Development of transdermal drug delivery system of diltiazem hydrochloride for the treatment of hypertension

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ABSTRACT

Development of transdermal system mainly focused on formulation and characterization of monolithic matrix type transdermal drug delivery system of diltiazem hydrochloride for the treatment of mild to moderate hypertension. In this study, seven formulations were prepared in different ratio of film forming polymers. Formulations TDDS1 to TDDS7 were composed of carboxy methyl cellulose, polyvinyl pyrrolidone and carbopol 934, 5% w/v in different ratio. Formulations also contained 5% (w/w) of diltiazem hydrochloride, 1% (v/w) of Polyethylene glycol 400 and 1% (w/w) of tween 60 (based on total polymer weight). Developed transdermal drug delivery system were characterized for various physicochemical properties such as thickness, moisture content, water vapor transmission, folding endurance, drug content and in vitro release study. Formulation TDDS7 was found to be better as compared to other formulations and it was selected as the developed formulation.

Keywords: Hypertension, diltiazem, transdermal, drug delivery

INTRODUCTION

Transdermal drug delivery system (TDDS) is defined as self-contained, discrete dosage forms. Which, when applied to the intact skin, delivers the drug(s), through the skin, at a controlled rate to the systemic circulation[1]. By delivering a steady flow of drugs into the blood stream over an extended period of time, transdermal system can avoid the "peak and valley" effect of conventional dosages form[2]. Transdermal drug delivery provides many advantages over conventional mode of drug administration as it avoids hepatic first-pass metabolism and improves patient compliance[1,3]. Transdermal drug can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g. gastrointestinal irritation, low absorption, short half-life necessitating frequent dosing, self-administration is possible with this system, the drug input can be terminated at any point of time by removing transdermal patch[1].

Diltiazem hydrochloride is an antihypertensive class of calcium channel blocking drug. It is commonly prescribed for the treatment of mild to moderate hypertension and angina. Diltiazem hydrochloride undergoes an extensive hepatic metabolism, mainly through cytochrome P-450. Oral bioavailability of diltiazem hydrochloride is approximately 30% to 40% due to biotransformation. It has an elimination half-life of 3.5 h and has an absorption window from the upper intestinal tract. Efficacy of the oral dose may get diminished due to incomplete drug release from the conventional dosages form at absorption site. Diltiazem requires multiple oral daily dosages in order to maintain therapeutic plasma concentrations. Therefore, diltiazem hydrochloride is a suitable drug for transdermal formulation, which offers controlled delivery of drug [5,6].

MATERIALS

Diltiazem hydrochloride (DH) was obtained from Modi Mundi Pharma Pvt. Ltd. Meerut, India as gift sample. Polyvinyl pyrrolidone (PVP), carbopol 934 and carboxy methyl cellulose (CMC) procured from Central Drug House Pvt. Ltd., Mumbai, India. All other chemicals and regents were of analytical reagent grade and used as received. Double distilled water was used throughout the experiment.

METHOD

The matrix type film was prepared on a mercury substrate using the method reported by Balasubramanyam and Vasavada (1979)[7] various TDDS1 to TDDS7 were composed of carboxy methyl cellulose (CMC), polyvinyl pyrrolidone (PVP) and carbopol 934, 5% w/v in different ratio. All the formulations were also contained 5% (w/w) of diltiazem hydrochloride, 1% (v/w) of Polyethylene glycol 400 and 1% (w/w) of tween 60 (based on total polymer weight). The composition of polymer was used as given in Table 1. Matrix film was prepared by solvent evaporation method and evaporation was controlled by an inverted glass funnel of a suitable diameter in hot air oven. After complete evaporation of the solvent at (45 ± 5^{o}C), the film was removed from the glass ring and stored at controlled humidity (RH 51%) and ambient temperature for further use[8,9].

CHARACTERIZATION OF DEVELOPED TRANSDERMAL DRUG DELIVERY SYSTEM

Thickness

The screw gauge (Mercer, USA) was used to determine the film thickness. Before the measurement, the pointer in dial gauge was adjusted to zero deflection[10,11]. The average value of film thickness is given in Table2.

Moisture content (MC)

The weighed film samples were kept in an IR moisture balance (CSI, Bombay) at a temperature of 100±2^{o}C to dry for one h[12,13]. The percent moisture content was observed directly from IR moisture balance reading scale.

Water vapor transmission rate (WVT)

The WVT was determined by the method reported by Kaning and Goodman[8,14] at 25±5^{o}C and 75% RH. WVT rates were calculated by the formula of Kanig and Goodman and results are recorded in Table 2. WVT = Amount of moisture transmitted/ Area x time.

Folding Endurance time

A strip of specific area was cut evenly and repeatedly folded at the same place till it broke[15]. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Drug content

Drug content was determined in 1cm^2 polymeric transdermal film. Drug and other ingredients were dissolved in double distilled water. The transdermal film was cut into pieces of 1cm^2 which was further fragmented into pieces. The drug from the transdermal film was extracted in double distilled water and volume made up to 100 ml in volumetric flask with double distilled water[16,17]. One ml of this solution was further diluted to 10 ml with double distilled water and absorbance was measured against double distilled water as blank at 235 nm using Shimadzu 1700 UV/Visible double beam spectrophotometer and percentage drug content given in Table 2.

In vitro release study

The in vitro release of diltiazem hydrochloride from transdermal film was determined using locally fabricated Franz diffusion type cell[18,19]. A commercial semipermeable membrane was employed in the study as the permeation barrier (Dialysis membrane-110, average flat width- 32.34 mm, average diameter 21.5 mm, molecular weight cut off 12 KD, HiMedia Laboratories Pvt. Ltd., India). The semipermeable membrane was mounted on the receptor compartment of the Franz diffusion cell and product approximately equivalent to 5 mg of the drug was applied. The receptor compartment contained 30 ml of the phosphate buffer (pH-6) solution at 37±5°C. Samples of 5 ml were withdrawn at a time interval of one h and the same was replaced with 5 ml of the fresh media solution in order to maintain the sink condition. The withdrawn samples were diluted with isotonic buffer (pH-6) solution. The samples were analyzed spectrophotometrically for drug content at 235 nm using double beam Simazdu 1700 spectrophotometer[18].

RESULTS AND DISCUSSION

The matrix type transdermal drug delivery system of diltiazem hydrochloride was developed by the film casting on a mercury substrate to obtain a controlled drug delivery of diltiazem hydrochloride. Seven formulations were developed which differed in the ratio of matrix forming polymers. These transdermal drug delivery systems characterized for various physicochemical parameters such as thickness, moisture content (MC), water vapor transmission (WVT), folding endurance, drug content and in vitro release studies. Thickness of the film specimens were found from 0.43±0.14 mm to 0.56±0.16 mm. MC is a part of film composition which affects WVT, structural characteristic of film and hydration of skin. It was found in the range of 14.34±0.76% to 17.44±0.73%, the difference may be attributed due to the nature of polymer composition. WVT directly

influence the absorption of drug by affecting hydration of skin. Higher WVT remove water from stratum corneum and low WVT keeps skin hydrated and enhances drug permeation through skin[18]. It was found in the range of 1.68±0.34 to 2.53±0.47 (g/h/cm^2). Folding endurance of all the formulation was found under acceptable limit i.e. more than 200 time. Drug content was determined by weighing the prepared film (1cm^2) and dissolving in the double distilled water and analyzed at 235 nm using double beam Simazdu 1700 spectrophotometer. The drug content was found in the range of 88.34 to 98.67 % in all the formulations. The in vitro release of diltiazem from transdermal drug delivery were determined using modified Franz diffusion type cell and artificial membrane mounted on receptor compartment [20,21]. It was found from 53.57 to 69.34% in 8 h. The release mechanism of diltiazem from transdermal formulations was also determined on the basis of theoretical dissolution equations viz. zero-order, first-order, Higuchi matrix and Peppas-Korsmeyer kinetic models[22]. The regression coefficients from in vitro release profiles of diltiazem were calculated and are reported in Table 3. Release pattern of diltiazem from transdermal formulations mainly followed zero-order and first-order model, which may be due to the composition of the formulations, presence of some of drug in crystal stage and diffusion of drug from matrix. Formulation TDDS7 was found to be better as compared to other on the basis of evaluation and release profile. It may be conclude that diltiazem hydrochloride could be administered transdermally.

Hence, on the basis of method of preparation and evaluation, it can be concluded that the transdermal systems are easy to prepare and can be produced commercially for drugs employed for effective treatment of hypertension, cardiac arrhythmias and angina pectoris. Various ingredients used in this method are of economic and does not use any specific instrument. Product can be produced on large scale for commercial purpose.

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TABLE 1: COMPOSITION OF TRANSDERMAL DRUG DELIVERY FILMS

S. No.	Film Code	Polymer Composition (g) CMC: PVP: Carbopol 934
1.	TDDS1	1:0:0
2.	TDDS2	0:1:0
3.	TDDS3	0:0:1
4.	TDDS4	0:0.5:0.5
5.	TDDS5	0.5:0.5:0
6.	TDDS6	0.5:0:0.5
7.	TDDS7	0.33:0.33:0.33

CMC, Carboxy methylcellulose; PVP, Polyvinylpyrrolidon,

TABLE 2: EVALUATION DATA OF TRANSDERMAL DRUG DELIVERY SYSTEM

Film Code	Thickness mm	% M C	WVTx10^{-4} g/h/cm^2	% Drug Content
TDDS1	0.48±0.15	17.43±0.69	2.53±0.47	88.34
TDDS2	0.49±0.22	17.44±0.73	2.35±0.53	92.76
TDDS3	0.56±0.16	15.37±0.66	2.32±0.45	89.12
TDDS4	0.48±0.29	14.34±0.76	1.96±0.78	92.66
TDDS5	0.46±0.18	16.34±0.98	2.46±0.23	92.34
TDDS6	0.45±0.14	15.40±0.47	2.13±0.98	96.12
TDDS7	0.43±0.14	16.55±0.56	1.68±0.34	98.67

TABLE 3. THE REGRESSION COEFFICIENTS FOR IN VITRO RELEASE STUDY OF TRANSDERMAL DRUG DELIVERY SYSTEMS.

Formulation code	Zero order	First order	Higuchi Matrix	Peppas-Korsmeyer
	r^2	r^2	r^2	r^2
TDDS1	0.8829	0.9734	0.8297	0.8836
TDDS2	0.8722	0.8954	0.9332	0.9734
TDDS3	0.8876	0.9734	0.9155	0.8743
TDDS4	0.9834	0.9603	0.8874	0.8732
TDDS5	0.9765	0.9621	0.8985	0.8985
TDDS6	0.9874	0.9732	0.9246	0.9231
TDDS7	0.9987	0.9351	0.8641	0.8982

*H-M, indicates Higuchi matrix; P-K, Peppas-Korsmeyer; r, indicates correlation coefficient; TDDS1 to TDDS7, different transdermal drug delivery systems.

FIGURE 1: In vitro release profile of diltiazem hydrochloride from transdermal drug delivery system