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Oral transmucosal drug delivery for pediatric use☆

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ABSTRACT

The formulation of medicines for children remains a challenge. An ideal pediatric formulation must allow accurate dose administration and be in a dosage form that can be handled by the target age group. It is also important to consider the choices and the amount of excipients used in the formulation for this vulnerable age group. Although oral formulations are generally acceptable to most pediatric patients, they are not suitable for drugs with poor oral bioavailability or when a rapid clinical effect is required. In recent years, oral transmucosal delivery has emerged as an attractive route of administration for pediatric patients. With this route of administration, a drug is absorbed through the oral mucosa, therefore bypassing hepatic first pass metabolism and thus avoiding drug degradation or metabolism in the gastrointestinal tract. The high blood flow and relatively high permeability of the oral mucosa allow a quick onset of action to be achieved. It is a simple and non-invasive route of drug administration. However, there are several barriers that need to be overcome in the development of oral transmucosal products. This article aims to provide a comprehensive review of the current development of oral transmucosal delivery specifically for the pediatric population in order to achieve systemic drug delivery. The anatomical and physiological properties of the oral mucosa of infants and young children are carefully examined. The different dosage forms and formulation strategies that are suitable for young patients are discussed.

Contents

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1. Introduction

The development of formulations for pediatrics is a challenging field of research. Pediatric patients include newborns, infants, children and adolescents. The upper age limit used to define pediatric population varies among different countries, usually including adolescents up to 18 or 21 years of age. The different age groups have different physiological and pharmacokinetic consideration, and their ability to handle formulation is also vastly different [1,2].

Oral transmucosal drug delivery is an attractive route of administration to achieve systemic drug delivery for pediatric patients. Absorption of drugs across the oral mucosa can bypass hepatic first pass metabolism and similarly avoid drug degradation in the gastrointestinal tract. Because of the abundant blood flow to and the relatively high permeability of the oral mucosa, fast onset of drug action may readily be achieved [3,4]. This is particularly desirable during an emergency situation when a rapid clinical response is required [5]. It is also a useful route of administration during a state of patient unconsciousness, when swallowing is impaired. Compared to parenteral administration, delivery of drugs via the oral cavity is relatively simple and non-invasive. Medication can be easily administered by the parents or carers of young patient without special technical skills, although the cooperation of the patient is sometimes necessary. Oral cavity delivery may also avoid the risk of blood borne infections or injury associated with parenteral administration. In addition, the absence of needle administration and the pain associated with this can also improve compliance in young children.

A drug candidate should possess the necessary physicochemical properties before it is considered for oral transmucosal delivery development. These include good lipophilicity and water solubility at physiological pH, as well as high potency. In addition, the drug must not cause any local irritation in the oral cavity. Apart from the intrinsic drug properties, there should also be a clear clinical benefit in developing a product for this route of delivery. To achieve systemic drug delivery through the oral mucosa effectively, several physiological barriers presented by the oral cavity must be overcome, namely the intrinsic enzyme activity, the relative permeability of the oral mucosa and the small fluid volume for dissolution and absorption. A mucoadhesive drug delivery system is a commonly employed strategy to increase the contact time of formulation at the site of absorption and also minimize any saliva wash-out effect which may lead to involuntary swallowing [6]. For these reasons, apart from the conventional tablet and liquid dosage forms available, newer dosage forms such as oral thin films and wafers are being developed. Oral transmucosal dosage forms must also allow for accurate and convenient dose measurement as the dose of all drugs varies with age and the weight of children. Other considerations include the ability of young patients to handle the particular dosage form, the physiological differences of the oral cavity between the adults and children, the palatability of the formulation and the cost effectiveness.

Buccal and sublingual routes, which are the two most common oral transmucosal routes of administration, are focused in this review. The oral transmucosal delivery systems have been reviewed recently in a number of publications without the specific consideration of the age of patients [3,4,7–10]. The development of buccal and sublingual formulations for systemic delivery targeting the pediatric population is the primary focus of this review.

2. Anatomy and physiology of the oral mucosal

Drug absorption through the oral mucosal surface is potentially effective because it is generally rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation or metabolism by gastric juice, gastrointestinal enzymes and first pass hepatic metabolism. The outer quarter to one-third of the oral mucosa is comprised of closely compacted, squamous stratified epithelial cells (Fig. 1). Beneath the epithelium are the basement membrane, lamina propria (an underlying supportive connective tissue layer) and submucosa which contains blood vessels and nerves, together with many taste sensory receptors dispersed among oral mucosa. The oral epithelia serve as a major penetration barrier to protect the underlying tissues against potential harmful materials or microorganisms in the oral environment, and also to prevent excessive loss of fluid from the underlying tissues to the exterior. Histologically, epithelia can be further developed into superficial keratinized and non-keratinized cells, which affect drug permeability, with the latter having a higher permeability [11]. This is due to the differences of lipid composition of the membrane coating granules in the keratinized and the non-keratinized cells, rather than the presence of keratin itself [12].

There are three major types of oral mucosa: the lining mucosa (60%), the masticatory mucosa (25%) and the specialized mucosa (15%). The lining mucosa contains the non-keratinized buccal and sublingual tissues in the oral cavity. The masticatory mucosa consists of keratinized hard palate (the upper surface of the mouth) and gingiva (gums), while specialized mucosa refers to the keratinized and some non-keratinized dorsal surface of the tongue. The highly keratinized palatal parts have poor drug permeability and are seldom pursued for drug delivery. Since lining mucosa is not subjected to masticatory activity, this non-keratinized mucosa is thinner than the other two mucosal types, and is more suitable for efficient drug absorption. Therefore, the buccal and sublingual routes are of primary interest for oral transmucosal drug delivery due to their higher overall permeability compared to the other forms of oral mucosa [7].

There are differences in permeability between the buccal and sublingual mucosa. Buccal tissues are the outer oral vestibule. With the buccal route of administration, drugs are usually placed on the inner cheek of

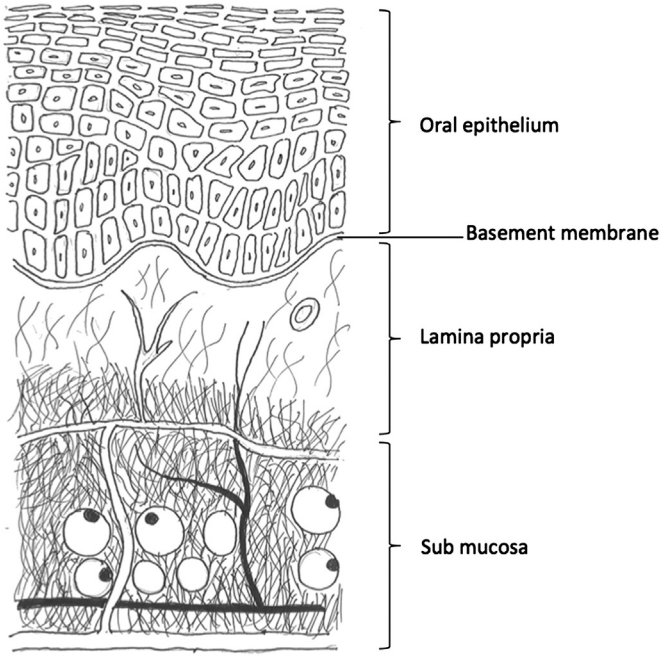

Fig. 1. The schematic diagram of the structure of oral mucosa.

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