D9G : Oro-Mucosal Dosage Forms Development Background Paper

Introduction

This background paper is intended to provide a basic rationale for initial formulation efforts, and define some of the terminology which will be used in future discussion as the project advances.

Initial Formulation Objectives

To develop suitable formulations for the delivery of medical marihuana (cannabis)/ phytocannabinoids derived therefrom (e.g. CBD), and terpenoids, to human patients in need of treatments for specified clinical conditions. Initial clinical indications would be in the areas of oncology (cancers, of various types), pain relief, immuno-stimulation, and inflammatory conditions. All four target areas would often be inter-connected, and simultaneously present in the same patient, so a multi-pronged approach to product development should be adopted.

Our initial focus will be upon Oro-Mucosal dosage forms, containing phytocannabinoids and terpenoids active agents, as delivery systems. The development of additional, supportive, non-cannabinoid botanical formulations is also planned.

Background Physiology Considerations

A schematic of the human oral cavity is presented (*Figure 1*).
There are four basic regions which may be targeted for delivery of active ingredients when the administered dosage form is retained in the mouth:

- Sublingual (floor of mouth, under the tongue)
- Buccal (cheeks)
- Gingival (gums)
- Palatal (roof of mouth)

Collectively these are referred to as the Oro-Mucosal absorption routes.

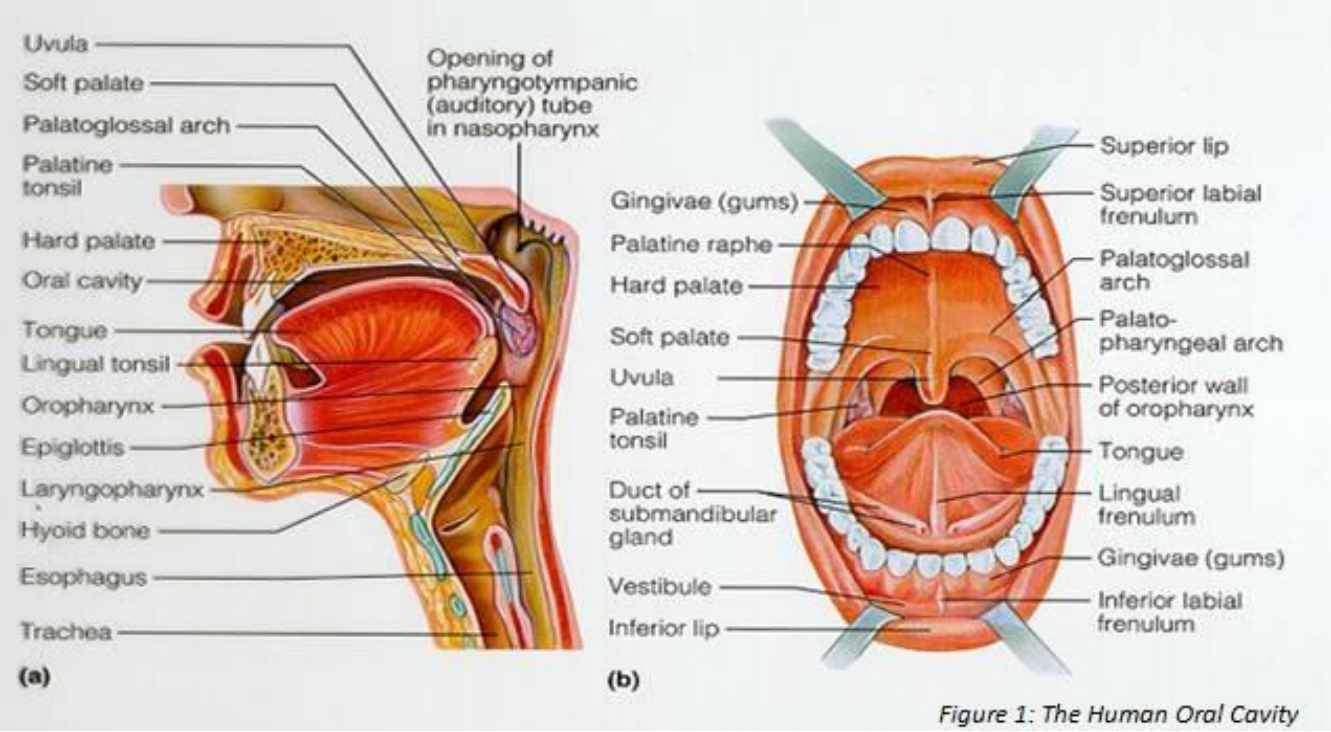

Figure 1: The Human Oral Cavity

When medicinal products are ingested orally and immediately swallowed they traverse the gastro-intestinal tract (GIT), with disintegration/dissolution occurring in the acidic gastric fluid (stomach) and the majority of absorption occurring from the small intestine, which possesses the major exposed luminal (internal) surface area present within the GIT. Some substances are absorbed from the large intestine (colon), and this is also a site of major water absorption from the digestive fluid content of the GIT (water is also absorbed from the stomach).

Undigested and body metabolic wastes, and certain toxins ingested in the diet, are subsequently voided from the body as semi-solid feces, via the rectum.
Dissolved wastes, metabolites, and some intact actives are excreted via the urine and skin secretions. Some volatile wastes are exhaled via the lungs. Upon absorption of substances across the epithelial (lining) membranes of the GIT they pass through the portal circulation to the liver and thence into the general systemic blood circulation.

The liver is the major organ of detoxification, and contains a number of enzyme systems (including the microsomal P450 system) that metabolise and inactivate a wide array of molecular structures that are essentially foreign to the body (a basic defence mechanism against potential toxins), e.g. many administered drugs. This initial inactivation is referred to as the hepatic first pass metabolism, and can significantly reduce the amount of an active drug that initially reaches the systemic circulation and is available for its desired pharmacological activity at the target site, i.e. it can seriously diminish the bioavailability of the drug.

Some administered active ingredients are also partially metabolised during their passage across the GIT epithelial lining, with a concomitant result that they are also less available for activity at the target sites.

The Oro-Mucosal route of administration, whereby the dosage form is retained in contact with one or more of the target absorption regions for a period of time, essentially avoids hepatic first pass metabolism.

All of these regions are provided with a rich source of blood, via their respective capillary networks, which drain directly into the venous circulation via a common trunk. The following sequence of drainage then occurs: internal jugular vein → subclavian vein → branchiocephalic vein → superior vena cava → general systemic circulation. Thus they avoid the hepatic first pass metabolism, and can rapidly and directly reach their target sites, at higher concentrations than would generally be realised by oral ingestion (swallowing).

Hence dosage forms that access these sites of absorption are of significant interest as a means of improving the bioavailability of a therapeutic agent (and, potentially, reducing the effective dosage level compare to simple oral ingestion).

Product Development Considerations: Oro-Mucosal Dosage Forms

The pH range of the oral cavity (salivary pH range typically 5.6 to 7.6) is more restricted than that of the GIT, hence provides less of a challenge in producing stable formulations of active ingredients that may be degraded by extremes of pH, for example the acidic gastric fluid of the stomach. The mucus component of saliva is negatively charged, so may interact with certain active molecules that ionise in aqueous solution and bear a positive charge, thereby potentially reducing the degree of absorption.

Systemic absorption of molecules occurs by one or more of the following mechanisms:

- Simple (passive) diffusion
- Carrier-mediated diffusion
- Active transport
- Internalisation by epithelial membranes (pinocytosis, receptor-mediated endocytosis)

Basic routes of absorption, depending upon the physicochemical characteristics of candidate molecules, are:

- Transcellular transport (across cell membranes) – generally lipophilic molecules, or some hydrophilic molecules via aqueous pores in the membranes
- Paracellular transport (via intracellular aqueous spaces) – generally hydrophilic molecules

Molecules possessing dual hydrophilic and lipophilic characteristics (amphiphilic) may access a combination of both routes.

It is generally considered that uncharged molecules cross epithelial membranes in a more facile manner (in the absence of any specific active or carrier-mediated transport mechanism).

We are planning to develop a series of patent pending Oro-Mucosal formulations, comprising solution, emulsion, and micro-emulsion delivery systems. Other dosage forms scheduled in our research and development program include muco-adhesive and rapidly dissolving sublingual solid dosage forms, lozenges, gummies, and sprays.

Oro-Mucosal Route Advantages

- ✓ Rapid onset of action (generally within minutes)
- ✓ Relatively large surface area for absorption
- ✓ Higher initial concentration at target sites
- ✓ Avoids hepatic first pass metabolism
- ✓ Avoids potential food effects
- ✓ Avoids extreme pH (e.g. gastric fluid), most GIT digestive enzymes, and bile degradation effects. Note that saliva does contain a limited number of digestive enzymes, e.g. amylase (starches) and lingual lipase (lipids)
- ✓ Suitable for elderly and younger patients who may have difficulty in swallowing oral solid dosage forms
- ✓ Potentially improved patient compliance
- ✓ May be more appropriate for those patients prone to emesis on ingestion, as a result of their treatment regimen or disease

Oro-Mucosal Route Disadvantages

- Not ideally suited for larger doses (i.e. more suited to potent, relatively low-dose actives). The buccal region may be a more appropriate candidate for a higher dosage muco-adhesive delivery system
- Formulation challenges for high molecular mass (weight) molecules
- Possible flavour-masking requirements for actives having an objectionable taste
- Tendency to prematurely swallow saliva, before optimal absorption has occurred
- The sublingual and gingival regions are constantly washed by saliva and movements of the tongue, both of which would decrease the effective concentration of active ingredients at these sites, and tend to increase the possibility of a dosage unit being prematurely removed from the region due to swallowing. Note that the buccal and palatal regions are less prone to such effects.
- Smoking (tobacco) causes vasoconstriction of the capillary networks and may lead to reduced absorption.

Note: Our enabling formulation technologies optimise the advantages and minimise the disadvantages of this route of administration.

General Description of D9G Oro-Mucosal Delivery Systems In Vivo Characteristics

Oro-Mucosal dosage form – cannabinoid and terpenoid active ingredients in a homogeneous molecular solution/dispersion (true solution, suspension, or emulsion type) throughout the delivery system matrix →

Rapidly dissolve/disperse as a solution or solubilized fine emulsion and micellar dispersion in the saliva →

Active ingredients diffuse through the epithelial membrane – certain formulation ingredients render this more permeable to the active ingredients →

Rapid absorption through the epithelial membrane into the systemic circulation →

Active molecules interact with endocannabinoid system receptors to initiate their pharmacological effects →

Avoids initial passage through the liver and biotransformation into psychoactive 11-Hydroxy-THC, and other inactive metabolic conjugates (hepatic first pass metabolism)→

Advantages of D9G's Oro-Mucosal Formulations

1. Formulations designed for enhanced dispersion/micellization/dissolution into the saliva, thereby promoting improved bioavailability of the active ingredients

2. Permeability enhancers increase the rate and degree of absorption into the systemic circulation, thereby enhancing bioavailability

3. Pleasant to take, thereby improving dosage regimen compliance

4. All formulation ingredients of high purity/pharmaceutical grade, and suitable for Oro-Mucosal administration

5. Formulations are of consistent and reproducible physical and chemical properties

6. The Oro-Mucosal route of administration substantially avoids the hepatic first pass metabolism effect. Thus higher levels of un-metabolised circulating active ingredients initially reach the target receptors, prior to biotransformation of THC in the liver to 11-Hydroxy-THC, which is reported to be 4 to 10 times more psychoactive than the parent THC molecule. It is postulated that prior occupancy of the receptors with un-metabolized THC should effectively block them from interaction with 11-Hydroxy-THC for a period of time, thereby moderating the initial 'high'

7. Comprehensive analytical testing of active ingredients extract and dosage forms ensures consistent quality, freedom from unwanted contaminants such as pesticides/heavy metals/microbial species, uniform and predictable dosage delivery and potency of the active ingredient