Rectal Suppository 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 suppositories, containing phytocannabinoids active agents, as a delivery system. Other rectal dosage forms that may be considered include enemas. Additional, supporting non-cannabinoid, botanical suppository formulations are also under development.

Background Physiology Considerations

A schematic of the human gastro-intestinal tract (GIT) is presented (*Figure 1*)
When medicinal products are ingested orally (swallowed) they traverse the 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).

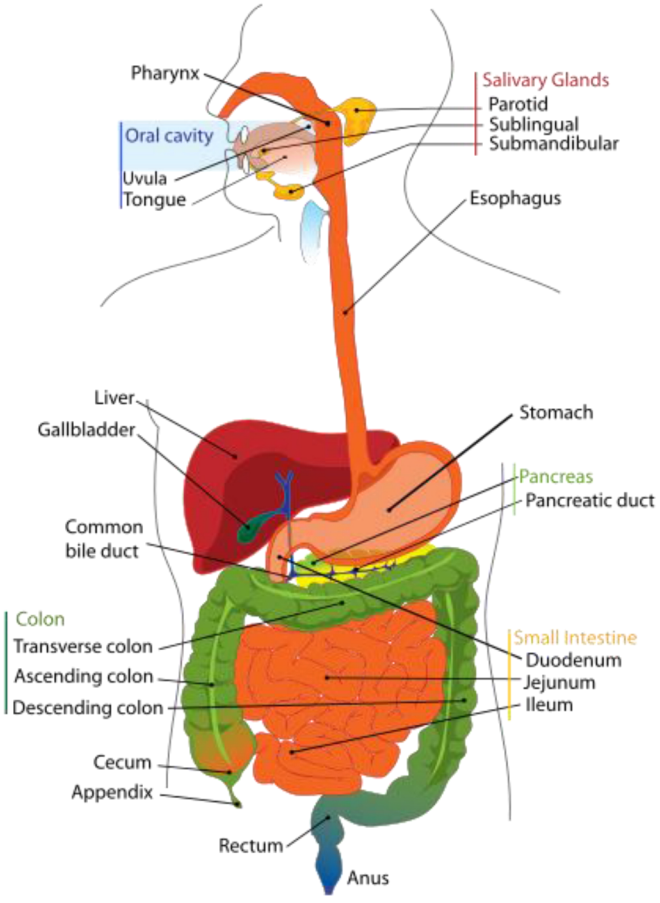

Figure 1: The Human Gastro-Intestinal Tract

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 (*Figure 2*) Dissolved wastes, metabolites, and some intact actives are excreted via the urine and skin secretions. Some volatile wastes and actives 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.

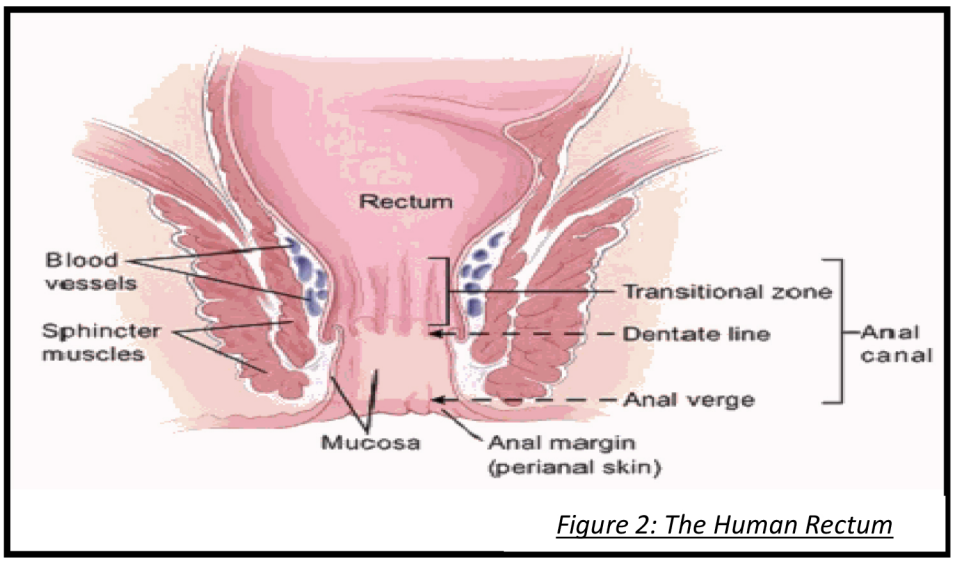

Figure 2: The Human Rectum

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 it's 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 unavailable for activity at the target sites.

The rectal route of administration (lower and middle regions of rectum) essentially avoids hepatic first pass metabolism. This region is richly supplied with blood (via the capillary network) and capable of significant absorption over a short period of time. Hence dosage forms that access this site 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: Suppositories

Let us consider the suppository dosage form, which will initially be a 2mL (approximately 2g) tapered unit, a common size for administration to adults. Other suitable unit sizes for adults are 2.3g and 2.8g. Suppositories for pediatric usage are smaller (e.g. 1g). This dosage form should be solid at ambient temperature (say up to 30C) and liquefy at 36-37C once present in the rectum.

We have designed a series of patent pending suppositories formulations having three different durations of in vivo activity: rapid release, intermediate release, and extended release. The particular onset of action, and active ingredients composition, chosen is tailored for the type of clinical treatment required, for example rapid release for pain relief, and intermediate or extended release for conditions of night-time pain relief, sedation, and insomnia. The rapid and intermediate release suppositories liquefy at rectal temperature, whilst the extended release suppositories dissolve over a set period of time for more prolonged release.

Spreading into the colon should not be significant. The rectum usually contains a limited amount of aqueous fluid (typically 1-3mLs, in the absence of feces), so the suppository formulation would be designed to facilitate dissolution of active agents as rapidly and completely as possible. Typically, the adult rectal region would be 15-20cm in total length.

General Description

- ✓ Solid dosage form (suppository) – cannabinoid and terpenoid active ingredients in a homogeneous molecular solution or dispersion (solid molecular solution/dispersion) throughout the solid suppository matrix) →
- ✓ Liquefies/dissolves at body temperature (37C/98.6 F) →
- ✓ Rapidly dissolves/disperses as a solubilized fine emulsion and micellar dispersion in the rectal fluid →
- ✓ Active ingredients diffuse through the liquid rectal contents to reach the epithelial membrane – certain formulation ingredients render the epithelial membrane more permeable to the active ingredients →
- ✓ Rapid absorption through the epithelial membrane into the systemic circulation via the extensive rectal capillary network →
- ✓ 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. Continued passage around the systemic circulation