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Formulation and Evaluation of Rectal Drug Delivery System of Atenolol & Diltiazem Hydrochloride

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Abstract – One of the most popular administration routes from complications moderate to severe is the Parenteral route and the complaince to patients is significantly lower for such delivery mode since it's is a technique too invasive and need needle pricking. Further this becomes evident that absorption rate quality and the metabolic elimination rate leads to the distribution of equilibrium of tissues of drug and of blood however, it is not present in the drug dosage form. The system of drug delivery would be in the form of controlled system of drug delivery and also there is a system predictive control across the release pattern along with blood vessels and the subsequent tissues that are achievable the absorption and the metabolism rate can be seen in delivery system of rectal drug.

Keywords: Rectal Drug, Drug Delivery System, Atenolol, Diltiazem Hydrochloride Etc.

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I. INTRODUCTION

The system of drug delivery would be in the form of controlled system of drug delivery and also there is a system predictive control across the release pattern along with blood vessels and the subsequent tissues that are achievable. An observation suggests that equality between the absorption and the metabolism rate can be seen in delivery system of rectal drug. Drug administration in a dosage form that is conventional needs high dose, regular administration and does not have extended duration, incorporation toxic changes. While in the delivery devices of controlled drug there occurs drug's efficient utilization, desireable duration extended, with lesser toxic chances, promoting patient's enhanced complication accounting for higher therapeutic management. The influential use of the drugs has an impact on the economy and the cost factor.

It appears that the delivery as controlled must be the product goal and today the firms drug shout allocate high resources for reformulation of the drugs that are old and previal in the controlled and sustainrd system of drug delivery leading to gains in economy.

Rectal administration of drugs offers several advantages over other routes due to reduction of side effects namely gastrointestinal irritation and the avoidance of both disagreeable taste and first pass effect [1] [2]. It represents also an alternative route when oral route is not possible in nausea, vomiting, and unconscious conditions [3]. Conventional suppositories are solids at room temperature and melt, soften or even dissolve at rectal temperature [4]. Cacao butter and witepsols are commonly used as fatty bases that melt at 37 ˚C. However, glycerinated gelatin and PEGs are used as water soluble bases [5] [6]. The drug release from suppositories could differ depending on its physicochemical properties and the nature of the base used. If the drug is highly released from the selected base and multiple drug administration is required to maintain therapeutic effects, it is important to retard drug release and make it sustained for long period of time [7] [8].

II. RECTAL DRUG DELIVERY SYSTEM

The medication of the conventional systems which need the therapy of multi dose need to pass to several issues. A new approach in the field is the drug Delivery that is controlled. It is desireable that the system must add a infusion not just passes the elimination of the first pass but additionally seeks a prolonged, constant and the body therapeutic level. Such can be attained by incorporating the skin along with the drug administration port of drug to aid regular delivery of the drug to the circulation of the system. Molecules of the drug are further sent to the site that is targeted and can be found on remote areas away from the administration site to build actions that are therapeutic [9] [10].

A. Advantages of rectal drug delivery system

- Risk Avoidance and the intravenous therapy inconveniences along with various Metabolism and absorption in association with the oral therapy.
- CDDS drug administration continuity allowing the usage of drugs they have biologically shorter life.
- It is seen tasty the delivery system of Rectal drug enhances the bioavailability reducing the daily dose of the drug.
- Avoiding the hepatic metabolism first-pass.
- Lesser possibility of the dosing either under or over owing to the outcomes of prolonged delivery that is pre-programmed at a rate needed for the therapeutic.
- Brings a decline in the side effects if gastrointestinal
- Eliminates interaction of drug food.
- Improves the compliance of patient as
- Providing regimen of simplified therapeutics.
- Painless drug delivery.

B. Disadvantages of rectal drug delivery system

- The Delivery system of rectal drug limitation has been linked with the function of skin barrier and severely limits the absolute drug amount which is absorbed in areas of reasonable skin at times of the period of dosing. Hence, the methods main disadvantage being the limiting power that need a dose of 20 mg or less daily.
- In case the drug is potent, yet it should satisfy the elements that need to be viewed as the rectal delivery candidate. For instance, the property of physiochemical should allow it to absorb. The weight of the molecules must not be more than 500 Daltons, also be soluble adequately in aqueous and lipophillic environments as, to attain the dermal micro circulation, or gaining the system of circulation and the same must have stratum corneum. It further shifts via the upper dermis and the epidermis. Lack of water or oil solubility leads to permeation at rate useful.
- The drug characteristics that are both pharmacokinetic and also pharmacodynamic should be one to sustain the input as given by the rectal delivery. The compounds that affect tolerance are not a choice intelligence for the administration mode till the time of wash out comes.

III. DILTIAZEM HCL

Ekapol Limpongsa and co-workers (2008) developed fitting polymeric films so they could form diltiazem hydrochloride drug delivery system [11]. Hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) did the work as hydrophilic and hydrophobic film formers. Researches were done on how HPMC/EC ratios and plasticizers affected the mechanical features. There was assessment done on the impact of HPMC/EC ratios on moisture usage, in vitro release and infusion via pig ear skin. Film comprised 8:2 HPMC/EC, 30% DBP and 10% IPM, IPP or Tween80 filled with 25% diltiazem HCl must be chosen to fabricate the Rectal patch with the use of a fitting adhesive layer and backing membrane. There are researches needed in the vitro permeation and in the vivo performance.

Prashant Satturwar and the colleagues (2008) stated in the end that when Rosin is combined with PVP and with Dibutyl phthalate (30% w/w), it generates soft flexible films where ductile force and percentage elongation have improvements [12]. When there is a growth in drug and PVP loading, there is a growth in the Diltiazem HCI rate from films too along with the permeation through the skin. Patches which comprise of Rosin: PVP (7:3) can be seen having potential for pharmacokinetic and pharmacodynamic performance assessment in the fitting animal model.

Gopal Krishna Murthy and colleagues (2008) developed the liniments of Diltiazem hydrochloride with the use of polymers such as HPMC, NaCMC, MC, Carbopol, PEG6000 and PVP. Correlation coefficient values shown dispersion profile following zero-order kinetic and means of drug release being controlled by Peppas model. Dispersion proponent of release outline comes with a value showing the case II transport dispersion [13].

T E Gopal Krishna Murthy and colleagues (2008) formed and assessed Eudragit RS 100 films as the rate regulating membrane for drug delivery systems with the use of Diltiazem HCl as a drug. Acetone-methanol (8:2), chloroform- methanol (8:2), dichloromethane-methanol (8:2) and ethyl acetate-methanol (8:2) did the work of solvents in film development. Dibutyl phthalate with concertation 15% w/w of polymer served the function of a plasticizer. Study of dry films was done for the purpose of physical appearance, thickness consistency, portable durability, water

vapor transmission, drug dispersion and permeability coefficient. Water vapor transmission and drug dispersion rate pursued the zero-order kinetics. Peppas model regulated the means of drug release. Dispersion proponent of release profiles comes with a value of n>1 and it shows non-analmous transport dispersion. Eudragit RS 100 films were used with ethyl acetate: methanol in 8:2 ratios as the molding solvent and generated low patch area which had anticipate emission rate for both the drugs [13].

A. Atenolol

Cho and colleagues (2004) formed and introduced the matrix film of Atenolol with the use of ethyl vinyl acetate. As the temperature grew, drug release rate from EVA matrix grew too. A linear relation was found between atenolol fluidity and loading dose square root. From all of the plasticizer involved, diethyl phthalate was considered to have ideal improvement effects on the drug release [14].

Gupta and colleagues (2013) formed and introduced the polymer matrix system in delivering Atenolol for the lengthened and regulated release general accessibility. Various mixtures of Eudragit RL with polyvinyl pyrrolidone and polyethylene glycol 4000 were applied to form the polymeric matrix system for accomplishing anticipated and regulated release rate. Their study was done for in vitro release and permeation of drug through pig skin. A linear relation was seen in the systems between drug releases (Q) versus time0.8 (hr0.8). Product showing the needed skin permeation 64 mcg/h/cm2 for accomplishing efficient plasma concentration was chosen for in vivo performance assessment. It was seen from the research that the formulated polymetric matrix rectal drug delivery system of Atenolol can be efficient if the performance is enhanced [15].

B. Classification of Diltiazem free base

The physiochemical features of Diltiazem free base were established with the use of subsequent strictures.

Establishing of liquefying point

Liquefying point of Diltiazem free base was established by selecting minor quantity of medication in a vessel cylinder shut at one side and positioned in a Liquefying point device, following which the heat for melting the drug was noted. The process was conducted in triple ways and mean rate was recorded.

Establishing partition constant 232-34, 237

The partition constant research was conducted with the use of n-octanol as lipid phase as well as phosphate shield, pH 7.4, as aqueous phase. Mixing of the 2 phases are done in an equivalent amount following which saturation was done with one another on a motorized water bath shaker NSW-133 at thirty-two degrees centigrade for twenty-four-hour period. Separation of the soaked phases were done through centrifuging at 2000 rpm on a REMI R-23 separator. Typical sections of the medication were arranged the octanol as well as phosphate buffer. The 2 phases were put in equivalent measurements (10ml apiece) in cone shaped containers and; 100mg of measured quantity of medication was combined with each of them. The containers were vibrated at a temperature of 32 degrees for 6 hours for achieving a comprehensive separating at 100rpm. Through centrifuge at thousand rpm for a period of 5 minutes, the two phases were detached following which analyzation was performed for corresponding medical substances using UV/VIS spectroscopy technique. The separation constant of the medication K o/w was measured with the use of the subsequent formulation:

Ko/w = (Intensity in octanol/ Intensity in phosphate buffer pH 7.4)

C. Researches on Dissolving

The research on Diltiazem base dissolving was conducted in phosphate buffer solution, pH 7.4, in, methanol, alcohol (95%), chloroform, purified H2O ether, toluene, acetone, liquid paraffin, glycerol, silicone oil and triethanol amine individually through combining extra quantities of medication in every instance along with putting the containers having the extra drug on a water bath shaker NSW-133 over a period of 24 hours at 32 degrees centigrade [16].

IV. FACTORS AFFECTING RECTAL PERMEATION

A. Diffusing physicochemical properties Partition Coefficient:

It is seen that Partition coefficient has a crucial role that help establish flux from the skin and the membrane and help attain fluid. The skin passage for drugs, the one that rate limit is startum corneum. The Coefficient of partition vehicle to the stratum corneum holds immense importance for establishment of the Diffusant in higher concentration of tissue first layer. Drugs that possess water as well as the lipid solubility gets skin absorbed. The Coefficient of Rectal permeability depicts linear dependency on the Coefficient of partition.

The Partition coefficient of the lipid water of more than 1 is needed for the permeability of optimum rectal. The drug molecule's partition coefficient can be shifted by the functional group chemical modification. Through vehicle variance or through incorporation of the drug lipophillic agent as

pentanol, affecting the partition Coefficient of skin vehicle.

B. Diffusant solubility:

Solute Flux is seen to be proportional to gradient concentration over the entire phase of barrier. Hence for the highest flxi, the Solute needs to be in saturation in phase of donor. The Solute solubility can be effectively controlled by solvent controlling solvent of vehicle composition.

C. Effective Concentrations:

The differential concentration is the diffusion driving force and also the gradient of the chemical potential being the parameter fundamental. The penetrant activities of thermodynamic either in the membrane or the donor phase can be altered radically through the phenomena as

- Changes in pH
- Complex formation
- Co-solvents,
- Presence of micelle, surfactants, etc.

D. PH variation:

As per the hypothesis of pH partition, only the molecules that are unionized will pass through the membranes of lipid in considerable amount. The Ionized species are not in favor of the free energies to aid lipid phase transfer. Weak bases and the acids dissociate to several degrees, based on pH and the values of diffusant pKa and pKb. So, the unionized drug fraction in phase of application finds the gradient of effective membrane and is pH function Usually drug flux rise with rise in pH of 1 to 2 pH more than the value of pKa or reduces to 1 to 2 pH less than the value of pKb upto the molecules of more than the form of non-protonated.

E. Surface Activity and Micellization:

When micelle is formed from the active agent, the total apparent agent's total solubility in aqueous phase leverages dramatically, and apparent decrease, in partition coefficient. When surfactant and drug are not same, the surfactant part is complicated. At time the same leads to decrease in permeation, portraying a reduced biological activity as rectal retarded absorption of the triiodophenol.

V. COMPOSITION OF DRUG DELIVERY SYSTEM

The vehicle that are used in the delivery system of the drug has been thought as "inert" but does not appear to be such. The vehicle composition along with the system of drug delivery has an impact on the drug particle Absorption. Further, it not just affects the drug release rate but additionally has an impact oj the stratum permeability through hydration, skin lipid mixing and effects sorption promoting.

Enhancers / sorption promoters:

Sorption promoters or the sorption promotes drugs and sold the molecules that alternatively reduce the stratum corneum nature of barricading. It further aids the penetration of the drugs into the skin amf permeate throughout owing to the readily availability of the system.

Sorption aids the act through interaction with the intracellular lipids causing organization disruption and boost fluidity.41 Few also hold interaction with the intercellular protein, and the keratin denaturation (oleic and azone acid) but others act via both the mechanism (DMSO and the propylene glycol).44 a different possible mechanism is via skin hydration.

The idea of the promoters of the sorption aids to an extent also relate to the Partition coefficient of the octanol/water. Recently, the partition theory of lipid-protein is formulated to provide description of the action potential mechanism of the sorption promoters. Penetration of the Mechanism promotes the skin.

Major enhancers mainly the chemical enhancer is seen to be the lipophilic part or the hydrophilic part of SC bilayer, altering the property and then boosts the drug Delivery to the skin. Chemical enhancers might work of the lipid bilayer's lipid portion or it might work on the cells protein part.

They might act as the lipid enhancer, hence here the portal of the total lipid rises which then can easily penetrate in the lipophilic drug, few of the chemical enhancers boost the portion of hydrophile and also boost the flux, few might not alter the bilayer polarity and as the thumb rule, drug dissolve of same polarity can easily penetrate.

Few enhancer work of the SC cellular part. Enhancers might increase the Cellular distance and hence huge molecule easily penetrate within the skin or it might alter the cellular keratin arrangements of fibers and then generate vacuoles so that it becomes drug permeable [17].

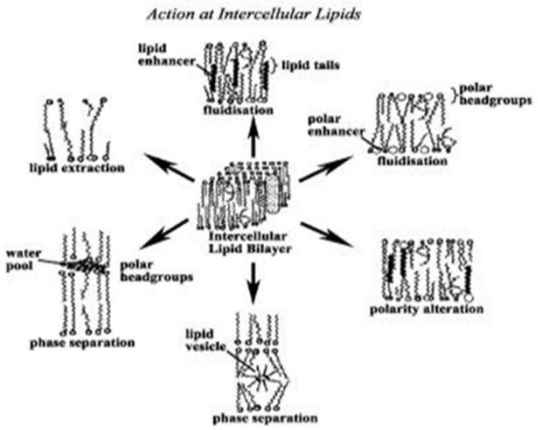

Figure 5.1: Action of the chemical enhancer based on the Intercellular lipids

Few enhancer lead to the bilayer phase separation and hence the drug easily penetrate through a skin. Few can develop hydrophiliv drugs pool increase in flux. Solvents such as the ethanol own the tendency to aid lipid dissolve and the extract the lipid of the SC. Hence the obstruction for the hydrophilic molecule further decreases.

VI. CONCLUSION

SR rectal suppositories of Atenolol were successfully formulated either by using HPMC as a mucoadhesive polymer, proniosomal technology in hydrophilic PEG or emulsification of WH15 base with Sp 60. The proniosomal type suppositories, the WH15/Sp 60 and WH15/ HPMC suppositories showed non-irritant, slow release and prolonged antihypertensive effects of Atenolol which was better than both oral and rectal administration of rapid release formulae. Finally, this study suggested the formulation of Atenolol into SR rectal suppository dosage form to enhance the drug absorption and prolonged its pharmacologic effect.

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