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RECTAL DRUG DELIVERY SYSTEM

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ABSTRACT

The route of administration is the way through which the dosage form is administered into the body for treatment of various diseases and disorders. Various routes of administrations play a marked role in the bioavailability of the active drug in the body. In present review these routes are included with their advantages and greater limitations. This is an attempt for the initials of field to familiarize with the routes of administrations with their significances.

Several routes of drug administration, including extravascular (oral, intramuscular, subcutaneous, transdermal, inhalation, etc.) and intravascular routes (intravenous and intra-arterial), are used to deliver drugs into the body. Oral administration of drugs is the most common route because it is relatively convenient and safe. Many factors - including the physicochemical properties of drugs, type of formulation, physiology of the gastrointestinal tract (GIT), other drugs, and food - affect the way in which drugs are absorbed after oral administration. Although drug absorption occurs in the mouth and stomach, it takes place mostly in the small intestine due to the large surface area. After oral administration, the drug must pass through the intestinal wall and liver in order to reach the general circulation. The drug metabolism enzymes in the intestinal wall and liver metabolize many drugs, thereby decreasing the amount of drug that is bioavailable. This phenomenon is often referred to as first- pass metabolism. The acidic environment and digestive enzymes in the stomach may also chemically degrade some drugs, resulting in erratic absorption. In contrast, drugs administered intravenously do not undergo absorption and therefore the entire dose reaches the general circulation intact.

ROUTES OF ADMINISTRATION

CLASSIFICATION :

Routes of administration can broadly be divided into

A. Topical:

Drugs are applied topically to the skin or mucous membranes, mainly for local action.

B. Oral :

Used for systemic (non-local) effect, substance is given via the digestive tract.

C. Parenteral:

A drug administered parenterally is one injected via a hollow needle into the body at various sites and to varying depth.

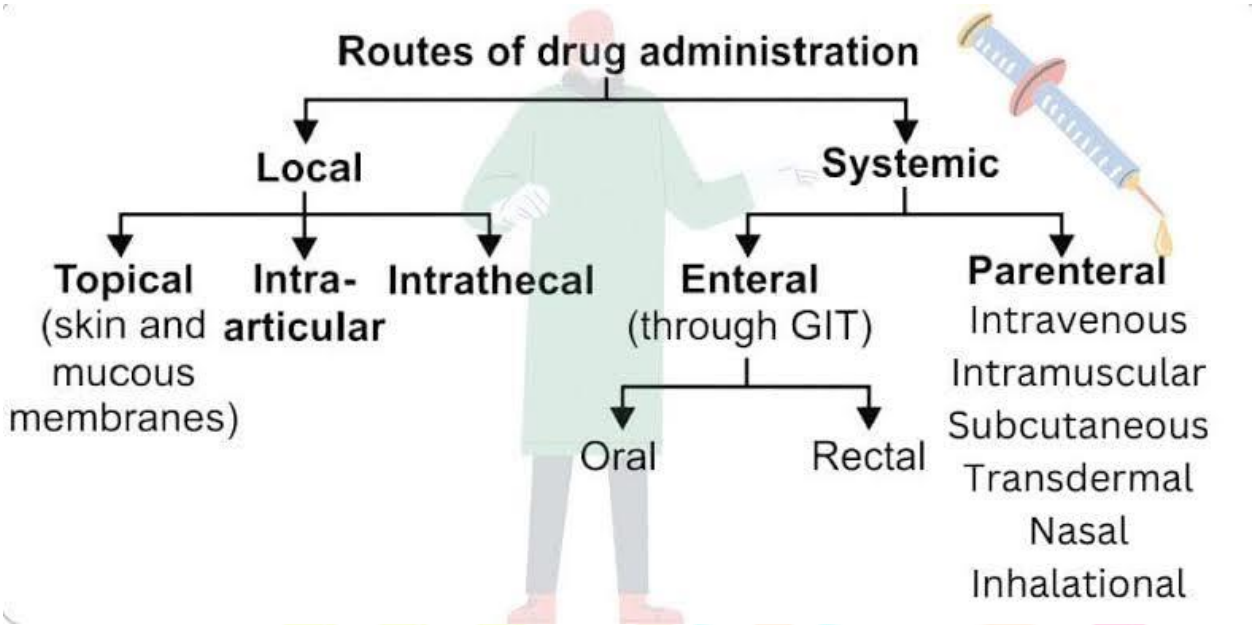
D. Rectal:

Drugs given through the rectum by suppositories or enema.

E. Inhalation:

The Jungs provide de an an excellent surface for absorption when the drug is delivered in gaseous, aerosol or ultrafine solid particle form.

ROUTES OF ADMINISTRATION



INTRODUCTION TO RECTAL DRUG DELIVERY SYSTEM

Rectal drug delivery is the practice of administering pharmaceuticals or remedies for either local or systemic effects through the rectum. Rectal medication delivery systems are one kind of mucosal adhesive drug delivery method .These systems offer mucoadhesion, or the drug's attachment to mucous membranes .the mucosal membrane in addition to a powerful carrier. Rectally Hydrogels employ hydroxyethyl, As evidenced by the given hydrogels.
The prototypical drug for rate-controlled medication delivery is methacrylate. containing antipyrine and cross-linked with ethylene glycol Dimethacrylate as well as theophylline .The rectal route was used for a very long time was only used as a vermifuge, anti-hemorrhoidal, and local anesthetic administration of laxatives and antibiotics
A standard suppository is a solid dosage form of medication that melts or softens with body temperature .It is a good dose form for babies, kids, and slumbering patients. One significant benefit of the advantage of suppositories over other oral doses Drugs administered by suppository do not go through the first pass effect on the liver and digestive systems .In addition, the suppositories are less uncomfortable and more superior to parenteral forms. Though, The typical solid-type suppositories frequently provide the Patients report feeling strange, uncomfortable, and unwilling Additionally, if the suppository without mucoadhesion reaches the end of the intestine, the drug released from the suppository will cause the first reaction. From a commercial perspective, wicks are difficult to manufacture and operate because heating is required to melt the wick and fill it into the container. To ensure that the quality of the suppository is maintained until application, the packaging must be packaged together. To solve the problems of traditional suppositories, a suppository that forms a gel at body temperature; it must have sufficient gel strength and no water from the rectum; There is sufficient bioadhesion to prevent reaching the end of the intestine[2].

A standard suppository is a semisolid dosage form that melts or softens at body temperature and is intended for insertion into a bodily cavity. Infants, kids, and patients who are unconscious can take it in an adequate dosage form. The fact that suppositories do not experience the first-pass effect in the liver and gastrointestinal tract is a significant advantage over oral dosing forms. However, the traditional solid suppositories have drawbacks that cause the patient to reject them due to their discomfort and alienation. Drugs may experience the first-pass effect if solid suppositories without mucoadhesivity reach the end of the colon. By creating a liquid suppository, the issue with conventional solid suppositories can be resolved.
It forms a gel at body temperature, has a strong enough gel to prevent leakage from the anus after administration, and has a strong enough bioadhesive force to prevent reaching the colon's end. Ibuprofen-loaded liquid suppositories were created by Choi and colleagues using an eutectic mixture system with menthol and poloxamer P 188 as a base. It was discovered that these suppositories could be inserted into rats' recta without difficulty or leakage. Additionally, it was believed that rats might absorb drugs from liquid suppositories more readily than those from solid ones. Pharmaceutical scientists have recently become more interested in mucoadhesive polymers as a way to enhance drug delivery by increasing residence time and contact time with the mucous membranes. Barkat created and tested a rectal etodolac poloxamer gel system made of bioadhesive polymers and poloxamer. They came to the conclusion that an in situ gelling suppository containing etodolac and mucoadhesive polymers such as microcrystalline cellulose and carbopol was a secure, practical, and efficient way to administer the drug. The goal of this review is to examine how to administer medications effectively. It focuses on the factors affecting medication bioavailability, the role of surfactants and mucoadhesive polymers in increasing bioavailability, and the rectal bioavailability of pharmaceuticals. Additionally, it emphasizes suppository bases, standards to assess liquid and solid suppositories For the treatment of partial and secondary generalized seizures, carbamazepine (CBZ) is frequently utilized. However, neither tablets nor powders are ideal formulations for kids who detest oral dosage or for some individuals with epilepsy who have trouble swallowing or have poor absorption from the gastrointestinal tract (70–80% of human patients). Due to CBZ's low water solubility, it is very slow and highly variable when it is absorbed from the gastrointestinal system. Rectal administration is therefore seen as more suitable for these young epileptic individuals. Regarding the clinical use of CBZ suppositories, The current study's objective was to assess the potential clinical utility of CBZ suppositories made with Witepsol H-15 and Witepsol S-55 bases made of polyethylene glycol and triglycerides of saturated fatty acids. The bioavailability of CBZ from the three different types of suppositories was compared to that seen in rats following CBZ delivery via intravenous and oral routes. Additionally, in vitro testing was done on the CBZ suppositories' CBZ release properties.

A] Cocoa butter is the natural fat extracted from the seeds of the Theobroma cacao tree. Its melting point is between 34 and 38 °C, and it is slightly soluble in water, very slightly soluble in boiling water, and practically insoluble in ethanol (95) and diethyl ether. Cocoa butter is pale yellow with a fragrant odour. Producers ferment, dry, roast, strip, and press cocoa beans to extract cocoa butter.

B] Hydrogenated vegetable oils extracted from , such as olives, sunflower, and soybeans it is Melting point are different types , type I, 57 - 85°C; type II, 20 - 50°C Iodine value: type I, 0 - 5; type II, 55 Hydrogenated vegetable oils Colour are white to Yellowish pleasant aroma and taste, there are Soluble in chloroform, petroleum spirit, and hot propan-2-ol; practically insoluble in water. C] Poloxamer 407 is made up of a hydrophobic residue of polyoxypropylene (POP) between the two hydrophilic units of polyoxyethylene (POE). Its melting point is between 53 and 57°C; there is a solubility in water and 95% in ethanol; the poloxamer 407 Colour is white. D) Polyethylene glycol is derived from natural gas or coal. Its melting point is 50°C, and polyethylene glycol is colorless and odourless . They are soluble in water.

MATERIALS AND METHODS

Combination base preparation:

Various suppositoriesbases were made using the fusion process.
Poloxamer 407, cocoa butter, and PEG 2000,and hydrogenated vegetable oil were blended in the 1:19 is the ratio.The many suppository base combinations
were exposed to the various evaluation criteria, including
such as form, toughness, melting point, and liquefactionhydroxyl value, timing range, and time.

METHODS

The fusion (pourmolding) approach was used to create hydrogenated vegetable oilsuppositories (Coben and Liberman, 1989).Vegetable oil that had been hydrogenated was placed in a porcelain dish and melted.The medication was dissolved in th melted oil, followed by the melted base in full dispersion, and the precalibrated mold was filled with the medication.(It is best to prevent quick cooling because it p roduces the suppositories into holes.) Gelatin is used for producing gelatin suppositories, was heated and added to the water. In the combination of weighed amounts of PEG 400 and propylene glycol drug and preservative (propylparaben) dosages, they added. The gelatin solution was then combined with this solution, which had been heated in a water bath to between 70 and 80 degree Put the solution into the calibrated mold and quickly cooled, which is highly important for suppositories made of gelatin. Drugs were placed into each .The 200-mg suppository. The suppositories were ready.were stored under were wrapped with aluminum foil refrigeration. 30 suppositories per batch were used in ready for every intended formulation

Combination base preparation: Various suppositories were made using the fusion process. Poloxamer 407, cocoa butter, and PEG 2000 and hydrogenated vegetable oil were blended in the 1:19 is the ratio. The many suppository base combinationswere exposed to the various evaluation criteria, including such as form, toughness, melting point, and liquefaction.the hydroxyl value, time, and meting range.

Evaluation of combinations of suppository bases:

appearance:

Suppositories were randomly chosen,and their surfaces were sliced lengthwise to examine how t hey appeared. evaluated with the unaided eye.

Weight variation:

The average weight of 20 suppositories was calculated after being weighed individually. The particular weight was assessed against the typical weight to make a decision. weigh differently.

Hardness:

By slicing the middle of three suppositories from each batch, the hardness of the suppository was assessed. It was assessed using a diametric measurement method Hardness measurement was made by a Monsanto hardness tester.

Melting range test:

The mixture was placed in capillary tubes with a 10 cm length and filled to a height of about 1 cm before being dipped in a beaker. having water in it. The temperature gradually increased, and the mass liquefied at a temperature of was recorded.

Liquefaction time:

It made use of a straightforward apparatus that was created in the lab. It was decided to cut a burette with a broken stopcock so that it has a narrow opening on one side and wide opening on the opposite side. They dipped the burette .With heated water that is kept at 37°C, with the thin end facing. direction of hot water. The test suppository contained injected through the broad end of the burette from the topand slowly pushed its length downward until it reached little end. After the suppository has completely melted, a glass rod reaches its thin end, which symbolizes the liquefaction period.

Hydroxylvalue:A 250ml conical flask was filled with suppository that was weighed to the prescri bed weight (W grams). APT reagent (acetic anhydride, pyridine, and toluene in 10 ml) It was then heated on a 3:2:10 ratio with the addition.until a clear solution was obtained, water b ath.the above solution was maintained at 60°C (30°F) in an oven (or water bath).25ml of distilled water were ad ded to it after a minute.The mixture was agitated briefly to hydrolyze theusing 1N KOH solution t o titrate the excess anhydride, utilizing phenolphthalein (A ml) as an indicator. The bottle was shook ferociously close to the end to flush out any acid from the top layer of toluene. The titration on a blank was carried out as before, but without the sample (B ml).

$$\text{Hydroxyl value} = \frac{(B-A) \times N \times 56.1}{W} \quad \text{----------(1)}$$

Where N, is normality of the KOH solution.

Method of preparation of solid suppository of CBZ

Utilizing several suppository bases, solid suppositories made of CBZ were created utilizing the fu sion method.The solubilizer was polyvinyl pyrrolidone, and sufficient preservatives and antioxidant were added.

Table 1. Composition of CBZ suppository

Batch	AC (mg)	BC (mg)	CC (mg)	DC (mg)
Carbamazepine	100	100	100	100
Cocoa butter	QS	42.5	-	-
Hydrogenated vegetable oil	-	QS	QS	QS
Poloxmer 407	-	-	42.5	-
PEG 2000	-	-	-	42.5
PVP K-30	50	50	50	50

Evaluation of CBZ suppositories:

visualcharacterization, melting range test, breaking strength (hardness), weight fluctuation, liquefa ction duration, and in vitro performance of the developed suppositories were evaluated. drug release in vitro.

Drug content:

Small fragments of five suppositories were removed.A precisely weighed quantity of fragments (1 00 mg) was added to a 100-ml volumetric flask along with 80 ml of phosphate buffer at pH 7.4. After 30 minutes of continuous shaking, buffers were applied.The loudness was then raised using the buffer.The resulting mixture was filtered and appropriately diluted, and at 286 nm, the solution's absorbance was measured.TheOn the basis of the calibration curve, drug co ntent was determined. (slope 0.50, intercept 0.022, and R2 0.993).typical of Three results were regarded as the average medication. the suppositories' composition.

In vitro drug release

CBZ suppositories' in vitro drug release experiments were conducted in USP XXII dissolving test equipment using a basket stirrer at 50 rpm and900ml of phosphate buffer pH 7.4 at 37° with 2 cc of tween 800.5oC. For each test, only one suppository w as used.At1 ml,samples were taken at predefined times,withdrawn, and replaced right away with 1 ml of fresh pH 7.4 for phosphate buffer. The samples underwent evaluation to assess the absorbance at 286 nm.To determine drug release,a UV-visible spectrophotometer was used. Cumulative Calculated and plotted was the percentage of drug released opposing time

Characterization of optimized suppository of CBZ:

IR Affinity's Attenuated Total Reflectance-Fourier Transform Infrared Spectrophotometer (ATR-FTIR) was used to capture the infrared spectrum of CBZ. Shimadzu MIRacle10, Japan. A small number of samples were taken and set down right on the IR platform. Next, the scans of spectra were performed in the range of 4000 to 400 cm1 at a 4 cm 1 resolution.Analysis using XRay Powder Diffraction (XRD)conducted to study the change in the CBZ's crystallinity in the suppository. XRD of CBZ, improved CBZ suppository formulation, Poloxamer and CBZ-free formulation were noted.using a Cu K-1 diffractometer and a Bruker D2 Phaserwith l = 1.5418 radiation.
Analysis using differential scanning calorimetry (DSC) was carried out to investigate the relationship between CBZ andbasis of suppository Using the Model-SDT Q600, DSC was performed on the CBZ and optimized formulations CC, poloxamer 407, and hydrogenated vegetable oil.
With a computerized data station, V20.9 Build20Samples were cooked in a pan made of aluminum at a rate of ten degrees Celsius per minute at 35–350°C.Thermal analysis was carried out inanatmospheric nitrogen.

CONCLUSION

Drug delivery via the rectum is a useful alternative route of administration to the oral route for patients who cannot swallow. Traditional rectal dosage forms have been historically used for localized treatments including delivery of laxatives, treatment of hemorrhoids and for delivery of antipyretics. However, the recent trend is showing an increase in the development of novel rectal delivery systems to deliver drug directly into the systemic circulation by taking advantage of porto-systemic shunting. The present review is based on research studies carried out between years 1969–2017. Data for this review have been derived from keyword searches using Scopus and Medline databases. Novel rectal drug delivery systems including hollow-type suppositories, thermo-responsive and muco-adhesive liquid suppositories, and nanoparticulate systems incorporated into an appropriate vehicle have offered more control over delivery of drug molecules for local or systemic actions. In addition, various methods for in vitro–in vivo evaluation of rectal drug delivery systems are covered which is as important as the formulation, and must be carried out using

appropriate methodology. Continuous research and development in this field of drug delivery may unleash the hidden potential of the rectal drug delivery systems.

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