IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A BRIEF ANALYTICAL REVIEW ON DESIGNING AND DEVELOPING SUPPOSITORY FORMULATIONS

[1]CHETNA.S.MALWAL, [2]NILESH.S.SHINDE,

[3]SANDESH.R.NIKAM, [4]AMOL.P.THAKARE.

[1]Author, [2]Author, [3]Author, [4]Assistant Professor.

[1]DEPARTMENT OF PHARMACEUTICS.

[1]DR. BABASAHEB AMBEDKAR TECHNOLOGICAL UNIVERSITY, LONERE, RAIGAD, INDIA.

ABSTRACT

Based on their physicochemical characteristics, modern suppository bases are analysed, and excipients from different pharmacopoeias around the world are categorised. For the purpose of making an informed decision on the creation of future drugs in the form of suppositories, particularly extemporal drugs, the benefits and drawbacks of various suppository bases are presented. [1-6]

KEY WORDS : suppository, suppository bases, and extemporal medications. [1-6]

INTRODUCTION :

Although rectal administration has a number of benefits, it is less popular due to cultural and psychological factors.

When taking a medication orally for nausea and vomiting, one may cause emesis to cause the drug to be vomited before it is absorbed. It is possible to prevent the stomach and small intestine irritation that is connected to some medications. High clearance medication first pass hepatic elimination may be partially prevented. By avoiding contact with stomach fluid, some drugs' acidic and enzymatic breakdown is stopped. when oral intake is limited, such as before radiological tests, before surgery, in patients with upper GIT illnesses, or when a patient is unable to swallow It is very helpful for paediatric, elderly, and unconscious patients.

It is helpful for children, the elderly, and patients who are unconscious, especially those who have trouble taking oral medications. 1. The dosage form can be removed to cease drug delivery, and accidental overdoses and failed suicide attempts can both quickly stop medication absorption. Drugs that are often only supplied parentally can now be delivered rectally. To provide the necessary drug delivery system, these benefits for rectal dosage necessitate devices or formulations with certain properties. Due to their limited bioavailability upon oral dosage, peptides and many other hydrophilic medicines are usually created as parental formulations. For instance, since the administrative location is close to the absorption site. It is possible to obtain rapid absorption along with a quick rise in plasma drug level. Formulations that offer the desired release can be easily created.

It is feasible to keep the medication and additive concentrations at the absorption site high. In the US and Japan, where suppositories were not previously widely accepted from a cultural or emotional point of view, the rectal absorption of medications has also emerged. Rectal administration was previously reserved for the treatment of

bacterial infections, asthma, nausea, anti-hemorrhoidal, vermifugal, and laxative medicines, as well as local anaesthetics, asthma, and nausea. Nowadays, most herbal and synthetic medications are also made as suppositories to have a systemic impact. Rectal delivery may help prevent a portion of a drug's first-pass impact in the liver or gastrointestinal system. Rectal suppositories' main drawbacks are that they are not Rectal suppositories' two main drawbacks are that patients dislike them and find them to be uncomfortable. Most medications' rectal absorption is typically irregular and unpredictable. After being inserted, some suppositories "leak" or are expelled . The oral absorption of various sorts of medications is first linked to two issues. First off, the majority of peptide medications as well as several antibiotics are susceptible to chemical breakdown in the stomach or the enzymatic environment of the small intestine. Oral dosing forms are typically not practical if the target medications are destroyed before absorption can take place. 4. Second, after oral administration, the majority of peptide medications and several antibiotics are just too slowly absorbed to produce useful plasma levels for treatment. Co-administration of some adjuvants or medicines that promote absorption is necessary for the small intestine.

o create an oral dosage form for these therapeutic agents, one must prevent the medicine from being degraded by enzymes (in some situations) and simultaneously get past the mucosal barrier's impermeable nature. .Free digestive enzymes are the issue of enzymatic breakdown by concentrating an absorption sites. Nasal and rectal mucosa have been used as these delivery routes. Lacking high concentrations of digestive enzymes, both of these potentially drug-absorbing regions maintain a selective barrier to medication absorption.

In order to solve the second issue—increasing the permeability of the target mucosa—permeation enhancers or absorption adjuvants have been found. Bile salts and synthetic or semi-synthetic surfactants are two examples.

1.Designing Bi-layered Suppositories Objectives Bi-layered suppositories are primarily made to give fixed dose combinations of various medications, to keep incompatible medications apart, and to regulate the rate at which one or more medications are delivered. Benefits of Bi-layered Suppositories, Section . Suppositories generally have excellent chemical and microbiological stability, don't need to be manufactured under sterile circumstances, are less expensive to produce, and are easier to administer, which leads to higher patient compliance. Suppositories can help cover up the unpleasant odour and bitter taste of medications that are administered recally. Comparing bi-layered suppositories to traditional mono-layer suppositories reveals some significant benefits. Typical dosage forms, for instance, call for repeated dosing, which can be avoided. [1-6]

2.For instance, bi-layered suppositories' sequential release of two medications can save the repetitive dosing necessary by conventional dosage forms, and physical separation can avoid the incompatibility of two or more pharmaceuticals. By combining layers with different release patterns or slow release and quick release layers in a single dose form, bi-layered suppositories have also made it possible to produce controlled administration of active medicinal components (Chicco et al, 1999; Mohamed Ali, 2017; Realdon et al, 1997; Yahagi et al, 1999). 47 Mohamed A. Muaadh As a result, two active ingredients—either different ones or the same one—can be administered in a single suppository at various rates.

3.Perfect Bi-layered Suppositories' Qualities Elegant and free of flaws like chips, cracks, discolouration, and contamination should characterise bi-layered suppositories. It must be able to release the therapeutic compounds in a desirable, predictable, and repeatable manner and possess the necessary chemical and physical stability to maintain its physical properties over time. Furthermore, bi-layered suppositories need to be strong enough mechanically to endure shock during production, packaging, shipping, and dispensing. [1-6]

SUPPOSITORIES :

The Latin root of the word "suppositories" means "to place under." Suppositories are a solid dose form for medication that is intended to be inserted into body orifices. The two most common ways to provide medication through the rectum are suppositories and creams. Both locally and systemically acting drugs can be administered using them. The suppositories are generally placed as a solid, then dissolve or melt inside the body to distribute the medication to the many blood arteries that follow the bigger intestine. The suppository was initially employed in nursing homes to deliver medications to elderly patients who were incapable of doing so. Suppositories are available in a variety of sizes and forms, which makes it easier for the body cavity to hold them there. Rectal suppositories for adults typically weigh 2 g, whilst those for kids weigh just approximately 50 g. For the long-term treatment of chronic disorders including essential hypertension, asthma, diabetes, AIDS, anaemia, etc., the suppository may be helpful as a sustained

release formulation. Additionally, there is growing interest in the idea of rectal administration for the management of cancer pain or post-operative pain. [7-30]

A) THE PREPARATION TECHNIQUES :

One of three ways can be used to impromptu make suppositories.

1)HAND ROLLING :

When only a small number of suppositories need to be manufactured in a cocoa butter foundation, this is the simplest and oldest way of preparing suppositories. It has the benefit of not requiring the cocoa butter to be heated. The active components and grated cocoa butter are triturated in a mortar to create a substance that resembles plastic. The bulk is first rolled into a smooth cylinder using a big spatula or a small flat board on a pill tile after being shaped into a ball in the palm of the hands.

Elements influencing the bioavailability of medications from suppositories To avoid partially hepatic first-pass elimination after rectal injection is one of numerous therapeutic reasons to discuss. The inferior rectal vein, which is connected directly to the systemic circulation, is located below the superior and intermediate rectal veins, which are related to the portal system. However, these venous drainages are not clearly distinguished from one another. It is generally agreed that the aforesaid direct channel accounts for at least 50–70% of the absorption of a medication suitable for rectal delivery. The rectum's absorption area is 0.02 to 0.05 m2, and a viscous rectal fluid dispersed throughout the surface is estimated to be equivalent to between 0.5 and 1.25 ml of pH. [7-30]

II) COMPRESSION MOLDING :

In this process, grated suppository ingredients and medicine are mixed and pressed into a special mold to make a suppository. The process involves first squeezing a small amount of base into the mold and determining the capacity of the mold by weighing the finished suppository. When adding an active ingredient, part of the suppository base should be omitted based on the density factor of the active ingredient. [7-30]

III) MELT 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 suppository molds. Once the mixture has set, remove the suppository from the mold. The fusion method can be used with all types of suppositories and should be used with most of them. occupy volume. Because the components are measured by weight, but assembled by volumetric density calculations and geometry calibrations to provide accurate dosages. [7-30]

B) NEW APPROACHES :

I) DOUBLE CASTING TECHNOLOGY :

The total amount of drug is mixed with an insufficient amount of base to fill the number of voids. The mixture is poured into a mold, partially filling each cavity and filling the rest of the cavity with the molten parison base. The chilled suppository is then removed, redissolved, mixed and poured again to evenly distribute the active ingredient.By recording the necessary information, the pharmacist determines the weight of the base displaced by the drug. , the density factor can be calculated. [7-30]

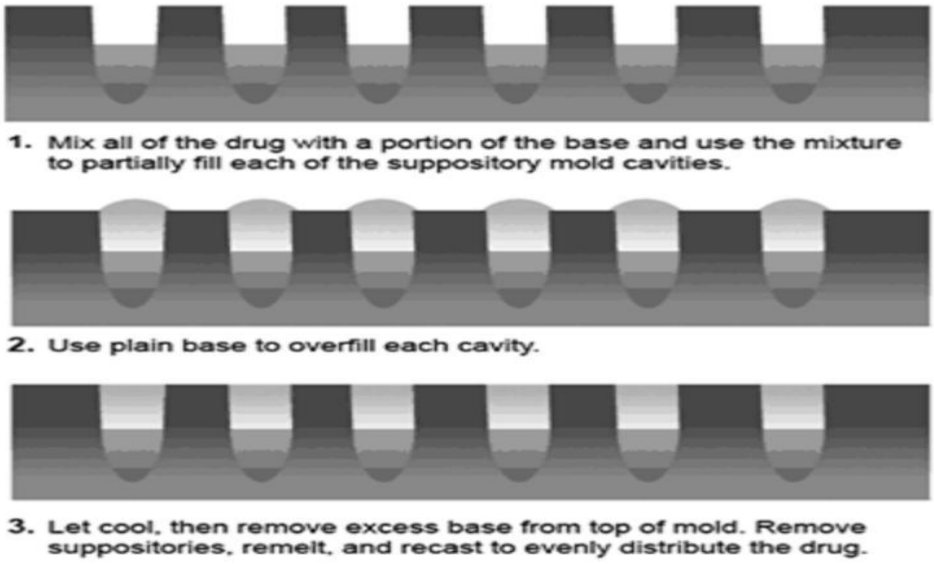

figure no 1: double casting technology [7-30]

C)INSERT TYPE :

In 1991 Abd-El-Maeboud studied the traditional form of rectal suppository. It is very clearly shown that the conventional torpedo shape strongly influenced the range of movement of the uvula inside, increasing its efficiency. There are good reasons for this. The tapered end was inserted first and used to close the greater distance of internal travel of the suppository after insertion. This was entirely a mechanical consequence of the natural influence of rectal composition. [7-30]

D)LIQUID SUPPOSITORIES :

A liquid, typically a laxative, is injected into the rectum using a small syringe. The drug is incorporated into a base such as cocoa butter, which melts at body temperature, or into a base such as glycerinated gelatin or PEG, which dissolves slowly in mucous secretions. Suppositories are particularly well suited to produce a local effect, but can also be used to produce a systemic effect or to exert a mechanical action that facilitates emptying of the lower bowel.Ideal A typical suppository base should be non-toxic, non-irritating, inert, drug compatible, and readily malleable by compression or molding. It must also dissolve or degrade in the presence of mucus secretions, or dissolve at body temperature so that it can release the drug. Similar to ointment bases, the composition of suppository bases plays an important role in both the rate and extent of drug release. [7-30]

A)ELEMENTS INFLUENCING THE BIOAVAILABILITY OF MEDICATIONS FROM SUPPOSITORIES :

To avoid partially hepatic first-pass elimination after rectal injection is one of numerous therapeutic reasons to discuss.

The upper portion of the rectal venous drainage is associated to the factors affecting the bioavailability of medications from suppositories (superior and middle rectal veins).

To avoid partially hepatic first-pass elimination after rectal injection is one of numerous therapeutic reasons to discuss.

The inferior rectal vein, which is connected directly to the systemic circulation, is located below the superior and intermediate rectal veins, which are related to the portal system. However, these venous drainages are not clearly distinguished from one another.

At least 50 to 70 percent of have embraced it. The above direct channel is used to absorb a medication suitable for rectal delivery. The rectum's absorption surface varies between 0.02 and 0.05 m2, and the amount of viscous rectal fluid that is dispersed across it is estimated to be between 0.5 and 1.25 ml of pH-approximately 7.5 with a very poor buffer capacity.

The pH partition theory accounts for a sizable portion of medication absorption after rectal delivery. Therefore, colorectal absorption is a straightforward diffusion process that occurs across the lipoid membrane and is mediated by carriers. such variations between the colorectal and upper gastrointestinal mucous membranes.

The colorectal mucous membrane is particularly promising for the formulation design of poorly absorbed drugs due to its high sensitivity to membrane-active adjuvants.

The drug component is frequently suspended within the vehicle of several suppositories. This indicates that particle size, solubility in water, and interfacial tension all influence medication absorption via the rectal route.

There are some systems, nevertheless, where the medication only partially or completely dissolves the base. It will be advised that a medicine be delivered rectally as an oily solution, with direct absorption from the oil of little concern, based on factors including solubility in base, water distribution coefficient, and relative phase volume. The solute is first released into the aqueous rectal fluid, and subsequently it is absorbed. Equilibrium circumstances are described by the equation.

However, there are some systems in which the drug is fully or partially soluble in the base. B. The base and water partition coefficients and relative phase volume solubilities suggest that the drug is administered rectally as an oily solution and that direct absorption from the oil is of little concern. Release of solutes into the aqueous rectal fluid and subsequent absorption occurs.

The amount of drug in oil (Mo), the amount of oil, and the distribution coefficient (K) are expressed by the following formula:

M w =Mo/ (KO)

where M w is the amount of drug in the aqueous phase and 0 represents the volume ratio of oil to water.

Furthermore, as the drug is slowly reached compared to absorption from the aqueous phase, equilibrium is never reached and oil-to-water transition becomes the rate-limiting process.
Elimination rate constant determined as the slope of the linear regression of the terminal log-linear portion of the concentration-time curve. The terminal half-life value was calculated as 0.693 divided by the excretion rate.
Maximum plasma concentration (Cmax) and corresponding sampling time(tmax).
Area under the plasma concentration-time curve calculated by the trapezoidal method and extrapolated to infinity as follows:

AUC (0-∞) = AUC (o-T) +CT/ ß

These AUC values provide model-independent estimates of systemic plasma clearance (CLp), where CT is the concentration at the last sampling time point.

CLP/F = D/AUC (o-∞)

Where D is the dose, F is the systemic availability, followed by incomplete release from the dosage form, disruption in the gastrointestinal tract, and potential losses due to first-pass metabolism, followed by systemic blood or It is the net percentage of the dose reaching the plasma circulation.
Therefore, the sink condition is an important cell developed for testing drug release from suppositories in vitro. of the dose reaching the plasma circulation. [7-30]

RESULTS AND DISCUSSION OF THEM :

However, you can find the following classification of bases in some sources, which is based on their melting or dissolving characteristics:

A glycerol-gelatin base that absorbs water and dissolves to release API; water-soluble or water-miscible polymers or surfactants; a group of bases that contain disintegrating agents, natural resins, effervescent agents, collagen, fibrin, hydrogels,

Suppositories (rectal) are solid single-dose medications intended for administration into the rectum to obtain systemic or local effects, while pessaries (vaginal) are solid single-dose medications intended for insertion into the vagina to provide local action, according to State Pharmacopoeia of Ukraine 2.0 and European Pharmacopoeia 8.0 [4, 5].

The term "suppository" is defined as follows in USP35: A suppository is a solid dose form of varying weights and forms intended for rectal, vaginal, or urethral ostium administration. It typically melts, softens, and dissolves at body temperature. The suppository can transport therapeutic medicines for systemic or local action, or it can operate as a protective or palliative agent for local tissues at the site of introduction. [1-6]

The State Pharmacopoeia of Ukraine and other pharmacopoeias contain a list of the specifications for suppository bases, which are the same everywhere in the world. These are what they are: No odour, visually pleasing appearance, chemical and physical resilience during storage and usage, compatibility with a variety of active medicinal ingredients and excipients, absence of toxicity, lack of sensitivity, and lack of irritation to sensitive tissues of the body; expansion-compression properties so that when cooled, suppositories must be compressed enough to be easily released from the moulds; to melt and dissolve in the intended cavity of the body to release a medicinal substance; to mix and absorb a small amount of water; the viscosity should be low enough in the melt for easy casting of the suppository mass into moulds, but high enough for the API to be suspended. [1-6]

Suppository bases used to create this dosage form are classified as hydrophobic, hydrophilic, and diphilic in accordance with the State Pharmacopoeia of Ukraine and the European Pharmacopoeia. Additionally, the USP lists the following six categories of suppository bases etc. are examples of bases that melt at body temperature and are used as suppository bases.

1 Cocoa butter.

2. Alternatives to cocoa butter.

3. Glycerin-based gelatine.

4. Glycerin-based gelatin Polyethylene glycol.

5. Basis of surfactants.

6. Tablet inserts or suppositories. [1-6]

However, you can find the following classification of bases in some sources, which is based on their melting or dissolving characteristics:

A glycerol-gelatin base that absorbs water and dissolves to release API; water-soluble or water-miscible polymers or surfactants; a group of bases containing disintegrating agents, natural resins, effervescent agents, collagen, fibrin, hydrogels, etc. are examples of bases that can be used as suppository bases and melt at body temperature.

The State Pharmacopoeia of Ukraine and other pharmacopoeias contain a list of the specifications for suppository bases, which are the same everywhere in the world. These are what they are:

No odour, an aesthetically pleasing appearance, chemical and physical resilience during storage and usage, compatibility with a variety of active medicinal components and excipients, absence of toxicity, lack of sensitivity, and lack of irritation the ability to melt and dissolve in the intended cavity of the body to release a medicinal substance; irritation to sensitive body tissues; expansion-compression characteristics; mixing and absorbing a small amount of water; and the viscosity should be low enough in the melt for easy casting of the suppository mass into moulds but high enough for the suspending of the API suppositories from the moulds. having wetting and/or emulsifying qualities to maximise API release. [1-6]

According to the physical and chemical characteristics of the APIs found in suppositories, a suppository base must be selected in order to create medications that would be suitable in a certain situation. It is required to undertake a more thorough analysis of the variety of suppository bases, their characteristics, benefits, and drawbacks for this aim. Of course, there are several suppository bases available today, but newer, more advanced carriers are always being developed. Some of these are therefore worth pausing for.NF24 cacao butter

Theobroma cocoa seeds, or chocolate beans, contain a lipid called cocoa butter that can be extracted by pressing the seed oil or by using a solvent. based on the chemical Specifically, stearic, palmitic, oleic, lauric, and linoleic triglycerides, as well as other saturated and unsaturated fatty acids, make up cocoa butter. It has a yellow hue and a distinct, strong stench. It is solid at room temperature but melts at body temperature.

Since cocoa butter doesn't have any emulsifiers, it doesn't absorb a lot of water. However, Tween-61, a tan, waxy, solid, nonionic surfactant, may be added, in a quantity ranging from 5% to 10%, if necessary. Although the use of nonionic surfactants causes instability of suppositories during storage, it increases cocoa butter's capacity to absorb water. [1-6]

The impact of various APIs on cocoa butter's melting point is one of the material's major drawbacks. In particular, a drop in the melting point of cocoa butter is seen when phenol, chloral hydrate, or thymol are added to suppositories. By adding between 4% and 6% white wax or between 18% and 28% cetyl ester wax, this can be done away with. However, you must calculate their amount precisely . Additionally, cocoa butter and products based on it should only be kept in the refrigerator due to their low melting point. Another key problem that must be considered is that this base is characterised by the presence of polymorphic forms with significantly lower melting points: 18, 24 and from 28 ° C to 31 °C. That's why there are difficulties in the manufacture of suppositories grounded on cocoa adulation, because this base can fluently heat and, as a result, turn into a form that has a lower melting point. This means that suppositories made inaptly can melt formerly at room temperature, or when the case tries to administer medice still, cocoa adulation has a number of real advantages, in particular, it's a soft base that doesn't irritate sensitive membrane apkins, fluently accessible and accessible to use in the manufacture of suppositories is the necessary outfit Given this property, it's necessary to easily control the manufacturing process of the medicine. When melting, the base should have a slightly iridescent appearance. As soon as the melted cocoa adulation has fully turned into a transparent, straw- colored liquid, this indicates that the asked melting point was exceeded, all stable chargers were destroyed, and the suppositories would melt at a temperature below the asked, videlicet 34°C. [1-6]

As with other adipose bases, cocoa adulation suppositories may have an deficient or kindly incorrect release of certain APIs. The release of substances from the fat base for suppositories, similar as cocoa adulation, into the waterless medium of the body depression depends on the water/ base distribution measure in the drug, because numerous organic motes of the medicinal substance are undoable in water and are lipophilic. An exception is the use of this substance in suppositories in the form of an ionized swab. That's why, in order to increase the bioavailability of APIs, it's judicious to use them in the form of water-answerable ionized(swab) forms, because they've high water/ base distribution portions. For illustration, if it's necessary to prepare suppositories with phenobarbital, it's judicious to use the sodium swab ofphenobarbital.However, in this case, cocoa adulation isn't a rational choice as the base for suppositories If the medicinal substance doesn't have a water-answerable form. [1-6]

ACKNOWLEDGMENT :

I wish to express my sincere thanks and gratitude to my esteemed Mentor **"Amol.P.Thakare "** Who has contributed so much for the successful completion of my review Article by his thoughtful reviews and valuable guidance.

COCLUSION:

In summary, rectal administration is indeed being investigated as a potential drug delivery system for drugs that are more effective, especially when the intestine is too irritating or not metabolized in the liver. provide patients with fewer options for This appeared to be a viable drug delivery system for rectal symptomatic patients. Furthermore, controlled absorption enhancement presents opportunities and problems related to the pharmacokinetics and pharmacodynamics of the enhancing agents and drugs absorbed with respect to the desired plasma concentration-time profile. Suppositories are useful as sustained release formulations for long-term treatment of chronic diseases such as essential hypertension, asthma, diabetes, AIDS and anemia. It is also given to unconscious and pediatric patients, and is used to treat pregnancy-, chemotherapy-, and allergy-related vomiting.

REFERENCES :

1. Block L. H. Medicated topicals. In: University of the Sciences in Philadelphia, ed. Remington: The science and practice of pharmacy, 21st ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005.

2. Coben L. J., Lieberman H. A. Suppositories. In: Lieberman H. A., Lachman L., Kanig J., eds. The theory and practice of industrial pharmacy, 3rd ed. Philadelphia: Lea & Febiger, 1986.

3. Plaxco J. M. Suppositories. In: King R. E., ed. Dispensing of medication, 9th ed. Easton, PA: Mack Publishing Co., 1984.

4. European Pharmacopoeia, 8th ed. Council of Europe, 67075 Stasbourg Cedex, France 2014.

5. Derzhavna Farmakopeya Ukrayini: v 3 t. Derzhavne pidpriemstvo «Ukrainskiy naukoviy farmakopeyniy tsentr yakosti likarskih zasobiv». 2-e vid. Harkiv: Derzhavne pidpriemstvo «Ukrayinskiy naukoviy farmakopeyniy tsentr yakosti likarskih zasobiv» 20142015.

6. USP 35-NF 30. General Chapter Pharmaceutical Dosage Forms, The United States Pharmacopeial Convention, Rockville, MD, 2009

7. N.K.Jain, "Progress in controlled and Novel drug delivery system" Ist edition, CBS Publication, 2008, 96-118.

8. Boylan J. C., Swarbrick J., "Encyclopaedia of pharmaceutical technology" Vol-I, 2nd edition, 2009, 32-940.

9. Nishihata T., Kate J., Kobayaahi M., Kamada A., "Formation and hydrolysis of enamine in aqueous Solution", Chem. Pharm. Bull., 32, 1984, 4545-4550.

10. Okamura Y., Knmada A., Higuchi T., Yagi T., "Enhanced bioavailability of insulin after rectal administration with emetine as adjuvant in depans cratered dogs". J. Pharmacol., 37, 1985, 22-36.

11. Nishihata T., Rytting J.H., Higuchi T. L., Selk S. J., "Enhancement of rectal absorption of water soluble antibiotics in dogs", int. J. Pharm. 21, 1984, 239-245.

12. Muranishi S., "Modification of intestinal absorption of drugs by lipoid adjutants", Pharm. Res., 2, 1985, 108-I 18.

13. Kanamoto I, Nakagawa T, Horikoshi I, "Pharmacokinetics of two rectal dosage forms of ketoprofen in patients after anal surgery", J Pharmaco biodyn, 11, 1988, 141- 145.

14. Abd-el-maeboud K.H., El-naggar T, El-hawi em, Mahmoud SA, "Rectal suppositories: commonsense and mode of insertion", Lancet 338, 1991, 798-800

15. D'haens G, Breysem Y, Rutgeerts P, Van besien B, "Proctitis and rectal steno sis induced by nonsteroidal antiinflammatory suppositories" J Clin Gastroenterol, 17, 1993,

16. Rejman F. "Use of Roinal suppositories in patients with ano rectal complaints Duodecim", 78, 1962, 727-729.

17. De Boer A.G., Hoogdalem E.J., Breimer D.D., "Rate controlled rectal peptide absorption enhancement, In Penetration enhancement for polypeptides through epithelia", Adv. Drug Delivery Reviews, 8, 1992, 237-253.

18. Vim Hoogdalem E.J., De Boer A.G., Bremer D. D., "Pharmacokinetics of rectal drug administration, part I general considerations and clinical applications of centrally acting drugs". Clin. Pharmacokinet, 21(I), 2006, I l-26.

19. Watanabe. Y. E., Hoosdalem J. A., De Boer A.G., "Absorption enhancement of rectally infused cefoxitim by medium chum monoglyderides in conscious rats" J. Pharm. Sci., 77, 2008, 47-84.

20. De Leede L.G., De Bow A.G., VeILen S.L., Breimcr D.D, "Zero-order rectal delivery of theophylline in man with an osmotic temp", J. Pharmacokin. Biopharm., 119, 2006, 525-537.

21. Singh J., Jayaswal, S.B., "Formulation, bioavailability and pharmacokinetics of rectal administration of lorazepam suppositories and comparison with oral solution in mongrel dog". Pharm. Ind., 47, 1985, 664-668.

22. Yoshihawa H. Takada K., Muranishi S., "Molecular weight dependence of permeation electivity to rat small intestinal blood lymph barrier for exogenous macromolecules absorbed from lumen", J. Pharmacobio-Dyn., 7, 1984, 1-6.

23. Lamanna C. Carr C.J., "The botulinal tetanal and entero taphylococcal toxins: a review", Clin. Pharmacol, Ther, 8, 1967, 206-332.

24. Muranishi S., Tokunaga Y., Taniguchi K., Sezaki H., "Potential absorption of heparin from the small and the large intestine in the presence of mono lein mixed micelles" Chem. Pharm. Bull., 25, 1977, 1159-1161.

25. Muranishi S., "Absorption enhancers", Crit. Rev. Ther. Drug Carrier Syst, 7, 1990, l-33.

26. Bocci V., "Evaluation of route of administration of interferon's in cancer: a review and a proposal" Cancer Drug Deliver, 1, 1984, 337-351.

27. Babul N., Darke A.C. Anslow, J.A. and Krishnamurthy T.N., "Pharmacokinetics of two novel rectal controlled-release morphine formulations" J. Pain Symptom. Manage., 7, 1992, 400-405.

28. Kurosawa N., Owada E., Ueda K., Takahashi A., "Bioavailability of nifedipine suppository in healthy subjects" Int. J. Pharm., 27, 1985, 81-88.

29. Kawaguchi T., Hasegawa T., Juni K., Seki T., "Rectal absorption of zidovudine" Int. J. Pharm., 77, 1991, 71-74.

30. Chicco D., Grabnar I., kerjanec A., Vojnovic D., "Correlation of in vitro and in vivo paracetamol availability from layered excipient suppositories" Int. J Pharm., 189, 1999, 147–160.