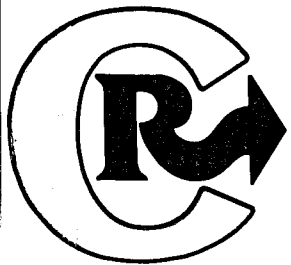
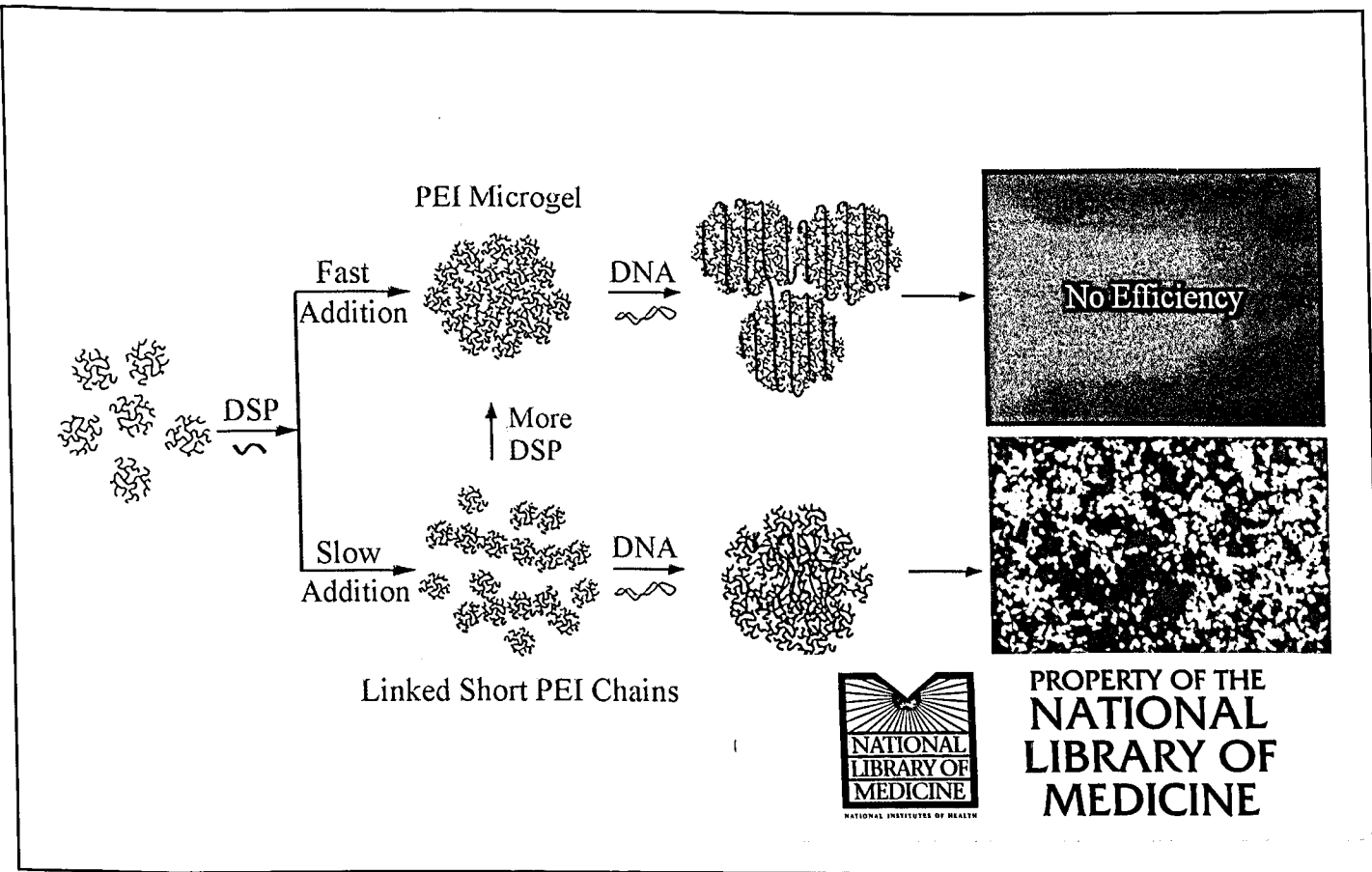


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## COVER STORY

PEI-DNA complexes with higher transfection efficiency and lower cytotoxicity

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## Review

# Orotransmucosal drug delivery systems: A review

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## ABSTRACT

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods and also enhances drug bioavailability because the mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism. The systems contact with the absorption surface resulting in a better absorption, and also prolong residence time at the site of application to permit once or twice daily dosing. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. Although many drugs have been evaluated for oral transmucosal delivery, few are commercially available. The clinical need for oral transmucosal delivery of a drug must be high enough to offset the high costs associated with developing this type of product. Transmucosal products are a relatively new drug delivery strategy. Transmucosal drug delivery promises four times the absorption rate of skin. Drugs considered for oral transmucosal delivery are limited to existing products, and until there is a change in the selection and development process for new drugs, candidates for oral transmucosal delivery will be limited. The present papers intend to overview a wide range of oro-transmucosal routes being potentially useful for transmucosal drug delivery and remind us of the success achieved with these systems and the latest advancement in the field.

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## 1. Introduction

Oral administration of pharmaceutical compositions has some drawbacks. For instance, it is difficult to keep the medicament at the desired location so that it can be absorbed, distributed and metabolized easily. Accordingly, there has been much interest in the use of the mucosal lining of body cavities. Regions in the oral cavity where effective drug delivery can be achieved are buccal, sublingual, palatal and gingival. Buccal and sublingual sectors are the most commonly used routes for drug delivery and they may be used for the treatment of local or systemic diseases. The permeability of the oral mucosa is probably related to the physical characteristics of the tissues. The sublingual mucosa is more permeable and thinner than the buccal mucosa and because of the considerable surface area and high blood flow; it is a feasible site when a rapid onset is desired. The sublingual route is generally used for drug delivery in the treatment of acute disorders, but it is not always useful. It is because its surface is constantly washed by saliva and tongue activity which makes it difficult to keep the dosage form in contact with the mucosa. Unlike the sublingual mucosa, the buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of controlled-release system which is well accepted by patients. The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. The buccal mucosa is relatively permeable, robust in comparison to the other mucosal tissues and is more tolerant to potential allergens which have a reduced tendency to irreversible irritation or damage. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies. However, salivary production and composition may contribute to chemical modification of certain drugs [1]. Moreover; involuntary swallowing can result in drug loss from the site of absorption. Furthermore, constant salivary scavenging within the oral cavity makes it very difficult for dosage forms to be retained for an extended period of time in order to facilitate absorption in this site. The relatively small absorption area and the barrier property of the buccal mucosa contribute to the inherent limitations of this delivery route. Both the buccal and sublingual membranes offer advantages over other routes for administration. For example, drugs administered through the buccal and sublingual routes have a rapid onset of action and improved bioavailability of certain drugs. These routes can bypass the first-pass effect and exposure of the drugs to the gastrointestinal fluids. Additional advantages include easy access to the membrane sites so that the delivery system can be applied, localized, and removed easily. Further, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity [2]. The palatal mucosa is intermediate in thickness and keratinized thus lessening its permeability. All of these epithelia are coated with a layer of mucus. Bioadhesive polymer can significantly improve the performance of many drugs, as they are having prolonged contact time with these tissues. These patient compliance controlled drug delivery products have improved drug bioavailability at suitable cost.

Drug selection for oral transmucosal delivery is limited by the physicochemical properties of the drugs themselves. To be delivered

i.e. a proper balance between solubility and lipophilicity. Generally only a few milligrams of drug can cross the oral mucosa, even if the drug has a favorable profile for oral mucosal delivery. Presently, new classes of drugs are typically not developed specifically for oral transmucosal delivery. Therefore, drugs considered for oral transmucosal delivery are limited to the existing products. Until there is a drastic change in the selection and development process of new drugs, candidates for oral transmucosal delivery will continue to be limited. Many products on the market, however, have shown unique properties and advantages of this delivery route. The key in the future will be to involve drug delivery and formulation scientists early in the drug selection process, so that more drugs that are suitable for delivery routes other than oral and parental can be developed [3].

## 2. Overview of the oral mucosa

### 2.1. Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium [4]. The epithelium of the buccal mucosa is about 40–50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

### 2.2. Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4–4000 times greater than that of the skin [5]. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeability of the oral mucosae decrease in the order of, sublingual greater than buccal, and buccal greater than palatal [6]. This ranking is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. Intercellular spaces at the upper one-third of the epithelium. This barrier exists in the outermost 200  $\mu\text{m}$  of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase and lanthanum nitrate. When applied to the outer surface of the epithelium, these tracers can only penetrate through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems apparent that flattened surface cell layers present are



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