Designing drugs for transmucosal delivery in the oral cavity, what are the optimum chemical properties?

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The clinical challenge:
Delivery of some drugs into the bloodstream can currently only be achieved via injection. This usually requires administration by a health worker, can be painful for the patient and can cause local tissue damage. While injections are practical for single doses an alternative delivery method is desirable where repeated treatment is required for chronic diseases.

The oral mucosa:
The oral mucosa is the epithelial lining of the oral cavity, which includes the tongue, cheeks, palate and gums. The oral mucosa provides a unique opportunity to deliver drugs into the bloodstream thereby avoiding the harsh environment of the gastro-intestinal tract and first pass metabolism in the liver that prevent many drugs from being delivered orally (eg. via tablets and syrups) [1]. The oral mucosa is a multi-layer stratified squamous epithelium comprised of cells called keratinocytes. The basal keratinocytes divide and replenish cells above to maintain a healthy epithelium. As the cells move towards the surface they differentiate and change their behaviour and composition. Cells stop proliferating, become flattened and produce large amounts of keratin, the protein responsible for the waterproofing of the skin.
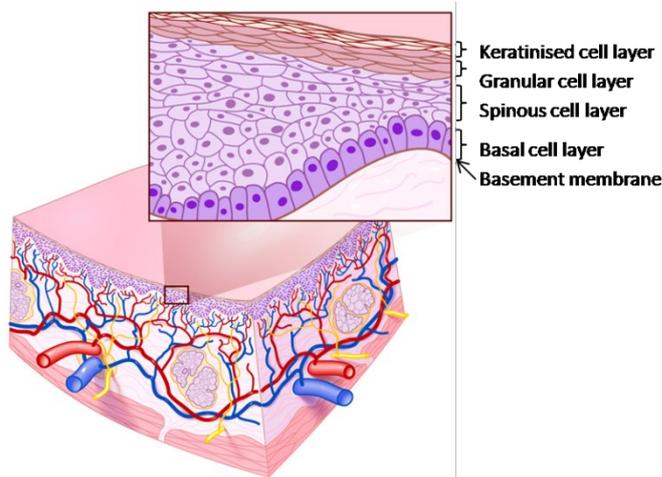

Figure 1 Figure taken from reference [2]. Cartoon showing the structure of the oral epithelium (in box) and the underlying structure of the connective tissue.

Why should we deliver drugs via the oral mucosa?
The oral mucosa has several features which make it an ideal site for drug delivery. The oral cavity is well hydrated aiding in the solubility of drugs and it is easily accessible for self administration. The oral mucosa repairs itself quickly and is well vascularised making entry into the bloodstream rapid and direct. Unfortunately, there are also limitations to this method of drug delivery method, most importantly the permeability barrier.

The permeability barrier:

The oral mucosa is a protective tissue designed to prevent unwanted materials such as pathogens from entering the body and keeps the underlying tissue hydrated by preventing fluid loss. This means drugs cannot freely pass across the epithelium but are hindered by the permeability barrier. The permeability barrier is predominantly found in the lipid rich upper layers of the epithelium (granular layer). The supra-basal cells have strong desmosomal junctions and form membrane coating granules, which release lipophilic materials into the extracellular space. This enhances keratinocyte adhesion but also slows the passage of hydrophilic materials. However, different areas of the mouth display different levels of permeability barrier and the area below the tongue (floor of mouth) has a thin epithelium that is significantly more permeable than other areas of the oral mucosa making it an ideal site for drug delivery.

What do we know?
There are large amounts of data available regarding the permeability of drugs across the skin, and there are several mathematical models available to predict trans-dermal permeability, reviewed here [3]. By comparison little is known about the materials which most easily cross the oral mucosa. While some of the features of the skin permeability maths models are adaptable to the oral mucosa, the stratum corneum of the skin, which is the predominant rate limiting step, is not present in most areas of the oral mucosa as there is far less keratinisation.
There are a number of studies which have looked at the permeability of select compounds across the oral mucosa: dextran [4], tritiated water [5], horseradish peroxidase [6], TGF-β3 [7] and various chemical markers [8] however extensive studies on a wide range of compounds has not been conducted.

Parameters that affect drug permeability
The permeability of a drug across the oral mucosa will be dependent on: the lipophilicity of the drug, the molecular weight of the drug, the probability of the drug binding to proteins or cells within the oral mucosa and the charge or ionisation of the drug. Compounds which have small molecular weight, good lipid solubility and non-ionised species are believed to be the most easily diffusible [2]. However, the relative importance of each of these factors and the optimum range of each parameter is yet to be elucidated. Other important practical factors include the susceptibility of drugs to be degraded by enzymes in the oral cavity, the solvent used to solubilise the drug prior to administration, the medium used to deliver the drug (paste, gum, spray, patch, lozenge or gel) and the concentration of drug at administration.
Designing the ultimate transmucosal treatment will be a trade off between drug efficacy, permeability through the epithelium and solubility in the bloodstream; information on the relative importance of compound properties will be crucial.

Questions for modellers:
- What drug properties are the best for diffusion across the oral mucosa?

- Which property contributes greatest to the permeability coefficient of a particular substance (eg. size, lipophilicity, charge etc.)?

- What data is needed to produce an accurately predictive model of drug delivery across the oral mucosa?

- What is the optimal concentration of drug that can be delivered per unit of time (drug stability may be a crucial factor) to reach the required therapeutic dose in the blood stream?

References
1. Wikipedia. *First pass effect*. 2012 [cited; Available from: http://en.wikipedia.org/wiki/First_pass_effect.
2. Hearnden, V., et al., *New developments and opportunities in oral mucosal drug delivery for local and systemic disease.* Adv Drug Deliv Rev, 2012. **64**(1): p. 16-28.
3. Anissimov, Y.G., et al., *Mathematical and pharmacokinetic modelling of epidermal and dermal transport processes.* Advanced Drug Delivery Reviews, 2012(0).
4. Hoogstraate, A.J., et al., *Diffusion Rates and Transport Pathways of Florescien Isothiocynate (FITC)-Labelled Model Compounds Through Buccal Epithelium.* Pharmaceutical Research, 1994. **11**(1): p. 83-89.
5. Galey, W.R., H.K. Lonsdale, and S. Nacht, *The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water.* J Invest Dermatol, 1976. **67**(6): p. 713-7.
6. Squier, C.A. and B.K. Hall, *The Permeability of Skin and Oral Mucosa to Water and Horseradish Peroxidase as Related to the Thickness of the Permeability Barrier.* J Investig Dermatol, 1985. **84**(3): p. 176-179.
7. Squier, C.A., et al., *Oral Mucosal Permeability and Stability of Transforming Growth Factor Beta-3 In Vitro.* Pharmaceutical Research, 1999. **16**(10): p. 1557-1563.
8. van Eyk, A.D. and P. van der Bijl, *Comparative permeability of various chemical markers through human vaginal and buccal mucosa as well as porcine buccal and mouth floor mucosa.* Arch Oral Biol, 2004. **49**(5): p. 387-92.