to disease-related alterations in the neurologic and muscular functions or anatomy. In principle, the alterations pronounce one or more age-related changes and increase their severity in co-morbidity patients suffering from stroke, Parkinson's disease, Alzheimer's disease, dementia, cancer or multiple sclerosis (Ekberg et al., 2002). Patients with cognitive impairments may have abnormal tongue and lingual pressure which can either be increased or decreased causing difficulties to control bolus formation and transit in the oral stage. The declining neuronal and muscular responses delay the swallowing reflex and the cricopharyngeal opening leading to residues in the laryngeal stage with risk of aspiration (Chadwick and Jolliffe, 2009). In frail elderly patients with different pathological conditions swallowing response, reconfiguration phase to the digestive pathway, maximal hyoid motion, as well as upper esophageal opening time was significant longer compared to healthy adults causing a slow bolus velocity and weak kinetic force (Rofes et al., 2010). Vertebral osteophytes in combination with myopathy can trigger dysphagia in older patients with co-morbidity including diabetes, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (Ney et al., 2009). Salivary overflow and drooling is often seen in patients with Parkinson and motor neuron disease. Combined with the impacted swallowing response in these patients, the excessive saliva cannot be swallowed completely and increases the risk for saliva aspiration (Johnson and Scott, 2006). In Parkinson disease, patients' salivary drooling increases with age and duration of the disease, but is independently associated with dysphagia (Kalf et al., 2007, 2011).

2.1.3. Medication or therapy induced dysphagia

2.1.3.1. Drugs. Medicinal products contain active pharmaceutical ingredients (drug substances) that are targeted to modify disease-related physiological changes and pathological conditions. Adverse drug reactions might cause swallowing dysfunctions through esophageal injuries or induction of xerostomia and dysphagia. Table 2 summarizes the main drug substances and drug classes known to cause swallowing dysfunction.

Certain drug classes with central-nervous, neuromuscular or immunomodulating effects have been reported to induce or intensify swallowing problems causing clinically relevant dysphagia. The major pathways can either be through a direct pharmacological effect (adverse drug reaction), an indirect effect related to the pharmacological activity (inflammation caused by antibiotics, immunosuppressive or antineoplastic agents) or a directly induced injury to the oropharyngeal and esophageal mucosa (Stochus and Allescher, 1993).

The extrapyramidal side effects of antipsychotic drugs reduce the tonus of the pharyngeal muscles by interfering with the dopaminergic and adrenergic receptors leading to dysphagia (Mendhekar and Agarwal, 2010).

Beside Sjögren's syndrome an autoimmune disease that is directed against the glandular cells (Valdez and Fox, 1991), so called xerostomia, is often seen in conjunction with certain drugs and in polypharmacy conditions. The underlying mechanism for drug induced xerostomia can be related to anticholinergic effects or a modulation of the signaling pathway in salivary tissue reducing the saliva production or release from the salivary glands (Cassolato and Turnbul, 2004; Astor et al., 1999). As reviewed by Cassolato and Turnbull there is evidence that xerostomia correlates with increasing age, the use of xerogenic medications and the number of drugs in a therapeutic regimen, especially if 3–9 xerogenic drugs are involved (Cassolato and Turnbul, 2004; Gallagher and Naidoo, 2009). However, drug-induced dysphagia and xerostomia are reversible and might be resolved by changing the medication regimen (Dziewas et al., 2007).

Esophageal injuries can be originated by drugs due to a direct, dose-dependent erosive effect on the esophageal mucosa or indirectly by modifying the pH in the esophagus. While there are

Table 2
Drugs involved in swallowing dysfunction.

Drugs causing esophageal injuries	Drug classes inducing xerostomia[a]	Drugs inducing dysphagia
Antibiotics	Anorexiants	Antipsychotics
– Tetracycline and derivatives	Antiacne agents	– Haloperidol
	Antianxiety agents	– Thioridazine
– Lincomycin and derivatives	Anticholinergics/Antispasmotics	– Risperidone
	Anticonvulsants	– Olanzepine
– Penicilline and derivatives	Antidepressants	– Paliperidone
	Antidiarrheals	– Loxapine
NSAID	Antiemetics	– Fluphenazine
– Acetylsalicylic acid	Antihistamines	– Trifluoperazine
– Indomethacin	Antihypertensives	– Clozapine
– Oxicam derivatives	Anti-inflammatory Analgesics	Anticholinergics
– 2-Arylpropionic acid derivatives	Antinauseants	Antidepressant
	Antiparkinsonian agents	– Nitrazepam
– Phenylacetic acid derivatives	Antipsychotics	– Clonazepam
	Bronchodilators	Analgesics
Others	Decongestants	Antiepileptics
– K^+, Ca^{2+} and Fe^{2+} salts	Diuretics	– Vincristine
	Muscle relaxants	Cytotoxics
– Biphosphonates	Narcotic analgesics	– Antimetabolites
– Ascorbic acid	Sedatives	– Intercalating substances
		– Alkaloids

[a] USP (2004).

more than 70 drug substances attributed to induce esophageal injuries, the majority of cases are attributed to anti-infectives of tetracycline type, penicillines, lincomycins and macrolides. Other drug classes prone to induce esophageal disorders are non-steroidal anti-inflammatory drugs (NSIAD) like acetylsalicylic acid, indomethacin and piroxicam and the antispasmodic drug emepronium, the electrolyte replenishing agent potassium chloride and the antiarrhythmic quinidine (Bott et al., 1987; Jaspersen, 2000). Drug induced relaxation of the lower esophageal sphincter has also been suggested as a root cause for increased reflux and esophageal injury (Jain and Pitchumoni, 2009) as well as age or disease related enlargement of the heart is supposed to reduce the esophageal lumen hindering the SODF to pass through or get lodged (O'Neill and Remington, 2003).

2.1.3.2. Radiotherapy and surgery. Radiotherapy alone or in combination with chemotherapy is a common treatment for several types of cancer. When the oro-pharyngeal region is treated, dysphagia is a serious side effect. The extent of dysphagia depends on the radiation dose, volume and area treated (Caudell et al., 2010; Peponi et al., 2011). The risk for dysphagia significantly increases with a concomitant chemotherapy. This risk can be reduced when the chemo- and radiotherapy was applied sequentially with radiation starting 21 days after finishing the chemotherapy (De Ruysscher et al., 2007). Radiotherapy as a treatment for oro-pharyngeal cancer may lead to irreversible damage of the irradiated tissue reducing the laryngeal sensitivity and tongue motion. By using an ipsilateral treatment the radiation does not reach one parotid gland which decreases xerostomia and the incidence of dysphagia (Jensen et al., 2007).

Surgical interventions are another frequently applied therapeutic strategy in head, neck, and lung affecting diseases in the thoracic area. Surgery and resection bear the potential risk to cause collateral damage to the enervation, muscle tissue or cartilaginous structures involved in the swallowing process. Surgery-related dysphagia is not only frequent in surgery procedures related to the oro-esophageal system, but also occurs in cervical spine surgery (Riley et al., 2010) and other unrelated surgical interventions (Han et al., 2009).

2.2. Diagnosis of dysphagia

Despite of the severe consequences regarding the general health status of elderly patients the prevalence of dysphagia and swallowing dysfunction is still underestimated. These consequences include weight loss, poor nutritional status, cachexia, failure to thrive, recurrent infections, aspiration and asphyxia. Background information about patient's history can help to confirm the suspicion of swallowing problems. A further cornerstone in the diagnostic process is the observation of the patients during eating and drinking. Daniels et al. (1997) described a clinical assessment of swallowing and prediction of severity of dysphagia. This screening tool is quite simple. There is no need for a specialist or special equipment. It can also be done by a general practitioner in a nursing-home. A positive result is an indication for further examinations. The "gold standard" in the diagnosis of swallowing impairments and dysphagia are the fiber-optical endoscopic evaluation of swallowing and video-fluoroscopic swallowing studies. A clinical examination by a neurologist, otorhinolaryngologist, geriatrician and gastroenterologist should be an obligation to detect the underlying reasons of the swallowing impairment.

2.3. Prevalence of dysphagia

Up to one third of people in all age groups experience swallowing issues during their lifetime. Although the frequency of occurrence is low for the majority of people, a considerable number have one or more incidences per week (Eslick and Talley, 2008). However, when independently living older people were asked about their swallowing capability 15% responded to have difficulties with swallowing (Chen et al., 2009). The increased prevalence for swallowing issues and the development of clinically significant dysphagia can be observed with increasing age, intensity of required care and number of diseases as well as in diseases with dysphagia inducing co-morbidity.

The prevalence for swallowing issues has been identified to increase with age in community-dwelling older people. In a cohort of people beyond 65 years 8.8% of the 65–74 years old Japanese had signs of dysphagia which increased to 19.0% and 28.2% in the 75–84 years and over 85 years old respectively (Kawashima et al., 2004). These data are in agreement with a study

investigating swallowing problems in people admitted to a geriatric ward of a German community hospital. From the older people of a mean age of 83 years, 23.9% were diagnosed having swallowing issues (Volkert et al., 2010). In older patients with various health conditions and drug therapies independently living in Spain, dysphagia was reported in 16.6% of the 70–79 years old patients compared to 33.0% beyond 80 years of age (Serra-Prat et al., 2011). A similar result was reported in a study performed on independently living population of senior citizens in the USA having life time prevalence of swallowing issues of 35% beyond 65 years (Roy et al., 2007). Assessment by video-fluoroscopy of volunteers with a mean age of 83 years showing no sign of dysphagia revealed that only 16% had comparable deglutination with 30 years younger adults, while the other 84% of older adults showed at least some kind of swallowing dysfunction (Ekberg and Feinberg, 1991). 13.7% of this age group confirmed to have swallowing issues diagnostically classified as dysphagia (Turley and Cohen, 2009).

The prevalence for swallowing issues and signs of dysphagia increases with the level of care that needs to be provided to the patients (Steele et al., 1997). However, the level of care is correlated with the number and/or severity of the health conditions and basically represents the patient population with several malfunctions. Swallowing issues in long-term facilities might also reflect long-term treatment with drugs causing dysphagia, e.g. antipsychotic drugs (Regan et al., 2006).

Central-nervous disease pathologies are known to have the highest prevalence for dysphagia due to behavioral, neurological and motoric implications. The reported dysphagia prevalences for patients with Parkinson's disease are between 52 and 82%, amyotrophic lateral sclerosis up to 60%, myasthenia gravis 40%, multiple sclerosis 44% and Alzheimer's disease of 84% (Clavé et al., 2004). There is evidence that all patients with Parkinson's or Alzheimer's disease will develop dysphagia at a certain time-point in disease progression (Suh et al., 2009; Miller et al., 2009).

In patients with cerebrovascular events like stroke, the development of dysphagia depends on size and location of the affected brain area. In a recent study evaluating more than 2900 patients with a history of stroke, dysphagia was diagnosed in 50.5% of the patient population (Guyomard et al., 2009). These results are complementary and inline with the results reported by Martino et al. In this literature review the prevalence for dysphagia varied between 37 and 78% depending on the method used and the stroke specific characteristics (Martino et al., 2005).

In patients suffering from schizophrenia about one third are developing dysphagia similar to patients with bipolar affective disorders (Regan et al., 2006). These data are quite in accordance with a very recent paper (Aldridge and Taylor, 2012).

Aggressive therapeutic interventions in patients with severe disease conditions bear a high risk for dysphagia. Radiotherapy to treat pharyngeal cancer has a probability for developing dysphagia of 83% (Jensen et al., 2007). Radiotherapy induces long-term dysphagia in 38.5% of patients treated for squamous cell carcinoma of the head and neck of which 21.7% remained percutaneous endoscopic gastrostomy (PEG) tube dependent (Caudell et al., 2010). When surgery was the therapeutic intervention anterior cervical spine diseases, the prevalence varied from 1 to 79% with a mean value of 33.1% within the first week of surgery and declined to 12.9% after two year (Riley et al., 2010).

2.4. Health implication of dysphagia

Accurate swallowing is an essential physiological function required for safe breathing and alimentation. Perceived swallowing dysfunction directly affects the quality of life for the affected patient. The social function of communal eating may fade into the background or being replaced by anxiety or panic attacks (Ekberg et al., 2002). While one quarter of the older people believe that dysphagia is an inevitable part of aging (Chen et al., 2009), two thirds of patients accept the disease considering dysphagia as an untreatable condition (Ekberg et al., 2002). Besides the unawareness of treatment options, common acceptance of dysphagia as a normal aging process and various reasons for not consulting a physician, patients outweigh the efforts against the benefits of seeking help for their swallowing issues (Turley and Cohen, 2009). Even half of the younger patients suffering from dysphagia did not consult their medical doctor despite their symptoms and the potential treatment options (Wilkins et al., 2007). Reasons of older people for not consulting their medical doctor and addressing the swallowing issues is the fear to appear incompetent or even to be judged as being unable to continue caring for themselves (Kottke et al., 1990). Medical doctors and other caregivers on the other hand do not consider dysphagia as a serious health issue which requires thorough diagnostic evaluation and reporting (Ekberg et al., 2002; Volkert et al., 2010) and do not tend to systematically investigate swallowing issues of their patients (Strachan and Greener, 2005).

Dysphagia has been found to be an important pathological factor in malnutrition and dehydration. Patients suffering from swallowing issues try to avoid drinking and eating or change their behavior to an unbalanced and inadequate nutrition (Chadwick and Jolliffe, 2009; Gaskill et al., 2008; Mudge et al., 2011). In older people, malnutrition (Carriere et al., 2008), sarcopenia (Fischer, 2004) and cachexia (Thomas, 2007) are important markers for mortality and disability. Malnutrition and sarcopenia can also reflect inflammatory processes and cytokine activation due to chronic diseases (Carriere et al., 2008; Bales and Ritchie, 2002). Patients who develop dysphagia due to a stroke event have a significant higher probability of death and the duration of hospitalization independently of their age (Guyomard et al., 2009).

Because of the dual function of breathing and nutrition, dysfunction of the swallowing process increases the mortality due to asphyxiation and aspiration induced pneumonia. Asphyxiation mainly occurs upon choking on food, whereas aspiration is caused by the presence of pharyngeal residue and laryngeal penetration (Aldridge and Taylor, 2012; Chouinard, 2000; Cabre et al., 2010; Rofes et al., 2010; Martino et al., 2005; Chadwick and Jolliffe, 2009). The incidence and risk for aspiration in dysphagic patients depend on the volume and the consistency of the bolus. Smaller volumes with higher viscosity significantly reduce the risk for aspiration in dysphagia patients (Clavé et al., 2008).

3. Oral medication in dysphagia patients

3.1. Swallowing solid oral dosage forms

The preferred route for drug administration is the oral administration. Medicinal products based on SODF technology are distinct solids of round or oval shape that are intended to be swallowed intact. SODF have usually dimensions of less than 1 cm and a weight of normally a maximum of 1 g and mainly appear in the tablet or capsule form.

The incidence of swallowing issues and dysphagia correlate with increasing age and morbidity, which are both typical conditions of growing medicinal product usage. Swallowing a SODF intact is a consent patient decision and focuses on the sole purpose of swallowing the solid form with a certain amount of liquid. Impaired swallowing functions can be expected to affect the safe transit of the SODF through the oropharyngeal and esophageal stages and may cause considerable problems.

As described before, dysphagia has different pathological origins and each patient must be seen as an individual case. The individual assessment has to take into account the variety of different

patient-related factors affecting the ability to swallow medicinal products, the therapy-related factors determined by the complexity and challenges of the material to be swallowed. Patient-related factors of oral drug delivery are the ability to swallow solid forms, the ability to co-administer larger amounts of liquids, the position (supine or up-right) of the body, the willingness to swallow and the perceived ability to swallow the SODF. Therapy factors include the number of medications to be swallowed, the medication itself (e.g. size, shape, surface, texture, taste, and number of doses) and the administration schedule (e.g. frequency of doses and dosing time). However, until today there are only limited studies available investigating the swallowing performance of SODF in patients with dysphagia (Kelly et al., 2010a).

One of the first conducted studies investigated patients' complaints regarding swallowing difficulties of capsules and tablets in a population of community based older people. Swallowing issues were reported as "often" in 23.3% of the population for capsules and 28.9% for tablets. Within the same study about 20% of the control group, consisting of young students, also reported difficulties with swallowing tablets and capsules (Kottke et al., 1990). Similar results were published in a recent survey of independently living older patients showing a prevalence of 22.4% for oral drug administration problems with an increasing prevalence with age (Payot et al., 2011). Moreover, both studies found a higher prevalence for issues related to oral drug administration in females than in males. A recent study confirmed that 45.5% of older patients with dysphagia living independently in senior citizen centers have issues with swallowing medications, but also 12.3% of non-dysphagic patients reported problems with oral drug administration, which is a total prevalence of 24.8% in the studied population (Roy et al., 2007). When pharmacists were instructed to interview patients that were suspected to have swallowing dysfunction 59.7% of the patients confirmed having issues with swallowing SODF (Strachan and Greener, 2005). Another patient group that has been identified having significant difficulties with swallowing SODF are adolescents between 11 and 20 years of age. In this population 36% reported issues with swallowing tablets due to taste and size properties as well as a general aversion against swallowing medicinal products (Hansen et al., 2007).

The importance of the SODF formulation has been addressed as the second important aspect in taking oral drugs by dysphagia patients (Kelly et al., 2010a). The decisive criteria for SODF swallowability were size, shape and surface texture of the drug dosage forms. Smaller sizes, oblong forms (capsule shape and torpedo-shaped tablets) and smooth surfaces were preferred and considered as easier to swallow. These patient reflections have been confirmed in an earlier study comparing the esophageal transit times of different SODF in patients between 19 and 80 years of age using fluoroscopy. In essence, larger and round uncoated tablets had the longest transit times with high incidence of swallowing failure when taken with small volume of water or in a supine position (Hey et al., 1982). It should be noted that the difficulty of SODF swallowing is potentiated in multi-morbid and bedridden patients by their supine position and their inability to drink larger amount of water in one big sip, which negatively impacts the orogastric transit (Osmanoglou et al., 2004; Gallo et al., 1996).

The increasing prevalence for carcinogenic diseases with age comes along with a constant decrease in mortality due to an increasing number of new drug therapies (Lichtenberg, 2010). As mentioned above, cytotoxic drug are known to cause dysphagia as well as serious gastrointestinal side effects. While recent developed new drugs are moved from parenteral to chronically administered oral dosage forms the effect of the adverse drug reactions on the swallowability, especially for the chronic therapies, should be considered and investigated during product development (Andreyev et al., 2012).

3.2. Managing medication swallowing issues in dysphagia

The significant prevalence of issues related to SODF administration raises the question on the impact on oral drug therapy in the affected patients. Patients living independently are presumed to be able to manage their medication on their own and are normally not questioned by the medical doctors or nurses whether they would be able to swallow the prescribed medication (Strachan and Greener, 2005). Hence, there is very limited knowledge on how independently living patients with swallowing issues coop with their oral drug therapy. Some indications have been obtained in a recent study where the patients reported that bigger sizes and poor quality of tablet coatings led to conscious non-compliance and probably discontinuation of drug therapy (Payot et al., 2011). The same results were found in an Irish survey where two third of the patients with dysphagia dealt with this issue by opening the capsule or crushing the tablet before administration and two thirds by simply discontinuation of the medication (Strachan and Greener, 2005). This has also been reported for adolescent patients with swallowing issues in which tablet crushing, mixing with food and discontinuation were major strategies to coop with the swallowing difficulty (Hansen et al., 2007). This study confirmed again that omitting the drug intake, tablet crushing and capsule opening are most likely the major interventions used by and for out-patients. This hypothesis is supported by the huge number of different tablet crusher devices available for purchase (e.g. http://www.alibaba.com/showroom/tablet-crusher.html).

There is clear evidence that patients take decisions on therapy adherence which is based on swallowing problems experienced with a medication and that these are often not reported to the medical doctors. The impact of this daily practice on drug therapy and adherence in a home-setting environment should not be underestimated.

When patients enter into assisted living, nursing homes or secondary long-term care facilities, the medication management is normally shifted into the responsibility of the nurse or caregiver, who is taking care about the patients in all daily aspects. Nurses often do not feel comfortable taking over this challenging task and making decisions within the medication administration process that would require knowledge about drug therapy and medicinal products (Barnes et al., 2006). Major issues the nurses are facing are the difficulties related to drug administration to the patients who either are unable to swallow or refuse to swallow the medication.

A literature survey was conducted in the Medline (1946–2011) and Embase (1980–2011) data base to identify scientific studies conducted to evaluate the impact of swallowing issues on drug administration and the relevant interventions. The searching criteria and key words were 'swallowing', 'swallowing issue', 'medication administration', 'tablet crushing', 'capsule opening', 'crushing tablets', 'opening capsules'. Relevant articles were screened for those that fulfilled the objectives. After removal of the duplicates and the articles not meeting the specified criteria 9 out of 28 papers were identified, which are summarized in Table 3.

The results suggest that in secondary care nurses are frequently altering the prescribed dosage forms to overcome administration issues with SODF. Crushing tablets and opening capsules are the main alterations of dosage forms and account for up to one third of oral drug administrations in long-term nursing homes. The crushed tablets and opened capsules are often mixed with food or beverages for ease of administration either with or without patient's knowledge. Drug alteration implies a high risk for potential drug instability and modification of the product performance that is neither tested nor authorized by the pharmaceutical manufacturer and the regulatory bodies. Such alterations may lead to serious adverse effects or severe intoxication of the patients (Cornish, 2005) as well as causes other administration issues like the bad taste of

Table 3
Summary of studies investigating medication administration issues in patients with swallowing issues.

Study	Objective of the study	Patient population	Dosage form modification	Related issues
Haw et al. (2007)	Frequency and nature of medication errors in psychiatry	Patients in long-stay wards	25.9% medication errors of which 30.1% were related to tablet crushing and 27.1% to drug omission	
Jackson et al. (2008)	Exploration of medication administration by nurses on two occasions	Long-term care facility with 37% and 40% dysphagia patients	68% modified medications in dysphagia	
Kelly et al. (2011)	Administration practice in patient with and without dysphagia and exploration of appropriateness and errors in administration	Patients in stroke and care-for-elderly wards of which 34.2% had dysphagia	Medication administration errors occurred in 13.8% of non-dysphagic and 32.6% of dysphagia patients	Medication errors increased from 25.3% to 56% in patients with enteral tubing
Kirkevold and Engedal (2005)	Examination of the practice of concealing drugs in patients' food	Regular nursing homes and special care units	12% of patient drugs were routinely mixed in food or beverages. 28% of cases this was due to swallowing issues	In 54% of cases the reason was non-acceptance of therapy by the patient. Reporting of the administration with food was reported in 40% of the cases. Patients receiving drugs with food get less drugs (4.4 vs. 5.2 drugs)
Kirkevold and Engedal (2010)	Investigation of crushing of tablets and mixing them with food for drug administration and of the appropriateness for the medication	Regular nursing home patients and patients in Special Care units for dementia	23.3% received at least one drug with food	Patients receiving altered drugs get less drugs (6.0 vs. 6.7 drugs)
Paradiso et al. (2002)	Evaluation of the extent of medication alterations and methods	Age-care facilities with high and low care need patient	34% at least one medication was altered. 17% of the medication alteration was inappropriate	In 100% where more then one medication was altered it was done in the same vessel. In 59% the vessel was not cleaned between alterations. In 70% of alterations spillage occurred.
Strachan and Greener (2005)	Determination of medications swallowing issues in secondary care	Community living patients with suspected swallowing issues determined by the pharmacist	60% had medication swallowing issues. 68% of these patients crushed tablets/opened capsules. 69% of these patients omitted the medication	72% of patients had never been asked about swallowing issues
Stubbs et al. (2008)	Evaluation of the frequency of medication alteration and consequences	Long-term stay wards for mentally ill inpatients and review of incidence reports in the UK National Reporting and Learning System (NRLS)	25.5% medication alteration of which 44% were unauthorized and 4.5 were specifically contra-indicated	In the NRLS only 17 incidences were reported over 13 months, compared to the 266 incidences identified in 1045 applications
Wright (2002)	Exploring the difficulties of drug administration in nursing homes, the interventions used and their appropriateness	Patents in nursing homes of which 21.6% had medication swallowing issues	56.5% of nurses mixed rug with food. 26.9% Omitted the dose. 61.3% altered the medications (crushing/opening). 87.6% obtained liquid form	Unlicensed medication alteration took place on a weekly base in 80% of nursery homes

ingredients (Kelly et al., 2009, 2010a). While nurses are aware of the potential implications they feel themselves in the ambiguous situation of being responsible for the execution of the prescription as well as for the decision on the how (Barnes et al., 2006). A lag of information, guidance and support by other healthcare professionals was seen by the nurses as their major concerns, which also explains the different ways in which nurses' deal with the situation when faced with patients with swallowing problems (Wright, 2002; Kelly et al., 2010a). Especially when patients are unable to swallow the medication needs to be delivered via a PEG tube. Then, crushing of tablets and opening of capsules were used by 85.5% of the nurses in the first instant and later in different ways to convert them into an applicable form for enteral tubing. Also for enteric-coated or extended-release drug formulations different approaches were used for administering the product via enteral tube, but 23.7% and 39.8% of the nurses confessed they will never administer either an enteric coated or an extended-release formulation respectively through the tube (Phillips and Endacott, 2011). Recently, an expert group has proposed guidelines for the management of drug administration to patients with swallowing issues in order to raise the level of awareness and provide some helpful information for doctors and nurses (Wright et al., 2006). These guidelines consider SODF manipulations as the last option after thorough considerations and consultations, which might not solve the urgent challenge the nurses and caregivers are faced in front of the patient.

Manipulation of drug products remain a significant source for medication errors and harmful outcomes (Kelly et al., 2011) as well as it might have some legal implications. As the manipulation is neither an approved and labeled product characteristic nor it is prescribed by the physician and, especially (Wright, 2003) if it is mixed with food without patients' consent, this practice can be judged as unlawful according to the civil law. The professional code of conduct and the employment contracts may derive criminal charges in serious cases affecting all stakeholders involved in the patient's treatment (Griffith, 2003; Wright, 2002).

The advancements in pharmaceutical technology have revealed plenty SODF formulation options that may overcome the major drug administration problems in patients' swallowing difficulties, for both the paediatric and the geriatric population (Breitkreutz and Boos, 2007). Patient-centered formulations comprise multiparticulates in the form of pellets, sprinkles or miniaturized tablets, that provide palatability and dosing flexibility being safely administered with food or beverages. Orodispersible tablets offer a more sophisticated formulation approach that may

facilitate the swallowing even so the incidence for oropharyngeal residues, penetration into the endolarynx and aspiration was not different to a conventional tablet (Carneby-Mann and Crary, 2005). The reason for this observation is unclear but might be attributed to the small amount and velocity of saliva transport. Based on the recent study results showing a better swallowing acceptance of 2 mm mini-tablets compared to a liquid formulation in children of 6 months to 6 years (Spomer et al., 2012) reinforces the need for further studies in patient subpopulations with swallowing difficulties to proof the acceptance and appropriateness of the different types of new drug formulations.

4. Conclusion

Swallowing issues are originated by structural and functional changes in the swallowing process. They can develop into clinically relevant swallowing difficulties of solid oral drug products. As such, the swallowing functions show the same age- and disease-related decline patterns like other sensory and motoric functions during life-time and must be seen from a geriatric as well as gerontological perspective (Stegemann et al., 2010). With increasing age, morbidity and level of care as well as in specific disease conditions swallowing issues and dysphagia are becoming an evident health problem. While there are a variety of different physiological changes and forms of swallowing impairment and hence the clinical definition of dysphagia, the individual implications differ from each other. They can occur as an acute incidence or gradual development and they can persist either for a short time or become chronic. Swallowing issues contribute to malnutrition, dehydration and psychological and social burdens (Ekberg et al., 2002).

Older people and people with several disease conditions are the patient population which receives most of the drug products, often tending to polypharmacy, and is at the same time the cohort with the highest risk and prevalence to develop swallowing dysfunction. The increasing prevalence of dysphagia is correlated with the level of care which is a result of health and functional declines causing the need for intensive care like dementia, Alzheimer's and Parkinson's disease. The reported data suggest that about one third of the older patients in long-term care facilities experience swallowing problems with solid oral drug products. The prevalence for developing swallowing dysfunctions is significant higher in central nervous or neuromuscular disease conditions like Parkinson's disease, Alzheimer's disease, stroke, amyotrophic lateral sclerosis or motor neuron disease. However, symptoms of dysphagia are experienced by all age groups and are not solely to the older and multi-morbid patient (Eslick and Talley, 2008). Swallowing dysfunctions can severely influence patients' quality of life and social integration (Ekberg et al., 2002). People with swallowing dysfunctions tend to refrain from food and beverages which leads to malnutrition and dehydration.

Swallowing difficulties and dysphagia is also being considered to affect smooth and safe oral medication intake. It is well established today that medication adherence is influenced by various factors with the patients taking the ultimately decision on being adherent to the therapy (Sabaté, 2003). Medication adherence is directly affected by difficulties of swallowing or administration of a SODF to the patient as it increases the risk for omission of the drug products in independent living as well as nursery care facilities (Strachan and Greener, 2005; Haw et al., 2007; Kelly et al., 2011).

Swallowing difficulties with solid oral drug products are major issues that find its expression in the incidence of drug product alterations in intensive care facilities. Alteration or manipulation of the dosage forms comprise crushing tablets, opening capsules, mixing with food or beverages and dispersing or dissolving the solid dosage forms for enteral tube administration. This risky practice is often applied by nurses who receive the responsibility for the drug therapy instead of patients who are unable to manage the medication by themselves. In daily practice, nurses are often not educated to deal appropriately with drug manipulation and administration to the patients (Kelly et al., 2010b), which causes serious concerns about safety and efficacy and questions the lawfulness of this practice (Wright, 2002; Griffith, 2003). Many older people and patients with several chronic disease conditions however reside at home or receive supportive care from relatives or nurses. Problems related to the swallowing of SODFs have a similar magnitude as in long-term care facilities (Strachan and Greener, 2005; Payot et al., 2011). How these patients manage their oral medication at home is poorly understood and a matter for urgent future research.

Healthcare professionals directly or indirectly involved in treating patients with swallowing issues should consider alternative dosage forms and alert the industry to provide suitable dosage forms where they do not exist yet. Manipulations of medicinal products should not be accepted by the pharmaceutical manufacturers and the regulatory bodies, but should encourage pharmaceutical industry to consider providing better suitable appropriate dosage forms, patient-centered formulations in particular for patients with swallowing issues.

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