



# Novel methods of drug administration for the treatment and care of older patients



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## ABSTRACT

The number of older people globally is increasing, contributing to a growing burden of morbidity and mortality. With this shift in population demographic, comes a new challenge in terms of appropriate healthcare for the over 65 years age group. As medication is the principal therapeutic intervention, it is essential that it be fully optimised, to meet the needs of this heterogeneous population. The most common routes of drug administration are oral and injectable, which may display some limitations for older people, in cases of dysphagia or frailty for example. This review considers alternative methods of drug delivery to the norm, specifically discussing the nasal, pulmonary and transdermal routes, as well as novel orally disintegrating tablets. The changing physiology as ageing occurs must be considered in the development of novel drug delivery devices. This review considers the various aspects of ageing that will influence future drug formulation design and development.

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## 1. Introduction

The number of older people globally is increasing, with the number of people aged over 65 years predicted to treble, reaching 1.5 billion by the year 2050, representing 16% of the world's population (National Institute of Aging, 2011). This changing demographic is a tribute to modern healthcare, yet simultaneously a burden, as increased strain is placed on healthcare providers to cater for the ageing population. With population ageing directly proportional to the overall global burden of death and illness (Prince et al., 2014), it follows that this burden of chronic morbidities and related decline in wellbeing is set to increase in coming years. Older people represent a diverse group due to varying manifestations of ageing over a range of numerical ages, primarily in terms of physical health and cognitive function, and goals such as quality of life can be as equally important alongside longevity of life (Perrie et al., 2012). Healthcare providers need to be adequately trained and prepared to manage the specific needs of this group, as effective and comprehensive healthcare is central to 'ageing well.' In tandem, the pharmaceutical industry needs to adopt an approach more sympathetic to that of the older person to optimise geriatric drug therapy for greatest therapeutic benefit

and patient outcomes. Appropriately prescribed, and correctly used, medication is a crucial intervention in the management of ageing and contributes to older people retaining their independence, remaining in their own home, and being active members of society for as long as possible (Topinková et al., 2012). With the prevalence of chronic conditions in those aged over 65 years and related medication use, it could be said that as we age, we become the pharmaceutical industry's greatest consumer, yet the particular medication needs of the older patient are still not always adequately considered in research and development terms (Stegemann et al., 2010).

Older people are predisposed to encounter a number of problems relating to medication use (Jansen and Brouwers, 2012). Physiological changes due to ageing can have pharmacokinetic and pharmacodynamic implications for drug handling, potentially altering the volume of distribution, metabolism and clearance of many drugs, which can prolong the half-life, increase the occurrence of adverse drug reactions and also the potential for toxicity (Davies and O'Mahony, 2015). One example of particular significance is that of reduced renal clearance, with dose adjustment necessary with a number of common drugs for use in older people (BNF, 2015). The increased incidence of chronic conditions in the older population often leads to multiple drug use, with a recent US study reporting that 25.1% and 45.6% of adults ages 65–69 and 70–79 years, respectively, used  $\geq 5$  medications during 2009–2010 (Charlesworth et al., 2015). This can subsequently cause an increased risk of drug interactions, adverse effects and a potentially negative impact on adherence, which may, in

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turn, lead to negative health outcomes such as therapeutic failure, disability and more frequent health service utilisation (Topinková et al., 2012). Prescribing for an older population is further complicated by a lack of evidence as to disease outcomes and patient satisfaction for older people, stemming from an insufficient number of older people participating in clinical trials. A number of factors lead to this exclusion such as multimorbidity, existing complex medication regimens and practical issues regarding functional and cognitive decline (Van Spall et al., 2007). Overall, older people are a vulnerable population in terms of medication use, with a study reporting that 12.7% of hospital admissions in a sample of geriatric patients could be attributed to a 'drug-related problem,' with a further 8.2% of admissions partly due to this (Somers et al., 2010).

Medication administration in the older person presents a number of unique issues, with certain factors often pre-empting the conventional drug delivery routes. Geriatric patients may not be able to take drugs orally due to the presence of dysphagia, a major and often overlooked healthcare problem in older people; a recent study reported the prevalence as 14.7% in community-dwelling older adults (Lau et al., 2015). A further increase in dysphagia prevalence in nursing home residents can be expected, with levels as high as 68% reported (Sura et al., 2012). Modification of the dosage form, such as crushing of tablets and opening capsules, is often the solution for many patients and healthcare professionals to enable administration in these situations; however this poses a number of safety issues, alongside the risk of decreased medication efficacy (Mercovich et al., 2013). Parenteral delivery may be more difficult in frail older people due to limited venous access as a result of low body weight and decreased muscle mass. Frailty can also lead to a greater tendency for the formation of bruises on the skin, as a consequence of obtaining vascular access. In addition, there is a greater likelihood of older people taking antiplatelet or anticoagulant drugs, which can potentially increase the risk of bleeding complications (Moist et al., 2012), particularly an issue when used concurrently with certain other drugs, such as selective serotonin re-uptake inhibitors (SSRIs) (Schalekamp et al., 2008).

Considering medication as part of patient-centred care, the optimised intervention needs to be an age-appropriate approach, considering and acceding to the needs of the older patient. Dosage forms must be designed to ensure the older patient is able to manage the drug therapy easily and confidently with adherent behaviour, despite other factors relating to age or chronic conditions, which may co-exist. In the context of this review, alternative methods of drug administration to the conventional oral and injectable routes will be considered, focusing on orally disintegrating tablets, nasal, pulmonary and transdermal formulations. Examples of each method are provided to highlight recent developments, but are in no way exhaustive of the investigations in each field. The rectal route has not been discussed, as although an alternative route for drug administration, it is neither convenient nor patient-friendly, often reserved for use in palliative or emergency situations.

## 2. Orally disintegrating tablets

The convenience and familiarity of the oral route of drug delivery has led to new research in this field to permit medication administration, despite the presence of swallowing difficulties and dysphagia. A relatively recent innovation is that of orally disintegrating tablets (ODTs), also commonly known as 'fast melt', 'quick melt' and orodispersible systems (Parkash et al., 2011). These tablets dissolve or disintegrate rapidly in the oral cavity upon contact with saliva, without the need for chewing or additional water, thus facilitating administration of medication

orally. The dispersion or dissolution of the drug in the saliva allows for easy swallowing, even in patients with previously reported difficulties (Carnaby-Mann and Crary, 2005). A number of ODTs have been developed for the treatment of conditions that are common in the older population such as pain, depression, Parkinson's disease and Alzheimer's disease (Slavkova and Breikreutz, 2015), indicating that there is already a considerable body of evidence supporting patient acceptability of such a dosage form and the potential for improvements in adherence. Patient preference for an ODT compared to a conventional oral tablet or capsule has been demonstrated in cases of dysphagia (Carnaby-Mann and Crary, 2005), depression (Wade et al., 2012) and Parkinson's disease (Nausieda et al., 2005), for example.

Despite the progression to market, with a number of products already available and used in older people, for example, Aricept<sup>®</sup> ODT (donepezil) and Parcopa<sup>®</sup> (carbidopa/levodopa), there remain some aspects of ODTs that may still be improved upon. The challenges in this area generally lie in that of formulation, with difficulties in finding a balance between appropriate mechanical strength and fast disintegration time, incorporation of high doses of drug or poorly soluble drugs, taste-masking of unpleasant or unpalatable drugs and the ability to sustain release (Al-khattawi and Mohammed, 2014). There has been some progress in addressing these concerns, which is likely to be reflected in further marketed preparations in the coming years. For example, with older patients in mind, novel coated dextrin microcapsules have been used to incorporate amlodipine free base into an ODT, resulting in both improving absorption and masking the bitter taste of the drug (Jang et al., 2014). A sustained release ODT of the antihistamine and antiemetic, promethazine, was prepared, using drug-loaded chitosan nanoparticles, coated with polymer layers, displaying disintegration within 40 s but able to maintain drug release over 24 h (Elwerfallia et al., 2015). To enhance the solubility of the hydrophobic drug meloxicam,  $\beta$  cyclodextrin inclusion complexes have been formed to prepare ODTs with the fast disintegration time required (<30 s) and also dissolution of the poorly soluble active (Comoglu and Unal, 2015).

Although many orally dispersible preparations are highlighted for their use in the geriatric population, the prevalence of dry mouth in this population may preclude their use in a significant proportion. The major risk factor for dry mouth is the administration of particular medications and the anticholinergic burden associated, leading to this characteristic side effect (Chew et al., 2008). With a conservative estimate of 1 in 5 older people suffering from xerostomia (Thomson, 2015), it is unclear whether an orally dispersible dosage form would be convenient for use in these patients, given the low levels of saliva that would be present for tablet disintegration, without supplementation with water or another fluid. With no current universal technique for ODT disintegration assessment and a number of published methods using varying experimental parameters (Al-khattawi and Mohammed, 2014), the volume of saliva required will need to be considered in any future standardised test to ensure their suitability in all population groups.

## 3. Pulmonary delivery

Recent advances in novel particle technologies have facilitated increased interest in pulmonary drug delivery as the range of potential therapies that can be absorbed from the alveolar surface has been extended (Zhou et al., 2014). Particles can now be effectively targeted to the large surface area of the alveoli, rich in blood vessels for subsequent systemic absorption. The thin alveolar membrane (0.1–2  $\mu$ m), low enzymatic activity and avoidance of hepatic first-pass metabolism promote high bioavailability and rapid onset of action following drug absorption, even

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