A INTRODUCTION AND AIM OF THE STUDY

1 Introduction

The oral cavity has been investigated as a site for drug delivery for a long period of time. In 1847 Sobrero found that nitroglycerine was absorbed from the oral cavity (Ponchel 1993). Since then various active substances have been investigated for local or systemic use (Kellaway 1990).

Drug delivery through the oral cavity offers many advantages. The oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of dosage forms. Furthermore, the oral mucosa is robust against local stress or damage and shows fast cellular recovery after such incidents (Rathbone et al. 1994). Active substances can be administered locally to treat oral diseases like periodontal disease, bacterial and fungal infections or aphthous stomatitis (Ali et al. 2002, Nafee et al. 2003, Singh et al. 2008). A systemic action can be achieved via drug permeation through the mucosal endothelium. For systemic drug absorption, various dosage forms and devices, e.g. buccal patches, buccoadhesive discs and mechatronic delivery devices have recently been developed (El-Samaligy et al. 2004, Chayed and Winnik 2007, Perioli et al. 2008, Scholz et al. 2008). The use of buccal patches allows drug absorption to be terminated immediately upon simple removal of the patch.

The aforementioned advantages of drug administration via the oral cavity offer new possibilities in the administration of drugs to “problematical” subpopulations like children and the elderly. These patients have special drug administration requirements as they are often unable to swallow solid dosage forms (e.g. tablets, capsules). Poor taste can also lead to medication being refused or spat out. Furthermore, the pediatric subpopulation is a very heterogeneous group. According to the reflection paper “Formulations of choice for the paediatric population” by the EMEA (Committee for medicinal products for human use 2005) the pediatric population is divided into six groups: preterm newborn infants, term newborn infants, infants/toddlers, pre-school children, school children and adolescents. As such, there are differences in the suitability of various dosage forms for the different pediatric age groups. However, it is not only the suitability of a dosage form that has to be taken into consideration. Dosing regimen, applicability, efficacy and safety must also be taken into account, but the missing clinical trials in children demonstrate the lack of relevant data. Therefore, it is not surprising that many drugs, especially in the preterm and term newborn infant groups, are used off-label and unlicensed ('t Jong et al. 2002, Conroy et al. 2000, O’Donnell et al. 2002, Pandolfini and Bonati 2005). For these two age-groups solid dosage forms are inappropriate due to an inability to swallow. The parenteral route is commonly used if the child is severely ill or still very young. In the case of repulsion of oral liquids, drugs are primarily administered via the rectal route to achieve systemic

effects but this route is not favored in some cultures. In particular, for the preterm and term infants liquid dosage forms (e.g. solution, drops, emulsions, suspensions) for peroral use are recommended (Committee for medicinal products for human use, 2005).

The poor stability of aqueous liquids is problematic. Substances like benzalkonium chloride, benzyl alcohol or parabens are commonly used as preservatives. Many such substances are known to be potentially allergenic which is a problem often underestimated. Moreover, preservatives can be toxic due to immature metabolic pathways in children.

Fast-dissolving solid drug dosage forms for application onto the oral cavity for the pediatric population seem to be very appropriate, especially in preterm and term newborn infants. The delivery of drugs via the oral mucosa offers easy application, prevents drug degradation by gastrointestinal fluids, avoids first-pass metabolism and potentially improves bioavailability (American Academy of Pediatrics Committee on Drugs 2007) with rapid drug absorption and fast onset of drug action.

Drug absorption through membranes depends on the drug concentration at the surface of the mucosa, the vehicle for drug delivery, the contact time with the mucosa, the constitution of mucosal tissue, the degree of ionization of the drug, the pH of the absorption site, the size of the molecule and the relative lipid solubility (American Academy of Pediatrics Committee on Drugs 2007). These parameters have to be taken into account when formulating dosage forms for oral mucosal delivery. The drug concentration at the surface can be increased by varying the solubility of the drug. The drug partitioning can be influenced by environmental changes such as pH modifications. The permeability coefficient values are often low, so the use of permeation enhancers is beneficial. The contact time at the mucosa may be prolonged by the use of mucoadhesive polymers such as chitosans (Langoth et al. 2006), poly(ethylene glycol)-tethered copolymers (Serra et al. 2006) or alginates (Juliano et al. 2004). The size of the drug delivery system (e.g. buccal patches) determines the contact area and can be varied depending on the physiological conditions. Other issues such as continual secretion and swallowing of saliva are unique problems and also need to be considered during formulation development. The salivary flow and/or movements of the tongue and cheeks may influence the area and time of contact between the drug and the mucosa and thus the rate of absorption. Limited loading capacities restrict the use of oral mucosal dosage forms to include only potent drugs which are extensively absorbed from the oral cavity (Ponchel 1993).

As bioadhesive systems have long residence times in the oral cavity and may lead to an unpleasant mouth feel, they are assumed to be inappropriate for use in young children. Consequently, this work focuses on the development of a fast-dissolving oral dosage form. Fast-dissolving technology platforms include orally disintegrating tablets (ODTs) and oral lyophilisates, both of which are listed in the ‘tablets’ monograph of the

European Pharmacopoeia, and the rapidly disintegrating drug-loaded films (RDFs), which are not yet included in the pharmacopoeias. They are designed to dissolve/disintegrate in the mouth within a few seconds without additional water and the need to swallow. The ODTs show a high porosity, low density and low mechanical strength (Mishra and Amin 2007). Oral lyophilisates are manufactured by freeze-drying (Zydis®, Quicksolv®). ODTs such as FlashDose® are prepared by a molding process, whereas WOWTAB® and Flashtab® are prepared by granulation followed by compression and OralSolv®, DuraSolv® and AdvaTab™ are directly compressed (Sandri et al. 2006). Recently, the RDFs have gained popularity as dosage forms for breath fresheners. Meanwhile the pharmaceutical industry has recognized their potential for delivering medicinal products and has launched several products for the OTC market using this formulation technology. The fast-dissolving film is placed onto the patient's tongue where it is instantly wet by saliva, hydrated and adheres to the mucosa. The film then disintegrates and dissolves, releasing the drug for absorption by the mucosa. The fast-dissolving oral films are hardly described and investigated in literature, but seem to be an ideal dosage form for use in young children, especially in preterm and term newborn infants. They combine the greater stability of a solid form and the good applicability of a liquid. Due to their fast-dissolving behavior and subsequent adherence to the mucosa it is almost impossible to spit them out after application onto the tongue. Because of the novelty of fast-dissolving oral films, no monograph exists in the pharmacopoeias. Due to the lack of standard methodology for preparation and analysis new procedures need to be developed and evaluated within this work.