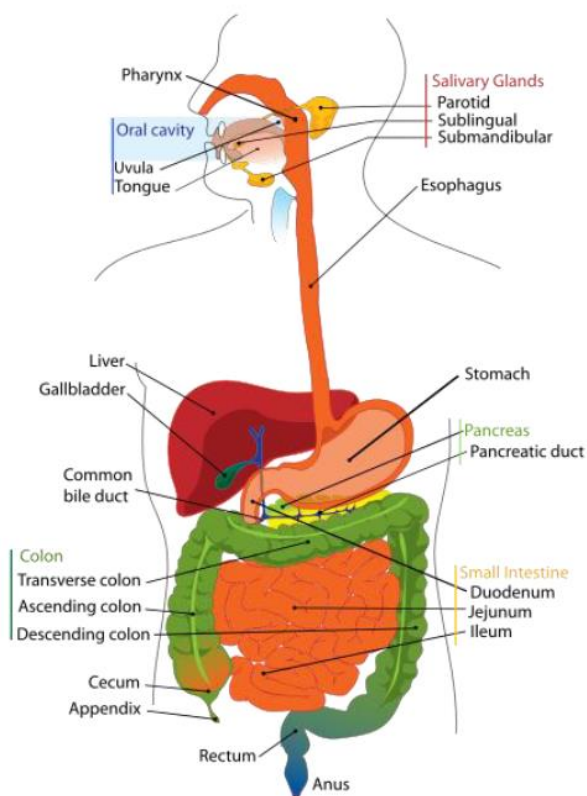


VAGINAL SUPPOSITORY INFORMATION USAGE AND DOSAGE PRIMER

This information applies to recreational and medical suppositories.



Background Physiology Considerations



This is a schematic of the human gastrointestinal tract (GIT). 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).

The liver is the major organ of detoxification and contains a number of enzyme systems that metabolise and inactivate a wide array of molecular structures that are essentially foreign to the body (a defense mechanism against potential toxins – ie many administered prescription 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.

The vaginal route of administration 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 compared to simple oral ingestion.

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Active ingredients administered via the vaginal route may exert either local or systemic effects.

The vagina (*Figure 2*) is richly supplied with blood, via the extensive capillary network and lymphatic vessels. This region is capable of significant absorption over a short period of time. Upon absorption across the mucosal epithelium active ingredients pass into the general circulation, bypassing the liver. Some active ingredients may also be absorbed into the lymphatic vessels, depending upon the physicochemical properties. This route of administration essentially avoids the hepatic first pass metabolism of active ingredients, when dosage forms are correctly inserted.

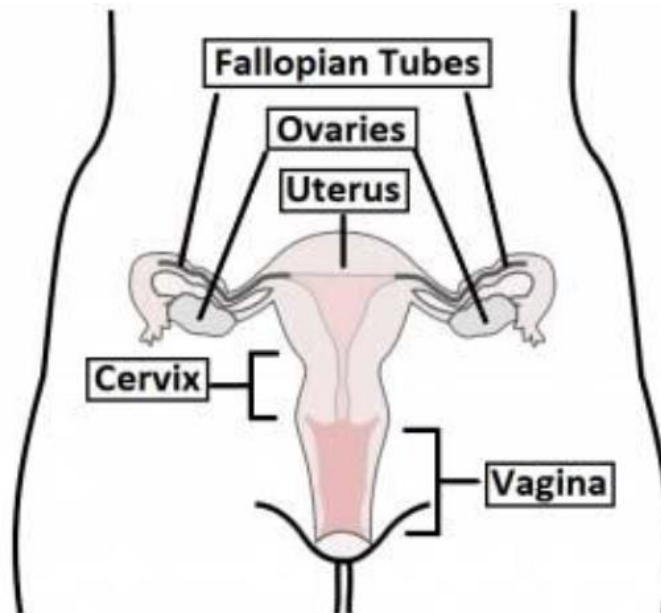


Figure 2: Female Reproductive System

Key Advantages of Vaginal Suppository Administration Route

1. When correctly inserted (1 ½ inches) significantly avoids the liver (hepatic) first pass metabolism, and initial significant conversion to 11-Hydroxy-Delta-9 THC (5-10 times as psychoactive as Delta-9 THC), therefore less of a 'high'. Gains direct access to the systemic blood circulation.
2. Compared to oral administration avoids degradation during digestion and absorption (by acidic gastric fluid, bile, enzymes).
3. Lower dosages of cannabinoids and terpenes than required when dosing orally should be equally effective.
4. Suitable for patients/consumers that have difficulty in swallowing oral solid dosage forms (e.g. the elderly), those suffering from vomiting (e.g. cancer patients on chemotherapy and radiotherapy), unconscious individuals, and those sensitive to gastric irritation or with gastric ulcers.



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5. No problems with unpleasant tasting active agents.
6. Rapid and extensive absorption directly into the systemic blood circulation, with a typical onset of activity within 15-30 minutes post insertion, and a duration of activity of several hours.

Specific Advantages of Suppositories Formulations

As compared to suppositories formulated with a coconut oil or cacao butter base:

1. Do not need to be refrigerated to prevent softening and subsequent difficulties in handling and insertion. OK for storage at ambient temperatures of up to 30 C/86 F.
2. Do not have the same problems in processing and storage as coconut oil/cacao butter-based suppositories, which are sensitive to processing and storage temperatures, leading to inconsistent in-use melting ranges and difficulties in handling/insertion.
3. All formulation ingredients are of pharmaceutical or food grade quality, and suitable for vaginal usage. Suppository base consists of highly refined vegetable lipids, with consistent and reproducible stability and chemical and physical properties.
4. Contain antioxidants, to protect the suppositories from development of rancidity on storage due to atmospheric oxidation.
5. Suppositories formulated to readily melt at body temperature and disperse to form a fine emulsion in the vaginal fluid. This creates a very large surface area of lipid droplets containing the active cannabinoids and terpenes, thus enhancing their rate and consistency of absorption into the systemic blood circulation. Simple coconut oil/cacao butter bases typically melt at body temperature but do not disperse into fine emulsion droplets, so would not be expected to demonstrate the same degree of effectiveness for a given dosage strength.
6. Formulations incorporate penetration enhancers, to facilitate absorption of active cannabinoids and terpenes across the vaginal lining membrane and into the systemic blood circulation.
7. Formulations specifically designed for enhanced bioavailability and superior effectiveness (efficacy).
8. Backed by comprehensive analysis of all formulation ingredients and the final suppositories finished products.

Dosage and Usage Information

- 1) Your suppositories come ready for use, in their own protective casings. It is recommended to wear disposable medical gloves whilst handling and inserting a suppository.



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- 2) Hold the suppository with the pointed end uppermost and facing you. The outer casing should be carefully removed, by gently peeling each side tag downwards to release the contents. Do not exert excessive sideways pressure on the casing during the operation.
- 3) For hand insertion, immediately insert the suppository, pointed end first by gently pushing it with the index finger in the vagina (about 1 to 1 ½ inches).
- 4) Try to minimise the length of time the suppository is in contact with your hands, to prevent softening.
- 5) You can insert the suppository in any comfortable position: standing, squatting, bending forward at the waist, standing with one foot raised on a chair or stool or lying on your left side. Discard the medical gloves if used and wash your hands.
- 6) Storage of your suppositories should be in a dry place, protected from light, and at a temperature not exceeding 30 degrees C (86 degrees F). Higher temperatures may cause progressive softening and could cause difficulties in handling and insertion. Should softening occur your suppositories may be placed in the refrigerator for 15 minutes...do not freeze! Always allow the suppository to reach room temperature prior to insertion.
- 7) Suppositories should not be used if you are pregnant, breast feeding an infant, have severe liver or kidney disease.
- 8) If you experience irritation or discomfort while using the suppositories, discontinue use.
- 9) KEEP OUT OF REACH OF CHILDREN