Review Article

Drug Delivery on Rectal Absorption: Suppositories

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ABSTRACT

Studies the rectal membrane are interesting for biochemical research as well as providing a basis for the development of new formulations of poorly absorbed drugs such as some moderately large water soluble drugs and peptides. The rectal routes avoid hepatic first-pass effect. The rectum offers a relatively constant environment for drug delivery provided the drug is presented in a well absorbable form**.** The rate controlled dosage forms resulting in constant steady-state concentration of drugs in plasma selected therapeutic indications. The release rate of a drug dose from suppositories is affected by characteristics of the excipients (melting temperature and rate viscosity at rectal temperature hydro-lipophilic characteristics) hence with a difference in drug availability. The most interesting publications which have appeared within the last decade on the bioavailability of drugs from suppositories are taken into consideration. The rate and extent of rectal drug absorption are often lower than with oral absorption possibly an inherent factor owing to the relatively small surface area available for drug uptake.

Keywords: Rectal Drug Delivery, Rectal Absorption, Suppositories.

INTRODUCTION

The rectal dosage forms are not common because of cultural and psychological bases there are several advantages to administration by rectal route.

In cases of nausea and vomiting act taking medication orally may induce emesis so that drug is vomited before it absorbed. Irritation to the stomach and small intestine associated with certain drugs can be avoided. Hepatic first pass elimination of high clearance drug may be avoided partially. Its contact with digestive fluid is avoided, thereby preventing acidic and enzymatic degradation of some drug. When oral intake is restricted such as prior to x- ray studies, before surgery or in patient having diseases of upper GIT or when patient is unable to swallow. It is useful in pediatric, geriatric and unconscious patient specially having difficulty in swallowing oral medicine [1]. Drug delivery can be stopped by removing the dosage form and drug absorption can be easily interrupted in cases of accidental overdose or suicide attempts. Drug which traditionally is only given parentally may be administered rectally. These advantages for rectal dosing require devices or formulations with specific features to give the desired drug delivery system. Peptides and many other hydrophilic drugs are primarily developed as parental formulations Because of poor bioavailability after oral dosing [2]. For example, because the absorption site is near for administration site. Rapid absorption with a rapid increase in plasma drug level can be achieved. Formulations can be readily prepared to provide desired release characteristics. To maintain high concentrations of the drug and additives at the absorption site are possible. The rectal absorption of drugs have also appeared in the US and Japan where suppositories had not been previously well accepted from the cultural or emotional points of view. For a long period of time the rectal route was used only for the administration of local anesthetics, asthma, and nausea, anti-hemorrhoidal, vermifugal and laxative agents, and bacterial infections. Now the majority of natural and synthetic drugs are also formulated in the form of suppositories to produce a systemic effect. The elimination of drugs subject to the first-pass effect in liver or in gastrointestinal tract may be partially avoided by rectal administration. The major disadvantages of rectal suppositories; they are not preferred by patients; they are inconvenient. Rectal absorption of most drugs is frequently erratic and unpredictable. Some suppositories "leak" or are expelled after insertion [3].

Two problems first are associated with the oral absorption of these kinds of drugs. Firstly, most peptide drugs and some antibiotics are subject to chemical breakdown in either the stomach or the enzymatic milieu of the small intestine. If the target drugs are degraded before absorption can occur then oral dosage forms are not usually feasible [4].

Secondly, most peptide drugs and some antibiotics are simply absorbed too slowly to provide useful plasma levels for medication after oral administration. The small intestine requires the co administration of some absorption-promoting agents or adjuvant.

In order to an oral dosage form for such therapeutic agents one must protect the drug from enzymatic degradation (in some cases) and simultaneously overcome the impermeable nature of the mucosal barrier[5].

The problem of enzymatic degradation by concentrating an absorption sites is free digestive enzymes. These

administration routes have been nasal and rectal mucosa. Both of these potentially drug-absorbing areas lack large concentrations of digestive enzymes maintain a selective barrier to the absorption of many drugs.

The second problem increasing the permeability of target mucosa has been approached by identifying permeation enhancers or absorption adjuvant. For examples, synthetic or semi-synthetic surfactant and bile salts [6].

FACTOR AFFECTING RECTAL ABSORPTION

A drug is dependent on such partition coefficient and molecular size observed for poor absorption from the small intestine. (Including rectum) route of administration such as: small partition coefficient, large molecular size, charge, and high capability of hydrogen bond formation. To improve intestinal/rectal absorption of poorly absorbed drugs.

Physical modification

The higher concentration greater solubility and the more efficient is transfer of medication. It may influence absorption in the rectum the mucus layer the variable volume of rectal fluid the basal cell membrane the tight junctions and the intracellular compartments may each constitute local barriers to drug absorption depending on histological factors and the molecular structure of the administered drug. In rectal absorption both low and high molecule weight compounds in a constant ratio of absorption. The rectum is an interesting area for drug absorption because it is not buffered and has a neutral pH. It has a very low enzymatic activity enzymatic degradation does not occur. It provides a sufficiently adequate surface area for drug absorption. The surface area is also permeable to non-ionized drug. The formulations are efficient in different bases to increase absorption [7].

Chemical modification

To increase the partition coefficient and decrease hydrogen bond formation to improve the affinity to the membrane. It is also used to increase the solubility of very poorly aqueous soluble drugs to improve dissolution [8].

Formulation modification

A Drugs or medicament are administered through a different route the most common oral and parenteral route while rectal route is less commonly used in routine practice.

Its poorly aqueous soluble drugs to improve the dissolution step development (e. g insulin suppository) involved a combined technique of formulation modification and modification of the barrier system. The barriers function of the rectal mucosal membrane using absorption-promoting adjutants [9].

A Drugs mixed with various adjuvant and administered through the rectal route provide satisfactory pharmacokinetics with acceptable local tolerance. In (osmosis process) drug

Transfer from the vehicle in the suppositories formulation across the membrane through rectum into the hemorrhoid veins.

The transcellular and paracellular route, it depends on lipophilicity and involved in a typical transcellular transport route. Active transport for amino acids, carrier mediated transport for beta lactam antibiotics and dipeptides, pinocytosis, microvilli fusion.

The paracellular transport mechanism implies that drugs diffuse through a space between epithelial cells [10].

RECTAL MEMBRANE

The surface area absorbing of the rectum is smaller than that of the small intestine as the lack villi and micro villi. However, the epitheliums of the rectum the upper intestinal tract are similar and then compare abilities to absorb drugs. In humans rectum comprises the last 12-19 cm of the colon and the rectal epithelium is formed by a single layer of columnar or cubical cells and goblets cells its surface area is about 200-400 cm^2 [11].

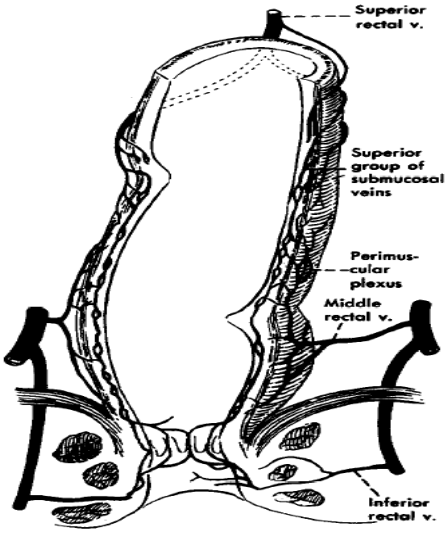

Figure 1: Human Rectum

The veins of rectum comprise the superior hemorrhoid vein which drains into the inferior mesenteric and portal system the middle and inferior hemorrhoid veins which enter systemic venous circulation via the internal iliac veins.

The inferior and middle hemorrhoid veins bypass through the liver and do not undergo first pass metabolism. The rectal mucus is more capable of tolerating various drug related irritations than the gastric mucosa [12].

Therefore, the drugs delivered through suppositories to the lower and middle hemorrhoid veins are absorbed rapidly and effectively.

Absorption Barriers

a) Mucus layer

It is providing a stable pH environment the mucus layer adjacent to the colonic mucosa acts as a diffusion barrier. It's a measured the movement through the colonic mucus

and compared it with movement through synthetic gels and the unstirred layer. They found no difference in the movement through mucus at different sites in the colon the movement was only 50% of that through the unstirred layer and equivalent to its movement through an area[13]. Mucus production in the colon is a function of goblet cells and as the proportion of goblet cells increases with age (though mainly due to a loss of other types of cell) this may be a factor that changes. Mucins are degraded by the colonic bacterial flora. Thus changes in the intestinal flora induced by diet or drugs may also affect the mucus layer. The mucus layer may also be affected by disease and is thinned by the action of prostaglandins [14].

b) Movable water layer

The centre of the colonic lumen to the mucosa it passes through regions of decreasing mixing. At the mucosal surface there is a layer of relatively unstirred water. All molecules must pass through this area by diffusion, and thus molecular size and other determinants of infusibility such as polarity will affect the movement of a drug towards the mucosa. Some viscous soluble dietary fibers may increase the thickness of this layer by reducing intra luminal mixing [15].

c) Chemical barriers

Some dietary fibers such as pectin and chitosan have cation-exchange properties which may bind charged molecules such as bile acids. This binding is increased at the low pH encountered in the colon and may be a factor in the immobilization of some drugs. In addition drug molecules could be trapped within the solid matrix of the concentrated dietary residue or within the entangled chains of a soluble dietary fiber [16].

Table 1: Category of Suppositories Indication and adverse effects

Category	Indications	Adverse effects
Local anesthetics	Anal pain due to strangulated hemorrhoids, anal fissure and post anal surgery.	Local irritation and anal cryptitis or proctitis
Steroids	Hemorrhoids, anal fissures pruritus ani	Systemic absorption on prolonged use
Astringents	Anal cryptitis, pruritus ani hemorrhoids	Local reaction
Vasoconstrictors	Hemorrhoids, hemorrhoidal thrombosis	Headache, flushing, tachycardia.
Antiseptics	Proctitis, anal cryptitis anal fissures	Pruritus, local irritation and burning

APPLICATION OF RECTAL DRUG DELIVERY

Controlled release dosage forms

The constant conditions of rectum environment offer interesting possibilities for controlled rectal drug delivery in an osmotic device with zero order drug delivery. In its characteristics, constant steady state concentrations in plasma and saliva were obtained. Concentration time profiles were not influenced by defecation and renewal of dosage form. It also used to study pharmacokinetic interactions and intensity time course of drug effects in steady-state [17].

Controlled rectal absorption enhancement

The rectum is quite constant and the rectal route has been considered to be interesting to achieve controlled rectal absorption enhancement of drugs. In addition the area under plasma concentration time curve (AUC) was significantly larger by following rectal infusion than rectal bolus administration. This indicates that the rate of administration of drug together with enhancement of rectal absorption is an important issue for resulting (AUC)[18]. Its recovery from cellular damage cause by absorption enhancers and the possibility of absorption and other compounds such as end toxins.

In case of repeated dosing and therefore information about repair it is necessary to apply safely for absorption enhancement. However, the liver functions important organ for detoxification which seems to reduce part of safety issues less importance although the partial by pass of liver following rectal delivery represent a compromising circumstance[19]. This relationship is complicated by pharmacokinetics (absorption rate, dose, etc., which influences the kinetics of enhancer in particular its concentration-time profile at its site of action) and the pharmacodynamics (intensity and duration of effect, etc. which determines its concentration-effect relationship) of the enhancer [20].

There may be substantial species differences in the rectal absorption enhancing effects. The extent and rate of drug absorption and the bioavailability of absorption enhancement and it's dependent on the concentration of enhancer at the apical membrane in rectal lumen. If the concentration changes absorption of enhancer like (t = 0) the apical membrane. Administration of drug with and without enhancer was assumed to be a bolus solution [21].

Sustained-release dosage form

It is quite observed in absorption or release of drugs from suppositories so this effect called lag time. However, it is not often considered for calculation of the area under the curve (AUC) and area under the first moment curve (AUMC) Plasma concentration (C)-time (t) plots of many drugs from suppositories are characterized by the difference in two exponentials:

$$C = Be^{-\lambda_2 t} - Ae^{-\lambda_1 t}$$

A and B are the corresponding zero time intercepts λ_1 and λ_2 denote the apparent first-order fast and slow disposition rate constants, respectively, and t is time. It should be taken into consideration that A exceeds B because there is a lag time (Tc=0).

A variety of approaches have been investigated for producing controlled-release suppository formulations of

different drugs. These include modification of the suppository base use of additives and polymer-coated drug particles [22].

A new type of double-phase suppository with two different drug release mechanisms (fast-release and sustained-release) was developed. However the double-phase suppository showed approx 2-fold enhancement of the mean residence time.

The use sustained-release suppository for reduce the frequency of drug administration. And it was prepared by direct hydroxyl propyl cellulose with drug. A glyceride base was used for preparation of a conventional suppository.

The plasma levels following the hydroxyl propyl cellulose suppository remained high greater than the supposed minimum level of effect being maintained over 6 h. Sustained-release formulations such as suppositories may reduce the dosing frequency [23].

Suppositories

The term suppositories have its origin in Latin and means, "to place under". Suppositories are a medicated solid dosage form intended for insertion into the body orifices. Suppositories and creams are the two main modes of administration of drugs through the rectum. They are used to deliver both systemically acting and locally-acting medications. The general principle is that the suppositories is inserted as a solid, and dissolve or melt inside the body to deliver the medicine pseudo received by the many blood vessels that follow the larger intestine. The suppository was first used in nursing facilities to be administered elderly patients who were not capable of taking medications. Suppositories come in various sizes and shapes which facilitate their insertion and retention in the cavity. Adult rectal suppositories weighed about 2 g while those for children are about half that weight. The suppository may be useful as a sustained release formulation for the long-term treatment of chronic diseases like essential hypertension, asthma, diabetes, AIDS, anemia, etc. Furthermore there is a growing interest in the possibility of rectal administration in the treatment of post-operative pain or malignant pain [24].

a) Methods of Preparation

Suppositories can be extemporaneously prepared by one of three methods.

I) Hand Rolling

It is the oldest and simplest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base. It has the advantage of avoiding the necessity of heating the cocoa butter. A plastic-like mass is prepared by triturating grated cocoa butter and active ingredients in a mortar. The mass is formed into a ball in the palm of the hands, and then rolled into a uniform cylinder with a large spatula or small flat board on a pill tile. The cylinder is then cut into the appropriate number of pieces which are rolled on one end to produce a conical shape. Effective hand rolling requires considerable practice and skill. The suppository "pipe" or cylinder tends to crack or hollow in the center, especially when the mass is insufficiently kneaded and softened.

II) Compression Molding

It is a method of preparing suppositories from a mixed mass of grated suppository base and medicaments which is forced into a special compression mold. The method requires that the capacity of the molds first be determined by compressing a small amount of the base into the dies and weighing the finished suppositories. When active ingredients are added, it is necessary to omit a portion of the suppository base based on the density factors of the active ingredients.

III) Fusion Molding

It involves first melting the suppository base and then dispersing or dissolving the drug in the melted base. The mixture is removed from the heat and poured into a suppository mold. When the mixture has congealed the suppositories are removed from the mold. The fusion method can be used with all types of suppositories and must be used with most of them. When they are mixed, melted and poured into suppository mold cavities they occupy a volume – the volume of the mold cavity. Since the components are measured by weight but compounded by volume density calculations and mold calibrations are required to provide accurate doses.

b) New Approaches

I) Double Casting Technique

The total quantity of drug is mixed with an amount of base which is inadequate to fill the number of cavities. The mixture is poured into the mold partially filling each cavity and the remaining portion of the cavities is filled with the melted blank base. The cooled suppositories are then removed, re melted, mixed and recast to evenly distribute the active ingredient. By recording the necessary information the pharmacist can determine the weight of base displaced by the drug and then calculate the density factor [25].

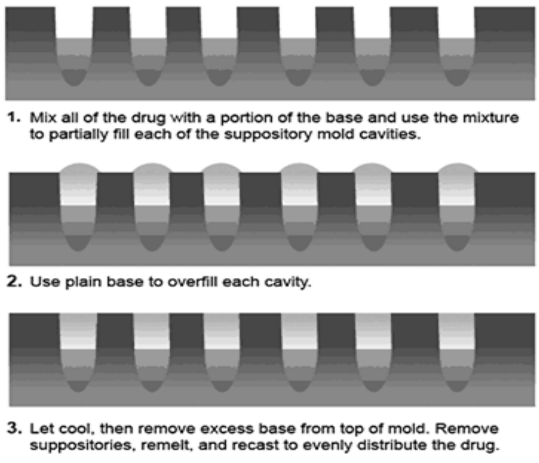

Figure 2: Double Casting Technique

c) Mode of insertion

In 1991, Abd-El-Maeboud study behind the traditional shape of a rectal suppository. It is very clearly demonstrated very good reason for the traditional torpedo shape had a strong influence on the extent to which the rectal suppository traveled internally and thus increased its efficiency. It was used mode of inserting the tapered end first and concluded the greater distance of internal travel of the suppository once inserted, which was entirely a mechanical consequence of the natural actions of the rectal configuration [26].

d) Liquid suppository

It involves injecting a liquid, typically a laxative, with a small syringe into the rectum. The medicament is incorporated into a base such as cocoa butter which melts at body temperature, or into one such as glycerinated gelatin or PEG which slowly dissolves in the mucous secretions. Suppositories are suited particularly for producing local action but may also be used to produce a systemic effect or to exert a mechanical effect to facilitate emptying lower bowel. The ideal suppository base should be nontoxic, nonirritating, inert, compatible with medicaments, and easily formed by compression or molding. It should also dissolve or disintegrate in the presence of mucous secretions or melt at body temperature to allow for the release of the medication. As with the ointment bases suppository base composition plays an important role in both the rate and extent of release of medications [27].

e) Factors affecting bioavailability of drugs from suppositories

There is several therapeutic reasons mention one of these to avoid partly hepatic first-pass elimination following rectal administration.

The rectal venous drainage is such that the upper part (superior rectal vein and middle rectal vein) is connected with the portal system and the lower part (inferior rectal vein) directly with the systemic circulation. However there is no sharp distinction between these venous drainages.

It has been accepted at least 50-70% of a drug suitable for rectal administration is absorbed via above direct pathway. The absorption surface of the rectum ranges between 0.02 and 0.05 m^2 and a viscous rectal fluid which is spread over the surface is evaluated to be equal to from 0.5 to 1.25 ml of pH approx. 7.5 with very low buffer capacity.

The drug absorption on rectal administration is a considerable extent the pH partition theory. Thus, colorectal absorption is a simple diffusion process through the lipoid al membrane in which carrier-mediated mechanisms. Such differences found between mucous membranes of the colorectal and upper gastrointestinal area[27].

The colorectal mucous membrane high sensitive to membrane-active adjuvant is most attractive for the formulation design of poorly absorbed drug.

In many suppositories the drug substance is in suspension of the vehicle. This means that the drug absorption by rectal route is governed by particle size, solubility in water and interfacial tension.

However, there are some systems in which the drug dissolves either fully or in part of the base. Such as solubility in base and water distribution coefficient and relative phase volume will suggested that a drug is administered rectally as an oily solution direct absorption from the oil of little consequence. The release of the solute into the aqueous rectal fluid and then absorption occur. The equation describes equilibrium conditions.

If the factors of drug amount in oil (Mo), volume of oil and partition coefficient (K) represented in the following equation;

$$M_w = Mo/(KO)$$

Where M w is the amount of a drug in the aqueous phase, 0 represents the volume ratio of oil to water.

Furthermore, the drug is achieved slowly in comparison with absorption from the aqueous phase then equilibrium may never reach and transfer from oil to water becomes the rate-determining process.

The elimination rate constant determined as the slope of linear regression for the terminal log–linear portion of the concentration–time curve. A terminal half-life value was calculated as 0.693 divided by elimination rate. Maximum plasma concentration (Cmax) and the corresponding sampling time (tmax).

Area under the plasma concentration versus time curve calculated by the trapezoidal method and extrapolated to infinite time as:

$$AUC_{(0-\infty)} = AUC_{(0-T)} + C_T/ß$$

Where *CT* is the concentration at the last sampling time, on these AUC values a model independent estimation of the systemic plasma clearance (CLp)

$$CL_P/F = D/AUC_{(0-\infty)}$$

Where *D* is the administered dose, *F* is systemic availability representing the net fraction of the dose reaching systemic blood or plasma circulation following possible losses from incomplete release from the dosage form, destruction in the gastrointestinal tract, and first-pass metabolism [28].

Hence, the sink condition is important cell designed for the testing of drug release from in- vitro suppositories.

Therefore, the conditions favor flow-through method with open supply of fresh fluid. Transport of dissolved drug out of molten mass and into the aqueous receiver requires a large and agitated area of contact between two

phases in order to make the release kinetics similar to those in vivo.

It uses a fat-like base for a water-soluble drug and a hydrophilic base for an insoluble drug in water. Furthermore the diffusion rate of a drug suspended in a fatty base of both low hydroxyl number and viscosity is increase.

Small particles of a drug do not always result in higher levels. It can be provided on the basis of the release processes melting, spreading, sedimentation, wetting and dissolution.

The rate-limiting step for the release of an insoluble drug from the vehicle could be transport rate through molten suppository it could favor larger particles of a drug readily soluble in the rectal fluid [29].

However the dissolution rate of drugs that are slightly soluble in that fluid usually will be limited and thus smaller particles (< 50) should be preferred.

The suppository base with a suspended drug in the rectal colon is dependent on the pressure exerted through the rectal wall by abdominal organs or by rectal wall muscles. The final spreading area decreases with increasing apparent viscosity of the spreading system[30].

The bioavailability of chemically stable rectal drugs is also influenced by the physical stability of suppositories during storage called hardening effect.

Its changes on melting times arise only with bases of higher melting ranges this hardening effect almost completely inhibited for example, addition of 7% Agar.

However, the higher surface-active agent concentrations produce retardant or irrigative effects. Thermal behavior hardening effects and brittleness are not only polymorphism but also lattice defects due to the thermal treatment of suppositories [31].

CONCLUSION

In conclusion, rectal administration is truly explored as a potential drug delivery system particularly for drugs that are either too irritating for the gut or more effective when not metabolized by the liver. Suppositories offer patients an option that is less invasive and less discomforting. It looked as a convenient drug delivery system in patients having rectal symptoms. In addition the controlled absorption enhancement into the possibilities and problems related to the pharmacokinetics and pharmacodynamics of the enhancer and the drug to be absorbed with respect to the desired plasma-concentration time profile. The suppository may be useful as a Sustained-release formulation for the long-term treatment of chronic diseases like essential hypertension, asthma, diabetes, AIDS, anemia, etc. It is also administered in unconscious and pediatric patients as well as for the treatment of pregnancy, chemotherapy and allergy induced emesis.

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