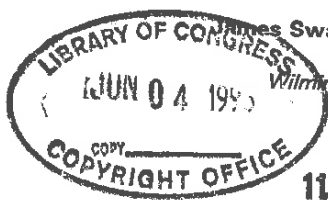


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**Oral Muc
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Specialized Oral M Delivery System

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I. INTRODUCTION

It is our view that the best illustration of what is involved in the development of mucosal (buccal) patches for the systemic delivery of drugs is our own experience. Our work covers the full range from development to clinical testing and assessing structure-property relations through studies in animals, tests of patch positioning and comfort in humans, and clinical studies of delivery efficacy. Recent publications on this subject are incorporated into this review, but much of what is reviewed here was published before. Our discussion is prefaced by a summary of the state of transmucosal drug delivery and the problems that must be overcome to produce a successful product. Many of these issues are reviewed in detail in the earlier chapters of this book.

The oral cavity has a number of features that make it an ideal site for drug delivery: a rich blood supply that drains directly into the systemic circulation bypassing the liver and sparing the drug from first-pass

of drug delivery even in unconscious patients and those who are permitted nothing by mouth [3]; ready termination of delivery by the healthcare practitioner or the patient; and an abundance of usable sites capable of recovering rapidly from any insult [3]. Therefore, despite its potential drawbacks - the physical and metabolic barriers to drug uptake and the numerous ways a drug or its delivery system can be lost [3] - many efforts have been made to utilize the oral surface clinically. The buccal mucosa was first investigated as a potential site for drug delivery several decades ago [4, 5], as it is an ideal surface for the placement of retentive delivery systems [2].

A. Pertinent Features of the Oral Mucosa

The mucosa of the mouth may be thought of as a multilayer laminate [6]. The outer layer is the saliva, which may take the form of an unstirred fluid layer [7]. Several components of the saliva may affect transmucosal delivery (TMD) systems. For example, the high molecular weight mucin known as MG1 [7] may be important in bioadhesion. Saliva also contains several proteins, including some enzymes, that may bind or inactivate a drug, reducing the concentration available to drive absorption [3, 8]. The pH of saliva is between 6.5 and 7.5 [3].

The next layer, the epithelium, may be either partly keratinized or entirely nonkeratinized, the former type being less permeable to hydrophilic drugs [8]. In the buccal region, the epithelium is nonkeratinized and approximately 500 to 600 μm in thickness [9]. Chronic inflammation and physical damage to the epithelium may reduce its barrier function (increase the permeability) [7]. Underlying the epithelium are a basement membrane (basal lamina) and the lamina propria. The latter is readily permeable to many drugs, whereas the former may limit the rate at which some drugs (e.g., β blockers) are absorbed [6]. The blood flowing through the vessels in the lamina propria acts as a sink for drugs delivered transmucosally [9].

B. Pertinent Features of Drug Uptake from the Oral Mucosa

Drugs applied to the oral mucosa gain access to the circulation principally by passive diffusion according to Fick's law¹ [1, 3]. For the most part, drugs move

¹ Specialized transport systems such as carrier-mediated transport or facilitated diffusion are operative for a small number of drugs; cefadroxil being one example [6].

Patches

extracellularly and follow, not the shortest path, but the path of least resistance [6], which for most agents is through the neutral lipid spaces that separate the cells. The lipid solubility of a candidate drug is an important measure of its suitability for a TMD system. The rate of passive diffusion involves nonionized species, and the rate is an important [6, 7].

C. Pertinent Considerations in the Design of a TMD System

Successful transmucosal drug delivery requires a vehicle that is (i) bioadhesive to maximize the intimacy of contact with the mucosa sufficient for optimal drug delivery and to retain the drug in the cavity; (ii) a vehicle to release the drug at an appropriate rate under conditions prevailing in the mouth; and (iii) a vehicle that is sufficiently permeable of the oral mucosa (increase bioavailability).

The drug selected for a TMD system must have properties, including size and pKa, that will allow it to be absorbed into the mucosa at a rate sufficient to produce a sustained level in the blood [1, 6, 10]. It must either resist or be able to overcome metabolic barriers in the form of salivary and tissue enzymes. The other materials must not damage the teeth (e.g., cause demineralization, keratinolysis, discoloration, irritation, allergenicity, or alter the microflora) and they must not produce an objectionable taste or odor.

A TMD system may be unidirectional (i.e., release drug into the mucosa) or bidirectional (i.e., release drug into the mucosa and absorb drug). It must be of a surface area and thickness acceptable for the drug and releasing sufficient drug for therapeutic need. Patches having a surface area of 0.5 to 1 cm^2 are generally acceptable. Patches may be tolerated. The shape and conspicuity are also other considerations. Lastly, the TMD system must be in the proper position.

The principal mechanism for bioadhesion of a TMD system is the physical entanglement of the adhesive polymer chains with the glycoprotein chains overlying the mucosa [11]. Other mechanisms, such as secondary (electrostatic, hydrogen, hydrophobic) interactions, may be less important mechanisms. The binding properties are affected by its molecular weight, configuration, and degree of ionization, concentration, and extent of crosslinking. The duration of adhesion is affected by the type of adhesive polymer, its viscosity, and the method of patch manufacturing.

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