A Strategic Formulation and Evaluation of Patches for Diltiazem Hydrochloride & Atenolol Used In RDDS

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Abstract : Transdermal drug delivery systems are becoming more popular in the field of modern pharmaceutics because it has many advantages over traditional drug delivery system and mostly used to overcome the problems associated with conventional delivery system of drugs. it is self-contained, non-invasive, painless, user- friendly and discrete dosage form. The main objective of transdermal drug delivery system is to deliver drugs into targeted organ or parts through skin at predetermined rate with minimal inter and intra patient variation. The present study was carried out to develop transdermal patches of atenolol with different ratio of EVA 40% copolymer, EC (ethyl cellulose) and ERS by solvent casting method. DEP (2%) is used as a plasticizer and Span 80 as permeation enhancer. The identification of drug and the possible drug polymer interactions were studied by FTIR spectroscopy. Formulated transdermal patches were evaluated with regard to physicochemical characteristics (thickness, folding endurance etc.) and In-vitro permeation studies were performed using Franz diffusion cell. The data obtained from in- vitro permeation studies was treated by various conventional mathematical models (zero order, first order, Higuchi and Korsmeyer- peppa's) to determine the release mechanism from the transdermal patches formulations. Selection of a suitable release model was based on the values of R2 (correlation coefficient), k (release constant) obtained from the curve fitting of release data. It was found that all the formulations follow the first order kinetics. The regression coefficients (R2) for the all formulations F1 to F4 of Higuchi plot was found to be almost linear. Keywords: Trasdermal patches, Atenolol, Permeation enhancer, In-vitro permeation study.

IndexTerms **– Diltiazem Hydrochloride, Atenolol, Strategic Formulation.**

I. INTRODUCTION

One of the most popular administration routes from complications moderate to severe is the Parenteral route and the compliance to patients is significantly lower for such delivery mode since it's is a technique too invasive and need needle pricking. .

All dosage in conventional form apart from the intravenous infusion, are in lieu with the kinetics of second-order. The dosage form would release drug at a faster rate initially and then causes a rise of the drug blood level which falls further exponentially till the further dose gets administered. This leads to the patterns of peak and the valleys of tissues and blood drug concentration. Hence for a longer time the drug concentration would either be more than the therapeutic level or could be less. The course time of administration modes has been represented below:

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. This along with the other elements like unpreventable and the repetitive dosing bring the idea of system drug deliver and the therapeutic system.

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. As evident from 1.1.1, an observation suggests that equality between the absorption and the metabolism rate can be seen in delivery system of rectal drug.

In controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. Continuous oral delivery of drugs at predictable and reproducible kinetics for predetermined period throughout the course of GIT. Controlled release drug delivery employs drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months. Such systems offer numerous advantages over traditional methods of drug delivery, including tailoring of drug release rates, protection of fragile drugs and increased patient comfort and compliance. Keyword: Controlled Drug Delivery, High Blood Level, Extended Release, Drug Toxicity.

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].

- *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.

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.

I. 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].

II. 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].

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)

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].

III. MATERIAL AND METHODS

Designing as well as evaluation of Diltiazem base and Atenolol rectal drug administering process for treating circulatory ailments. Widespread attempts have presently been dedicated to engaging a medication administering process in a specific area of physique for raising medical obtain ability as well as diminishing dosage reliant adverse influences. DTZ (Diltiazem hydrochloride), a medications applied for treating angina pectoris has lately acquired great popularity for treating of hypertension in old age. [227,228] The medication is metabolized properly from the digestive tract, yet its biological obtain ability is reduced because of widespread primary pass absorption. –

Medication molecule dispersal through a skin is affected by a physicochemical trait of the medication and film polymer. Generally, human epidermis is thought of being hydrophobic and the statement is [230,231] that the salt kind of primary medication molecule has reduced penetrability through the epidermis relative to its basal type. Ordinarily consumed skins for regulated discharge procedures have hydrophobic trait. An effort has been made, herewith, for testing the possibility of the pre-mentioned data for enhancing the discharge of Diltiazem in its basal type. The objective of current study is preparation as well as characterization of Diltiazem molecule in its basal types from equivalent salt types along with evaluating those in-vitro infusion dynamics.

Table 1: Pharmacokinetic Information of medication

Pharmacokinetic Data	Diltiazem	Atrenolol
Extent of absorption	80-90%	50%
Bioavailability	40-67%	45%
Time for peak plasma level	2-3 hr	2-4 hr
Protein binding	70-80%	6-16%
Therapeutic serum level	40-200 ng/ml	280 ng/ml
Volume of distribution	1.9-4.3 liter/kg	0.7 liter/kg
Half life of elimination	3.5-6 hrs	6-7 hrs

Each of the aforementioned features causes these medications to be possible contender for preparation for the rectal medication administration process. Research of pattern characteristics as well as different organic concern regarding Rectal Patches. Other than researching penetrability researches of particular medications different features such as plan, developing and organic concern are significant as well. These have been enumerated by us subsequently:

- Medical preservative reaction research
- Formulation of matrices as well as skin regulated Rectal medication administering process.
- Designing appropriate dispersal cell for researching in-vitro penetrability
- Penetrability research via living epidermis of humans.

Skin infection assessments for nominated medications as well as additional ingredients utilized in rectal patch.

IV. EXPERIMENTAL WORK

Formulation of Diltiazem free base from certified salt mode

Hydrochloric salt is used for preparing Diltiazem base. Diltiazem hydrochloride in 1-gram measure was liquefied in 20 ml of purified H_2O. Concentrated emulsion of ammonia was combined along with adjustment pH up to 9.5. Base free of Diltiazem was accelerated out. The base was obtained and disinfected with the use of ether diluter. Procedure of abstraction was performed 4 times with the use of twenty ml ether. Collection and evaporation of ether phase was done at forty degrees centigrade. Diltiazem base was acquired in white nebulous dust form.

UV /VIS Spectroscopic Analysis

UV spectrum of Diltiazem based is used to record both the UV and VIS spectrophotometer to scan 5 µg/ml of solution that comprises of Diltiazem in 0.01N HCL (Hydrochloric acid) and this is scanned at the range of 200 to 400nm with the help of UV/VIS spectrophotometer.

Infrared (IR) Spectroscopic Analysis

The Fourier Infrared (FTIR) spectrums are used to collect the moisture free samples that contains Diltiazem base and is recorded with the help of IR spectrophotometer using potassium bromide pellet technique (whose chemical formulae is KBr). This was canned at the range of 4000 to 400 cm^{-1} with the resolution of around 1 cm^{-1}.

Differential Scanning Calorimetry (DSC) Analysis

DSC will be scanning all the powered samples and these are recorded with the help of DSC- Shimadzu 60 and using the trend line software. The weight of the drug of around 7 to 10 mg and is heated and scanned at the rate of 10 degree c/min using a dry nitrogen flow (100ml/min) ranging between 50 to 350ºc. The equipment that is used to collect the sample of the drug is aluminum pans and lids. In addition to this, indium as well as pure water is also used to standardize the DSC temperature scale and get enthalpy response.

Melting point

Melting point of the Diltiazem base would be found with the help of capillary tube technique and this was around 102ºC±1.4337. The value of this would be the same as the was referred in the literature.

Melting point of the Atenolol would be found with the help of capillary tube technique and this was around 154ºC±1.277. The value of this would be the same as the was referred in the literature.

Table 2: Solubility of Diltiazem and Atenolol base of a wide variety of solvents

Solvent	Solubility
Phosphate buffer (pH 7.4)	Insoluble
Distilled water	Insoluble
Methanol	Freely soluble
Chloroform	Freely soluble
Ether	Freely soluble
Alcohol (95%),	Freely soluble
Acetone	Freely soluble
Toluene	Freely soluble
Glycerol	Insoluble
Liquid paraffin	Soluble
Triethanolamine	Soluble
Silicone oil	Insoluble
0.01N Hydrochloric acid	Soluble

There is an attempt that was made to gain knowledge about the media phosphate buffer, whose pH value is 7.4 is able to keep up the sink condition that was diffused and is in permeation studies. From the solubility perceived data, it was clear that the drug solubility was very poor with the phosphate buffer of around 7.4. Hence, it becomes highly challenging for one to keep up the sink condition in case of diffusion study.

Diltiazem base will be easily soluble in 0.01 N HCL and Atenolol base will be easily soluble in 0.1N HCL this is used as a diffusion medium.

Table 3: Permeation kinetic of Diltiazem with increasing concentration of alcohol

Concentration of ethanol (% v/v)	Skin flux (µg/cm2 hr)	Lag time (hr)	Diffusion coefficient (cm2/hr)	Permeability coefficient (µg/cm hr)
10%	34.95	0.51	$6.410x\ 10^{-5}$	0.4893
20%	56.05	0.42	$7.780\ x\ 10^{-5}$	0.7847
25%	65.58	0.33	$9.890\ x\ 10^{-5}$	0.9181

40%	71.00	0.26	1.256×10^{-4}	0.9940
95.5%	83.14	0.20	1.633×10^{-4}	1.1639

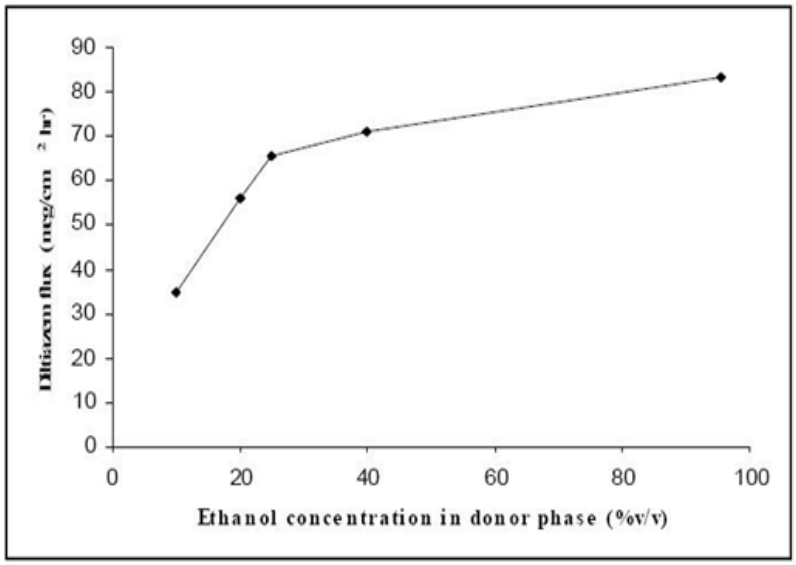

Fig 1. Effect of ethanol concentration on skin flux of Atenolol

After that 25% of Alcohol the enhancement in Cs turns out to be relentless. The conceivable clarification for the enhancement in saturation of Diltiazem base and Atenolol crosswise over the skin is usually given underneath. The lipid substance of stratum corneum as declared 267 was 44.5±1.17%w/w. The standard boundary for skin entrance rests in the stratum corneum. An arbitrary block display for medication transport crosswise over stratum corneum has been announced. 267 Stratum corneum comprises of the protein rich slight plates (cells) isolated from each other by dainty layer of intercellular lipids. Along with the similar alleys for medication diffusing crosswise over stratum corneum is announced.

- via the cell/intercellular in arrangement
- via the lipid intercellular courses
- via the smoothed protein cells.
- via the lipid intercellular course that is considered as lipophillic

It has been accounted for that lipid layers assume a huge job in skin saturation for the lipophillic drugs. The factor γ for the lipophillic sedate, γ = KDL/Dp >>> 104 showing a high inborn dissemination coefficient crosswise over the lipid layer (DL) when contrasted with inherent dispersion coefficient crosswise over the layer rich in protein (Dp) of the sratum corneum K, lipid-protein segment coefficient was present. Diltiazem base and Atenolol is known to be hydrophobic, openly dissolvable in the lipid solvents. It has been the lipophillic idea of this medication rendered the medication to travel openly (when contrasted with Diltiazem hydrochloride) from lipid layer. Liquor being lipid dissolvable appears to make the lipid hindrance of skin have fluidized encouraging arrangement dispersion layer system in the stratum corneum for the Diltiazem infiltration.

Ethanol is a decent dissolvable for the Diltiazem base and Atenolol appears to have enhanced the thermodynamic movement of Diltiazem base and Atenolol. It is accounted for higher the centralization of medication in the cells of stratum corneum higher will be flux. Liquor enhances the thermodynamic movement of the Diltiazem base and Atenolol in the stratum corneum keeping up high fixation in stratum corneum.

Preparation of polymeric matrix device

Grid – kind Rectal patches that contain Diltiazem base and Atenolol were readied utilizing distinctive proportions of medication to the polymers. Polymers were said something requirements proportions keeping the complete the polymer weight of 800mg, as well as broke down in a provided dissolvable. Diethyl Phthalate (2% w/w of the polymer organization), Di-n-butyl Phthalate (30% w/w of the polymer piece) as well as glycerin (40% w/w of polymer arrangement) were utilized in the form of plasticizer for EVA, ERL100, ERS100 as well as EC individually. Diltiazem (533.33mg) has been included and blended utilizing one mechanical stirrer. Constant scattering of polymeric arrangement of medication (10 ml) was discharged on the surface of the mercury (73.86 cm2), as well as allowed to get dried at the room temperature. Then after 24 hours, the films were divided into one 3.14 cm2 territory and support layer (biaxial arranged polyethylene film) was stuck after then. A shiny paper consisting of a surface that is smooth was utilized as a discharge liner. The gadgets were put away in the desiccators until utilized.

Table 4: Composition of polymeric matrix Diffusional patches of Diltiazem base and Atenolol

Formulation Code	Polymers	Plasticizers (%w/w of polymer composition)	Solvent
F1	EVA (VA 40%) Copolymer	DEP (2 %)	Toluene
F2	EC	Glycerin (40 %)	Chloroform

F3	ERS100	DBP (30%)	Chloroform
F4	ERL100: ERS100 (1:4)	DBP (30 %)	Chloroform

Fig 2. Matrix Diffusional rectal patch of Diltiazem base and Atenolol

Table 5: Results of thickness uniformity of F1 to F4 matrix formulations

Sr. No.	Formulation CODE	Average thickness (µm)			
		Trail-1	Trial-2	Trial-3	Mean±SD*
1	F1	172.5	175.0	172.5	173.33 ± 1.443
2	F2	115.0	117.5	117.5	116.66 ± 1.443
3	F3	150.0	152.5	150.0	150.83 ± 1.443
4	F4	85.0	87.5	82.5	85.00 ± 2.500

*Standard deviation, n=3

Table 6: Results of weight variations of F1 to F4 matrix formulations

Sr. No.	Formulation	Average weight (mg)			
	Code	Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	53.0	53.1	52.9	53.00 ± 0.100
2	F2	52.5	52.6	52.3	52.46 ± 0.152
3	F3	58.0	57.5	58.5	58.00 ± 0.500
4	F4	50.3	50.2	50.4	50.30 ± 0.100

*Standard deviation, n=3

Table 7: Results of % drug content of F1 to F4 matrix formulations

S. No.	Formulation Code	Drug Content (mg)			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	98.57	96.52	98.53	97.87 ± 1.172
2	F2	101.20	100.05	101.23	100.82 ± 0.672
3	F3	97.80	98.90	99.02	98.57 ± 0.672
4	F4	101.50	101.20	99.02	101.23 ± 0.251

*Standard deviation, n=3

Table 8: Time, Cumulative amount of drug release from device (µg/cm 2)

Time (hr 1/2)	Cumulative amount of drug release from device (µg/cm 2) (Formulation code)			
0.707	F1 (1105.51 ± 15.20)	F2 (486.25 ± 5.39)	F3(180.16 ± 5.34)	F4 (305.87 ± 6.32)
1.000	1499.85 ± 20.33	750.17 ± 10.34	339.65 ± 6.40	475.53 ± 8.44
1.414	2099.63 ± 25.46	1164.70 ± 15.34	540.96 ± 7.35	845.80 ± 10.32
1.732	2470.25 ± 26.59	1520.00 ± 18.45	688.56 ± 10.49	1050.56 ± 12.53
2.000	2985.46 ± 32.46	1775.24 ± 20.58	830.25 ± 11.40	1295.23 ± 15.42
2.236	3231.56 ± 30.29	1920.56 ± 22.59	940.56 ± 17.39	1475.47 ± 18.48
2.449	3500.23 ± 45.38	2100.36 ± 25.79	1075.82 ± 19.84	1675.69 ± 19.32
Q/√T (µg/cm2 √hr)	1488.10	946.30	503.29	794.08
Correlation coefficient	0.9976	0.9959	0.9990	0.9987

*Standard deviation, n=3

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V. SUMMARY AND CONCLUSION

The results of the present study indicate that rectal drug delivery of Diltiazem base and Atenolol patches It exhibited well controlled and delayed release pattern and on site application and action.

One of the most popular administration routes from complications moderate to severe is the Parenteral route and the compliance 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.

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