REVIEW ARTICLE

Rectal and Nasal Drug Delivery Systems: Next-Generation Solutions in Disease Therapy

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Abstract

For protein-peptide medications, rectal drug delivery is a good substitute for parenteral and oral modes of administration since it avoids first-pass metabolism and delivery. Drug therapy can be administered locally or systemically thanks to rectal delivery. For patients who are unconscious or unable to swallow, the rectal drug delivery device is a helpful substitute for the oral route of administration. Historically, localized treatments such as the delivery of laxatives, hemorrhoids, and antipyretics have been administered using conventional rectal dosages. The rectal drug delivery method may have untapped potential thanks to continued research and development in this field. The current study offers a number of benefits and drawbacks, as well as optimizations and drug selection criteria. There is a discussion of the rectum's anatomy and physiology, dose forms, rectum drug absorption-related aspects, absorption obstacles, and absorption enhancers for use and assessment. This review also covers polymers utilized for the rectal medication administration route.

Key words: Aggregation of amyloid, Alzheimer's disease, DDS and rectal drug delivery system, mucoadhesive drug delivery, RDDS

INTRODUCTION

When pharmaceuticals or treatments are administered through the rectum for either local or systemic effects, this is referred to as rectal drug delivery. Rectal medication delivery systems are one kind of mucosal adhesive drug delivery method.

These methods offer both an efficient carrier and mucoadhesion, or the drug's attachment to the mucosal membrane.[1] Rectally administered hydrogels have demonstrated that hydrogels, which are cross-linked with ethylene glycol dimethacrylate and employ hydroxyethyl methacrylate as a model drug to provide rate-controlled drug delivery, including theophylline and antipyrine.[2,3] For a long time, the rectal route was limited to administering laxatives, vermifuges, antibacterials, local anesthetics, and anti-hemorrhoidal drugs.[4] A better, more economical, and more efficient treatment for Alzheimer's disease (AD) is desired due to the irreversible damage of neurones, increasing loss of memory and cognitive function, the high expense of therapy, and the impact on society. The nose-to-brain administration method has the potential to reach the brain without the blood-brain barrier getting in the way. It also increases the bioavailability of anti-AD medications, which improves their therapeutic efficacy.

ADVANTAGES

It is possible to prevent the stomach and small intestine irritation that these drugs cause. Examples of non-steroidal anti-inflammatory medications include aspirin, ibuprofen, and naproxen.

- A greater number of medications, peptides, and low-molecular-weight proteins are absorbed.
- Steer clear of interactions with digestive juices to stop the enzymatic and acid breakdown of such medications.

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For instance, low amounts of protease activity, especially from pancreatic origin, are provided by rectal delivery of protein peptide medications.

- Hepatic first-pass elimination of high-clearance medications can be partially avoided. For example, lidocaine, morphine, and propranolol.
- Rectal drug delivery is beneficial for elderly, pediatric, and comatose patients, particularly those who have trouble swallowing oral medications.
- By altering the dosage and absorption of prescription drugs, drug delivery can be prevented. If oral intake is reduced, as is the case before X-ray testing, before surgery, or in patients with upper gastrointestinal tract issues, this can prevent accidental overdose or suicide.
- It is possible to provide medications rectally that are often exclusively given by parents. For instance, peptides and other substances.[5]

ANATOMY AND PHYSIOLOGY OF RECTUM

The colon, rectum, and anal canal all contain the four tissue layers shown in the basic organisation of the gastrointestinal tract. The longitudinal muscle fiber organisation is altered in the colon. Three bands known as taeniae coli are dispersed throughout the colon at regular intervals rather than forming a single layer of tissue. At the rectum-sigmoid colon junction, they stop. The colon appears sacculated or puckered because these bands of muscle tissue are much shorter than the colon's overall length.

Similar to the basic anatomy, the longitudinal muscle fibers completely enclose the rectum and the anal canal.[6]

The circular muscle layer thickens to form the anal sphincters. With more lymphoid tissue than any other area of the digestive tract, the submucosal layer offers broad protection against resident and microbial invasion. Numerous goblet cells create tiny tubular glands that secrete mucus in the mucosal lining of the colon and the upper portion of the rectum. They live inside the region where the anus and rectum converge. The anus lining membrane is composed of stratified squamous epithelium that merges in with the skin and is continuous with the mucous membrane lining of the rectum above.[6]

The stratified squamous epithelium that forms the anus lining membrane continues parallel to the mucous membrane lining of the rectum and merges with the skin beyond the external anal sphincter. The mucous membrane in the upper portion of the anal canal is composed of 6–10 vertical folds called anal columns. The superior rectal artery and vein have terminal branches in each column.[7]

Blood supply

The superior and inferior mesenteric arteries contain the majority of the vascular supply. The caecum, ascending, and a significant section of the transverse mesenteric arteries receive blood from the superior mesenteric artery. The proximal portion of the rectum and the remainder of the colon receive blood flow from the inferior mesenteric artery. Branches of the internal iliac arteries supply blood to the anus and the distal portion of the rectum. The superior and inferior mesenteric veins, which draw blood from the corresponding arteries, are the primary causes of venous congestion. Blood Supply and Venous Drainage. The portal vein is created when these veins combine with the splenic and stomach veins. The veins that drain the anus and the distal part of the body are entered by the internal iliac veins.[8]

DRUG ABSORPTION IN THE RECTUM

Transcellular and paracellular transport pathways are the two ways that drugs are absorbed from the rectal epithelium. The paracellular system involves the diffusion of medications over the gap between epithelial cells, whereas the transcellular pathway relies on lipophilicity for its absorption mechanism. Suspensions and suppositories absorb slowly and persistently, but alcoholic and aqueous solutions absorb rapidly. Compared to acidic solutions, alkaline solutions absorb more quickly.[9]

Among the strategies to improve the drug's absorption through the rectal route are: (i) Modifications to the mucosal membrane barrier's function. (ii) Chemically modified medications to increase the partition coefficient. Figure 1 illustrates the rectal

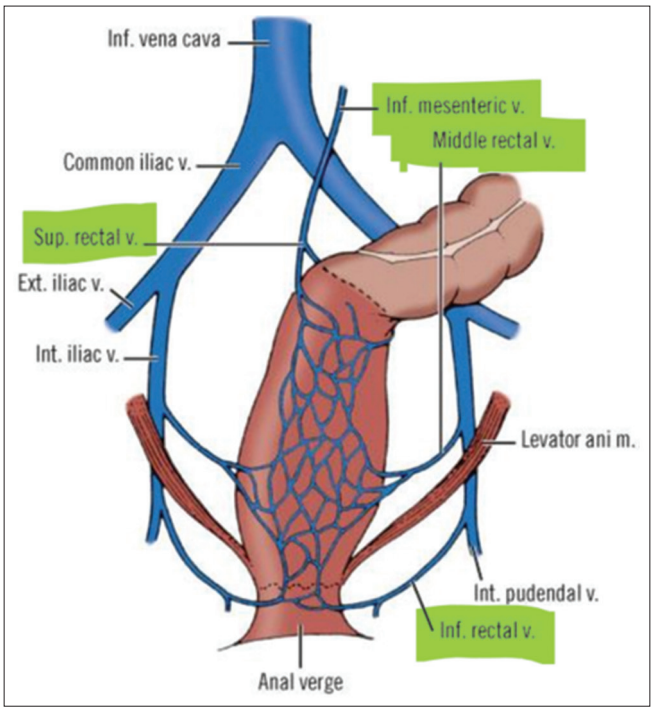

Figure 1: Rectal drug delivery

drug delivery pathway, demonstrating the administration and absorption of drugs through the rectal mucosa. This route improves systemic or local drug delivery while partially avoiding first-pass hepatic metabolism. Figure 2 illustrates the nasal drug delivery pathway, highlighting drug absorption through the nasal mucosa for rapid systemic and nose-to-brain delivery. This route offers a non-invasive approach with enhanced bioavailability and a rapid onset of therapeutic action.

METHODS

Rectal drug administration can be done in any of the following ways:

- A suppository is placed in the rectum
- A micro-enema is a tiny injection of a liquid medication solution into the rectum, often <10 mL
- A large enema is used to administer a liquid medicinal solution into the colon
- A specialized catheter that can be securely inserted and comfortably remain in the rectum for recurrent usage, intended for the rectal administration of medications and drinks.[9]

FACTORS AFFECTING RECTAL DRUG ABSORPTION

Physiological elements

- Colonic content: Strongly ionized acids and bases are absorbed more rapidly, while weaker acids and bases in the rectal cavity have a higher pH. The medicine may be more likely to be absorbed when the rectum is empty.

Physicochemical elements

- Ionization degree: Because unionized pharmaceuticals have a high degree of ionization, they are highly absorbed

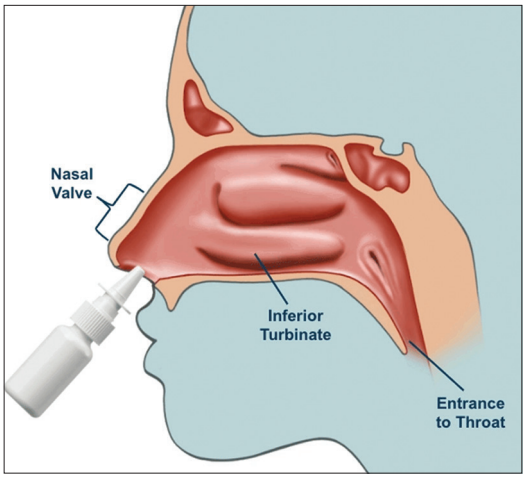

Figure 2: Nasal drug delivery

- Particle size: Better polishability and increased wear resistance are associated with smaller particle sizes. enhancing the intestinal and rectal absorption of poorly absorbed drugs.[10]

Physical alteration

Greater solubility and more efficient drug transfer are associated with higher concentrations. The compositions work in a variety of bases to maximize absorption.

Modification of chemicals

The primary objective is to maximize drug dissolution by improving the solubility of poorly water-soluble drugs. Increasing the partition coefficient and reducing hydrogen bond formation are also crucial for increasing membrane affinity.[11]

Changes to the formulation

- The dissolving stage of poorly water-soluble medications (such as insulin suppository) was improved by combining a barrier system with a formulation modification technique
- A typical transcellular transport pathway involves both paracellular and transcellular pathways, both of which rely on lipophilicity
- In the osmosis process, drugs are transported from the suppository formulation's carrier via the membrane and into the hemorrhoid veins through the rectum. Medications pass through the gaps between epithelial cells, according to the paracellular transport technique.[12]

Absorption barriers include things like a mucus layer, a movable water layer, and chemical barriers.

RECTAL DRUG DELIVERY APPLICATION

The diazepam solution is rapidly and fully absorbed, reaching a peak plasma concentration in 5–15 min; antiepileptic drugs are delivered rectally, and the first-pass metabolism of antiepileptic drugs may be partially blocked. When given by rectal formulation, carbamazepine, lamotrigine, levetiracetam, phenobarbital, topiramate, and valproate were found to be bioequivalent to oral tablets and oral suspensions.[13]

THROUGH THE RECTAL ROUTE, PAINKILLERS

Compared to oral controlled-release tablets, morphine controlled-release suppositories are used more frequently

(bigger area under the curve). In addition, it was employed to investigate medication effects and pharmacokinetic interactions in the steady-state intensity time course.[14]

Table 1 summarizes the major categories of rectal therapeutic agents, their clinical indications, and associated adverse effects. It provides a comparative overview of commonly used rectal medications, including local anaesthetics, steroids, vasoconstrictors, antiseptics, and astringents, to facilitate the selection of appropriate therapy based on clinical indications and safety profiles.

ENHANCERS OF ABSORPTION

- Chemical alteration, such as insulin's acyl derivatives and enamine derivatives
- Potent chelating agents
- Fatty acids
- Salicylates and their derivatives aid in the rectal absorption of hydrophilic antibiotics and polypeptides
- Cyclodextrins and protease inhibitors in the rectal cavity for medication administration.[15]

VARIOUS RECTAL DOSAGE FORM TYPES

- Creams, gels, ointments, and suppositories are examples of semisolid items used in the rectal area
- Rectal suspensions and liquid solutions.

The respiratory system's aerosols Ointments, gels, and creams for the rectal area: These medications include anti-inflammatory medications like hydrocortisone, lubricants like lanolin and cocoa butter, protectants, astringents like zinc oxide, and local anesthetics like pramoxine HCL. They are frequently applied topically to alleviate inflammation, anorectal pruritis, and the associated pain and suffering.

RECTAL SUPPOSITORIES

- Adult rectal suppositories are typically solid dose forms in the form of a torpedo, containing either water-soluble (dissolving) or fatty (low-melting) bases, and weighing between 1 g (children) and 2.5 g.
- Hydrophilic therapies are made in fatty base suppositories, while lipophilic medications are frequently added to water-soluble bases; the amount and rate of drug release are determined by the makeup of the suppository base
- Suppositories containing fatty bases may melt quickly at 37°C, which is close to body temperature
- Because the drug releases slowly from the suppository base, the resulting would readily melt and flow to offer modest, wide coverage to the rectal region, reducing lag time effects.[16]

TECHNIQUES FOR MAKING SUPPOSITORIES

(I) Compression molding (II) fusion/pour molding (III) hand rolling.[16]

METHOD FOR DOUBLE CASTING

- Following lubrication, the suppository is wrapped in aluminum foil or another appropriate material, with an adequate amount of lubricant and an indication (KEEP IN A COOL PLACE)
- These include commercial suppository products such as ANUSOL HC (hydrocortisone), CANASA (mesalamine), DULCOLAX (bisacodyl), NUMORPHAN (oxymorphone), and PANADOL (paracetamol).
- Acetaminophen, Eucalyptol, AnucortHC, and Glycero-Gelatin Laxative.[17]

RECTAL FLUIDS

Rectal dose forms have very few applications, primarily because they are inconvenient and patients do not follow instructions. These formulations are frequently employed to deliver imaging agents and contrast fluids for lower gastrointestinal (GI) roentgenography.[16]

Table 1: Applications of cyclodextrins in drug rectal delivery

Category	Indication	Adverse effects
Anaesthesia locally	Anal pain following anal surgery, anal fissures, and strangulated hemorrhoids	Anal cryptitis or proctitis and local discomfort
Steroids	Anal fissures, pruritus, hemorrhoids, and inflammatory anorectal conditions.	Absorption into the system for local use
Vasoconstrictors	Hemorrhoids, pruritus, anal cryptitis, and Cryptitis, and anorectal inflammation.	Local response
Antiseptics	hemorrhoids. Thrombosis with hemorrhoids	Flushing, tachycardia, and headache
Astringents	Anal fissures, anal cryptitis, and proctitis	Burning, local irritation, and pruritus

SUPPOSITORIES' EVALUATION

Variation in weight

The average weight is used to measure and estimate all suppositories; except for two, which may vary by up to 7.5%, no suppositories should deviate from the average weight by more than 5%.

Test of disintegration

Six suppositories are subjected to the disintegration process utilizing a tablet disintegration test instrument.

- The medium is 160 milliliters of distilled water at 37°C
- Calculate how long it will take for the suppository to dissolve entirely.

Breaking the test

- It is meant to serve as a method for determining brittleness or fragility
- The ideal breakpoints are the values that can tolerate the break forces brought on by the production, packing, shipping, and storage of variously shaped suppositories
- Water is injected into the device's double-walled chamber at 37°C.

The macro melting range test

For the macro melting range test, the temperature is gradually raised, and the temperature at which the mass liquefies is noted. The mixture is put into capillary tubes that are 10 cm long and 1 cm high. The tubes are then dipped into a beaker of water.

Drug content the suppositories are dissolved in the appropriate solvent to determine the drug content.

Liquefaction time and temperature

It is possible to determine the temperature and liquefaction/softening time using a designed apparatus. One side of a large pipette has a narrow opening, whereas the other side has a broad one. Immersing the pipette in heated water that is maintained at 37°C with the thin end facing the hot water.

Dissolution test

For *in vitro* dissolving testing of suppositories, a wire mesh basket or a membrane is utilized to isolate the sample chamber from the reservoir in the pill dissolution test apparatus.

- One suppository is used as a dissolution medium in each test, with a buffer at 37 ± 0.5°C and a predefined rpm
- At predetermined intervals, five milliliter samples are extracted using a syringe fitted with a pre-filter and filtered through Whatman filter paper. At each interval, the temperature is maintained at 37 ± 0.5°C, and the same volume of fresh dissolving media is added to the volume withdrawn.

After removing a suitable sample, the absorbance at a specific wavelength is measured using a UV-visible spectrophotometer to assess the sample for drug release.

CONCLUSION

The rectal drug delivery device provides patients with a less intrusive option by delivering the medication to sleeping patients, elderly patients, and kids. Given its benefits in enhancing drug absorption with enhancers and its effectiveness as a sustained-release formulation for the long-term treatment of chronic illnesses, rectal medication administration will surely be a pioneer in the formulation of many challenging substances.

Rectal administration can therefore result in a broader adoption of medication delivery methods by enhancing particular technologies to encourage patient acceptability. Pregnant women, children, and comatose patients are also treated with it.

Despite its benefits, the rectal route is still not widely used for medication delivery. The oral route is the most practical and advised way to deliver medications, despite a number of reported situations; sadly, this is not possible from a pharmacological or therapeutic perspective. Rectal administration of medication can be a helpful alternative to both systemic and local action in certain circumstances. Extensive research on the biological interactions of rectal pharmaceutical administration and continuous improvements in rectal drug formulation are required to fully realize the promise of this route to treat systemic and local disorders, chemotherapy, and allergy-induced emesis.

We conclude that to enhance efficacy and avoid adverse effects, it is crucial to optimize the various ways of administration in addition to creating novel medications.

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