

www.pharmaerudition.org

ISSN: 2249-3875



International Journal of Pharmaceutical Erudition

Research for Present and Next Generation

FEB. 2018

Vol: 07 Issue:04
(99-107)





Research Paper

FORMULATION AND DEVELOPMENT OF RECTAL DRUG DELIVERY SYSTEM OF DILTIAZEM HYDROCHLORIDE

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In the present work, rectal drug delivery systems containing diltiazem hydrochloride were prepared using various polymer blends of Ethyl Vinyl Acetate Copolymer, Ethyl cellulose, Hydroxypropyl methyl cellulose, Polyvinyl pyrrolidone. Physical evaluation was performed such as thickness, weight variation, % drug content. The experimental results shows that the rectal drug delivery system (RDDS) gives sustain release of the drug.

Key Words: Physical evaluation, Physical evaluation, diltiazem hydrochloride, sustain release of the drug

INTRODUCTION

Parenteral route is the preferred route of administration for moderate to severe complication, even though patients compliance are rather low for this mode of drug delivery as it is invasive drug delivery technique, requiring frequent pricking with needle.

All conventional dosage form except intravenous infusion, follow second-order kinetics. Dosage form releases drug initially at faster rate, leading to quick rise in blood level of drug and then falls exponentially until a further dose is administered. This results in peak and valleys pattern of drug concentration in blood and tissues. Thus, for most of the time the concentration of drugs either above the required therapeutic level or below it. The time course of various modes of administration.

It is evident that the quality of the rate of absorption and the rates of metabolic elimination would result on the equilibrium distribution of the drug in tissues and blood, but however missing in the case of conventional dosage forms. This factor as well as

some other factors such as repetitive dosing and unpredictable absorption, led to the concept of drug delivery system or the therapeutic system.

Experimental

Material

Diltiazem base was prepared from hydrochloric salt. 1 gm of Diltiazem hydrochloride was dissolved in 20 ml of distilled water. Strong ammonia solution was added and pH was adjusted upto 9.5. Diltiazem free base was precipitated out. The base was extracted and purified using solvent ether. Extraction process was carried out four times using 20 ml ether. Ethereal phase was collected and evaporated at 40°C. White amorphous powder of Diltiazem base was obtained.

Determination of melting point

Melting point of drug was determined by taking small amount of drug in a capillary tube closed at one end and placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplicates and average value was noted.



Determination of partition co-efficient

The partition co-efficient study was performed using n-octanol as oily phase and phosphate buffer, pH 7.4, as aqueous phase. The two phases were mixed in an equal quantity and were saturated with each other on a mechanical water bath shaker NSW-133 at 32°C for 24 hr. The saturated phases were separated by centrifugation at 2000 rpm on a REMI R-23 centrifuge. Standard plots of drug were prepared for both, the phosphate buffer and octanol. Equal volumes (10ml each) of the two phases were taken in conical flasks and, to each; 100mg of weighed amount of drug was added. The flasks were shaken at 32°C for 6h to achieve a complete partitioning at 100rpm. The two phases were separated by centrifugation at 1000 rpm for 5min and they were then analyzed for respective drug contents by UV/VIS spectroscopy method. The partition co- efficient of drug K_{o/w} was calculated using the following formula:

$$K_{o/w} = \frac{\text{Concentration in octanol/}}{\text{Concentration in phosphate buffer pH 7.4}}$$

Solubility studies

The solubility study of Diltiazem base was performed in phosphate buffer solution, pH 7.4, in distilled water, methanol, chloroform, ether, alcohol (95%), acetone, toluene, glycerol, liquid paraffin, triethanol amine and silicone oil separately by adding excess amounts of drug in each case and keeping the excess drug containing flasks on a water bath shaker NSW-133 for 24hr at 32°C.

UV /VIS Spectroscopic Analysis

UV spectrum of Diltiazem base was recorded on

UV/VIS Spectrophotometer by scanning 5 µg/ml solution of Diltiazem base in 0.01N hydrochloric acid and scanned between 200-400nm using UV/VIS Spectrophotometer.

Infrared (IR) Spectroscopic Analysis

The Fourier Infrared (FTIR) spectrums of moisture free samples of Diltiazem base was recorded on IR spectrophotometer by potassium bromide (KBr) pellet method. The scanning range was 4000 – 400 cm⁻¹ and the resolution was 1 cm⁻¹.

Differential Scanning Calorimetry (DSC) Analysis

DSC scans of the powdered samples were recorded using DSC- Shimadzu 60 with TDA trend line software. Drug was weighed (7-10 mg) and heated at a scanning rate of 10°C/min under dry nitrogen flow (100 ml/min) between 50-350°C. Aluminium pans and lids were used for drug sample. Pure water and indium were used to calibrate the DSC temperature scale and enthalpy response.

2 Partition co-efficient

Octanol and in vitro study fluid (here phosphate buffer, pH 7.4) are considered to be the standard system to determine drug partition coefficient between skin and in vitro study fluid. The logarithmic value of partition coefficient (log P) value was experimentally found to be 2.198. The result's obtained also indicate that the drug possess sufficient lipophilicity, which fulfills the requirements of formulating it into a Rectal patch. The biphasic nature of drug mimics the biphasic nature of skin, thus ensuring easy penetration through the skin. As per literature survey for



successful Rectal drug delivery system partition coefficient should be in the range of 1 to 4

PREPARATION AND CHARACTERIZATION OF ADHESIVE MATRIX DIFFUSIONAL RECTAL DRUG DELIVERY DEVICE OF DILTIAZEM AIM OF PRESENT INVESTIGATION

The adhesive matrix diffusional system tends itself to simple and easy processing of delivery device. The matrix (laminated, disc) being static in nature offers less problems of drug and formulation stability and results in robust product with near to no problems of handling and administration to patients. Laminated form of delivery device offers easy transfer of technique from laboratory operations to a large scale manufacturing. As preparation of sheets, laminates etc from polymer beads is the major activity of plastic industry. Screw extrusion or injection molding can facilitate the formation of drug laminates from the polymer beads mixed with additives and active agents.

This type of Rectal drug delivery system can be easily prepared on large scale as a continuous manufacturing process as compare to polymeric matrix diffusion controlled Rectal drug delivery device and membrane moderate reservoir type controlled Rectal drug delivery device.

The release rate is governed by Higuchi equation. The release in such system is proportional to square root of time and release is available until approximately 60 % of the drug is released. Thereafter release is related exponentially to time, exhibiting first order release.

Parameter influencing the release characteristics

of monolithic devices can be classified as solute dependent factors like solubility, partition coefficient and diffusion coefficient of drug in the matrix. The solute independent parameters are system variables like geometry, tortuosity, pores, concentration, volume fraction and diffusion layer etc. In the present investigation solute related factors were considered to fabricate the devices using adhesive.

With perception to above objective, it is necessary to modify current solid dosage forms in to controlled rectal drug delivery system. A first step in this process is to illustrate how formulation and process variables could give drug release through skin

The aim of present investigation is to formulate and optimize the Diltiazem adhesive matrix diffusion controlled rectal drug delivery system.

Formulation and evaluation of adhesive drug matrix device of Preparation of adhesive matrix device of Diltiazem

The rectal therapeutic system comprised a backing membrane, an adhesive layer containing drug and a release liner. Adhesive matrix – type rectal patches containing Diltiazem were prepared using different ratios of drug to adhesive (Table 1). Diltiazem was accurately weighed and dissolved in very small quantity of alcohol. This solution was mixed with natural rubber adhesive (Readymade received – Beta surgical, Rajkot). The uniform dispersion of drug and adhesive was spreaded on a drug impermeable polyethylene coated aluminum foil (5 x 3.5 cm²) with the help of TLC kit spreader to form a thin drug adhesive layer and dried at room temperature. After 24h, the films were cut

**Table 1: Different ratios of drug to adhesive**

Formulation	Adhesive (mg/cm ²)	Diltiazem (mg/cm ²)
F1	10	4
F2	10	6
F3	10	8
F4	10	10

into a 1.13 cm² area and covered with glossy paper which is used as a protective liner. Dosage forms were kept in desiccators until further used.

Physiochemical evaluation of adhesive matrix.

Thickness

The thickness of the patches was assessed at six different points using thickness gauge micrometer (0.001mm, Mitutoyo, Japan).

Weight variation

The weight variation for patch was determined using Sartorius electronic balance (Model CP-224 S), Shimadzu, Japan. Six patch from single batch (1.13 cm²), were weighed individually and the average weight was calculated.

Drug content

The Diltiazem content of drug adhesive matrix was estimated in triplicate and analyzed by UV-VIS spectrophotometer at 236.0 nm. Patches (n=3) of specified area (1.13 cm²), were cut and weighed accurately. The pieces were extracted using 10ml 0.01 N HCl in a 100 ml volumetric flask. It was shaken thoroughly and solution was transferred to a 100 ml volumetric flask. Similar procedure was repeated twice and collected fractions were mixed and filtered using whatman filter paper (Nyulge Nune, UK). This solution was diluted 100 times

using 0.01 N HCl and UV absorbance of the resulting solution was measured at 236.0 nm using 0.01 N HCl as a blank.

Moisture content (Loss on drying)

The inherent moisture presents in material may influence the stability of dosage forms, especially if it contains a drug that is sensitive to water. The absolute method is employed to determine the moisture content which gives a weight loss registered during storage.

Three patch from each batch (1.13 cm²), were weighed individually and the average weight was calculated. This weight was considered as an Initial weight. Then all the patches were kept in a desiccators containing activated Silica at normal room temperature for 24 hr. Then, the final weight was noted when there was no further change in the weight of individual patch. The percentage moisture absorption was calculated as a difference between initial and final weight with respect to final weight.

% Moisture content = [(Initial weight – Final weight)/ Final weight] * 100
Moisture absorption

Moisture uptake influences the stability of dosage form. Low moisture uptake protects the material from microbial contamination. So for rectal drug delivery system it was necessary to determine % Moisture absorption by matrices.

Three patch from each batch (1.13 cm²), were weighed individually and the average weight was calculated. This weight was considered as an Initial



weight. Then all the patches were kept in a desiccators containing 200 ml saturated solution of Sodium chloride (Relative humidity of 75%) at room temperature for 72h. The final weight was noted when there was no further change in the weight of individual patch. The percentage moisture absorption was calculated as a difference between final and initial weight with respect to initial weight. The % Moisture absorption was determined using below formula:

$$\% \text{ Moisture absorption} = \frac{[(\text{Final weight} - \text{Initial weight}) / \text{Initial weight}] * 100}{}$$

Results and discussion

The present investigation deals with the development of Diltiazem base adhesive matrix using different concentration of drug and adhesive. A diffusion mediated matrix controlled Rectal drug delivery system for Diltiazem base was successfully prepared using adhesive and it was evaluated using different physiochemical parameter

In vitro permeability study of Diltiazem through different polymeric membranes

The permeation studies were performed in a Fite's diffusion cell (cell capacity of 10 ml, cross sectional are 1.32 cm²).

The permeation studies were performed using polymeric membrane. A section of membrane was cut, measured and placed on the Fite's diffusion cell. A saturated drug solution (1 ml solution of Diltiazem base in ethanol having concentration 300 mg/ml) was kept in the donor compartment. The receiver compartment was filled with 200 ml of 0.01N HCl. The Fite's diffusion cell was kept in side the beaker containing receptor compartment. The temperature of diffusion cell was maintained at 37 ± 0.5°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and solution in the receiver compartment was constantly and continuously stirred during the whole experiment using magnetic bead.

The samples were withdrawn (2 ml, each time) at

Table 2: Result of thickness, weight variation, %drug content

Formulations	Thickness	Weight variation	%Drug content
1	83.333 ± 1.443	12.44 ± 0.1106	101.23±0.251
2	84.16 ± 1.443	14.20 ± 0.1301	97.87 ± 1.172
3	92.500 ± 2.500	15.44 ± 0.4225	100.82±0.672
4	110.00±0.000	17.53 ± 0.2042	98.57 ± 0.672

Results are the mean of triplicate trials observations ± S.D.

**Table 3: Parameters of permeation kinetic of Diltiazem across polymeric membrane.**

Parameter	Copolymer	EC	PVAC	ERS100
Flux	1633.40	10099.8	836.34	581.29
Correlation coefficient (Cg/cm hr)	0.9969	0.9958	0.9946	0.9910
Permeability coefficient (Cg/cm hr)	5.579	4.949	4.251	3.584

different time interval and an equal amount of 0.01N HCl was replaced each time. Absorbance of the samples was read spectrophotometrically at 236.0 nm taking 0.01N HCl solution, as a blank. The cumulative amount of drug permeated per square centimeter at each time interval was calculated and plotted against time. The release rate Hg/cm² hr was determined by simple regression analysis of steady state data.

All the membrane was sufficiently hydrophobic and Diltiazem base was also hydrophobic exhibited permeation across all the membrane. Membrane thickness independent permeation rate is an important tool to rate the membranes for permeation study. However, the permeation coefficient for EVA (VA 40%) copolymer was the highest; this is due to good partitioning of Diltiazem base from EVA (VA 40%) copolymer than other polymer used to prepare membrane. EVA (VA 40%) copolymer was selected as rate controlling membrane, to device reservoir type Rectal drug delivery system. This membrane was further characterized for various diffusion parameters

Results and Discussion

Drug permeability studies are important for

ensuring the sustained release performance and the reproducibility of rate and duration of drug release. In vitro release profile is an important tool that predicts in advance how the drug will behave in reservoir type drug delivery system. Drug permeability studies for different polymeric membranes were performed in a modified Fite's diffusion cell using 0.01N HCl, as a diffusion media at 37 ± 0.5°C. The release flux "Jss" was determined from the regression analysis of steady state data

STABILITY STUDY

Stability study of reservoir device containing Diltiazem

Membrane moderated reservoir device containing Diltiazem in form of solution and gel was subjected to accelerated thermal stability study. The accelerated stability studies were carried out according to ICH guideline by storing the samples at 25°C/60% RH, 30°C/65% RH and 40°C/ 75% RH for 90 days in a stability chamber (Thermo Lab., Mumbai, India). These samples were analyzed by UV Spectrophotometer method and checked for changes in physical appearance and drug content at an interval of 15 days



Intern

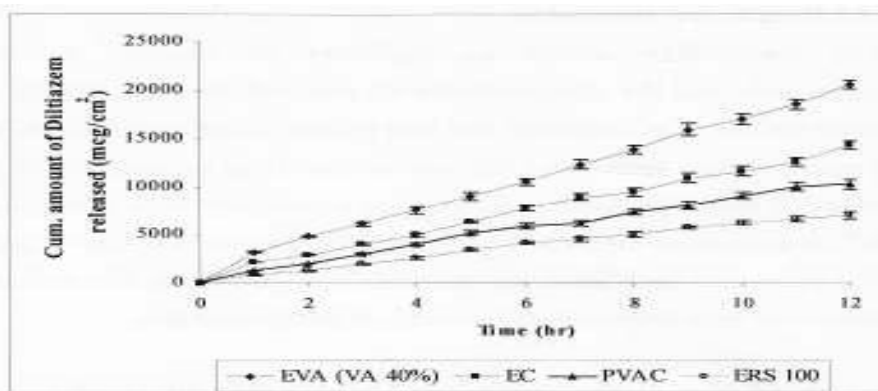


Fig 1: Release profiles of Diltiazem through various polymeric membrane

Standard deviation, n=3

Results and Discussion

Reservoir device containing alcoholic solution of Diltiazem and Diltiazem in carbopol gel was selected for stability study and observed for change in color, appearance, flexibility and drug content. Temperature and humidity values selected were as per the ICH guidelines and the test was carried out in a stability chamber. The stability studied was carried out at 25°C/60% RH, 30°C/ 65% RH and 40°C/ 75% RH for 90 days.

In case of reservoir device contains ethanolic solution of Diltiazem, it was observed that formulation stored at 40°C there is drastic change in physical characteristic of product. Crystals of drug was observed in the reservoir stored at higher temperature. The release rate for product stored at 30°C was also changed. The content of reservoir exhibited change in color from colourless to slight yellowish brown. However the product stored at 25°C exhibited a little change in the flux, but the flux was in order. There was no change in color and appearance for the product stored at room temperature. The first order rate constant of degradation for room temperature was 1.981×10^{-3} . The shelf life calculated was 53 week. The results

of stability study indicated that the products should be stored at a temperature not exceeding 25°C. Diffusion study of reservoir patch containing carbopol gel was carried out and it was observed that formulation stored at 40°C, exhibited burst effect phenomena. The release pattern and drug flux was altered. Due to decrease in viscosity of gel at an elevated temperature the content of reservoir turned quite soft. The drug flux for the product stored at room temperature was in order. There was no change in appearance, color for the product stored at room temperature. The first order rate constant of degradation for room temperature was 1.721×10^{-3} . The self life calculated was 61 week. Results of stability study indicates that product should be stored at temperature not exceeding 25°C.

Skin Irritation and Skin Sensitization Study

Skin irritation and skin sensitization though are different types of physiological responses yet they have several common indications. Skin sensitization is systematic response and skin irritation is primarily is local response.

A protocol was devised for evaluation of skin irritation and/or sensitization in such a manner that



the signs at the sight of application would be assessed in common for the both and further, to distinguish sensitization from irritation. The skin irritation and skin sensitization study was carried out as per procedure mentioned in chapter 5.8.1. The final Diltiazem reservoir patch containing solution (1.0 cm²) and reservoir patch containing Diltiazem gel (1.5cm²) was supported with aluminum foil. This was applied to the skin surface (shaved) and made adhered with the help of "3M Micropore"- medical adhesive tap (3M, corporation, U.K.).

Results and discussion

Once this sensitivity was established, the subsequent exposure to the chemical would lead to higher responses both locally (at the site of application) and systematically due to secondary immune reaction (hypersensitivity).

CONCLUSION

EVA (VA 40%) Copolymer membrane moderated Rectal drug delivery system of Diltiazem was successfully prepared. Among different polymers used to prepared rate controlling membrane, EVA (VA 40%) copolymer, 30 µm thick membrane provided promising Diltiazem flux. Two different formulations of Diltiazem (I) alcoholic solution (II) Gel were used to design two membrane moderated devices. On evaluation devices were found to be stable, non-irritant, non-sensitizing and safe. Devices complied to official and non-official pharmacokinetic specifications. The in vitro evaluation for drug release from device (I) and (II) across human live skin provided 43.95 and 23.78

µg/cm²hr, Diltiazem flux respectively. The fluxes were adequate to meet pharmacokinetic requirements of steady state plasma concentration of Diltiazem for 24 hrs from 12.61 cm² reservoir device containing alcoholic solution of Diltiazem and 23.31 cm² reservoir device containing gel, giving once a day drug delivery system of Diltiazem.

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