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Review Article

FORMULATION AND CHARACTERIZATION OF DILTIAZEM TRANSDERMAL SYSTEM FOR THE TREATMENT OF HYPERTENSION

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ABSTRACT

The present study deals with the formulation and characterization of matrix-type transdermal drug delivery system (TDS) of diltiazem hydrochloride for the treatment of hypertension. The TDS was prepared by the solvent evaporation method on a mercury substrate. Ten formulations were prepared which differed in the ratio of matrix-forming polymers. Formulations TDS1 to TDS10 were composed of HPMC (hydroxypropyl methylcellulose), PVA (polyvinyl alcohol) and gelatin 10%, w/v in the combination of single polymer, two polymers (1:1) and three polymers in the ratio of 1:1:1, 1:2:1, 2:1:1 and 1:1:2 respectively. All the ten formulations contained 5 % (w/w) of diltiazem hydrochloride, 1 % (v/w) of propylene glycol and 1 % (w/w) of tween 80 (based on total polymer weight). The transdermal drug delivery system characterized for various physicochemical properties such as thickness, moisture content (MC), moisture uptake, water vapor transmission (WVT), folding endurance, drug excipients interaction, drug content and *in vitro* release study. On the basis physicochemical properties and *in vitro* release study, formulation TDS8 was found to be better than the other formulations, and it was selected as the developed formulation.

Keywords: Diltiazem, Hypertension, Transdermal drug delivery, *In vitro* evaluation

INTRODUCTION

Transdermal therapeutic system 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 bloodstream over an extended period of time, the transdermal system can avoid the "peak and valley" effect of oral or injectable therapy [2]. Controlled drug release can be achieved by Transdermal drug delivery system (TDDS), also known as "patches". They are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin at a predetermined rate over a prolonged period of time [3].

Transdermal drug delivery provides many advantages over the conventional mode of drug administration as it avoids hepatic first-pass metabolism and improves patient compliance [1, 4]. The 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 a calcium channel blocker exhibits 40% oral bioavailability due to hepatic *first-pass* effect [5]. To overcome bioavailability problem, dose-dependent side effects and frequency of administration. Diltiazem hydrochloride monolithic matrix type transdermal patches were prepared and characterized.

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 an important 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 the transdermal formulation, which offers controlled delivery of drug [6, 7].

Main components of transdermal patch

Polymer matrix

The backbone of TDDS, which controls the release of the drug. The polymer should be chemically non-reactive, should not decompose on storage, should be nontoxic, cost should not be high. Example-cellulose derivatives, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone, etc.

Drug

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life. eg fenatyl, nitroglycerine etc.

Permeation enhancers

Increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug. These are of three types-lipophilic solvent, surfactants, and two component systems. Example-DMSO

Adhesive

Increase permeability of stratum corneum, to attain higher therapeutic levels of the drug.

Backing laminates

Should have low modulus or high flexibility. Example-vinyl, polyethylene.

Release liner

Protects the patch during storage. The liner is removed prior to use.

Other excipients like plasticizers and solvents [8].

MATERIALS AND METHODS

Diltiazem hydrochloride (DH) was obtained from Modi Mundi Pharma Pvt. Ltd. Meerut, India as gift sample. PVA, gelatin and HPMC

procured from Central Drug House Pvt. Ltd., Mumbai, India was procured. All other chemicals and reagents were of analytical reagent grade and used as received. Double distilled water was used throughout the experiment.

Method of preparation

The matrix type film was prepared on a mercury substrate using the method reported by Balasubramanyam and Vasavada (1979)[9] various TDS1 to TDS10 were composed of HPMC (hydroxypropyl methylcellulose), PVA (polyvinyl alcohol) and gelatin 10%, w/v in the combination of single polymer, two polymer (1:1) and three polymer in the ratio of 1:1:1, 1:2:1, 2:1:1 and 1:1:2 respectively. Diltiazem hydrochloride (5% w/w based on total polymer weight), propylene glycol 1% v/w (based on total polymer weight), as plasticizer and tween 80, 1% w/w (based on total polymer weight) as penetration enhancer were used to cast the drug containing transdermal film. The solvent evaporation was controlled by an inverted glass funnel of a suitable diameter. After complete evaporation of the solvent at (35±5°C), the film was removed from the glass ring and stored at controlled humidity (RH 51%) and temperature (25±2°C), the prepared film were characterized for thickness, MC, WVT, drug excipients interaction, drug content and *in vitro* release studies [10, 11].

Characterization of 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. The average value of film thickness is given in table 1.

Moisture content (MC)

The weighed film samples were kept in an IR moisture balance (CSI, Bombay) at a temperature of 100±2° to dry for one hour. The percent moisture content was observed directly from IR moisture balance reading scale.

Percentage moisture uptake

The weighed films were kept in desiccators at room temperature for 24 h containing a saturated solution of potassium chloride in order to maintain 75% RH. After 24 h, films were reweighted and percent moisture uptake was determined by the formula of percentage moisture uptake = final weight–initial weight/initial weight x 100.

Water vapor transmission rate (WVT)

The WVT was determined by the method reported by Kaning and Goodman [10] at 25±5° 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.

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 gm of anhydrous calcium carbonate was taken in the vials and the polymer films were fixed over the brim with the help of adhesive tape. Then the vials were weighed and stored in a humidity chamber at 75 % RH condition for a period of 24 h.

Folding endurance time

A strip of the specific area was cut evenly and repeatedly folded at the same place till it broke. 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 1 cm^2 polymeric transdermal film and the drug was extracted in double distilled water. The transdermal film was cut into pieces of 1 cm^2 which were further fragmented into pieces. The drug from the transdermal film was extracted in double distilled water and volume made up to 100 ml in a volumetric flask with double distilled water. 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.

Drug excipients interaction

50 mg of each ingredient was mixed separately into a series of 10 ml volumetric flask, containing 5 ml of 10µg/ml drug solution and allow keeping aside for 48hr at the ambient condition with intermittent shaking. The volume of each flask made up to 10 ml with phosphate buffer solution pH 6.0 and mixed thoroughly. After 48 hr, the content of each volumetric flask was filtered through Whatman filter paper no. 1 and then absorbance of the solution was measured at 235 nm with phosphate buffer solution pH 6.0 as blank, using Shimadzu 1700 UV/Visible double beam spectrophotometer [12].

Drug release study

The *in vitro* release of diltiazem hydrochloride from the transdermal film was determined using locally fabricated Franz diffusion type cell [13, 14]. 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 two hours 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 an isotonic buffer (pH-6) solution. The samples were analyzed spectrophotometrically for drug content at 235 nm using double beam Simazdu 1700 spectrophotometer [12].

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. Ten 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), percentage moisture uptake, water vapor transmission (WVT), folding endurance, drug excipients interaction, drug content and *in vitro* release studies. The thickness of the film specimens was found from 0.36±0.15 mm to 0.45±0.12 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 10.90±0.50% to 15.65±0.30%, the difference may be attributed due to the nature of polymer composition. Moisture uptake of the formulation was from 04.35±0.87% to 31.56±0.82%. WVT directly influence the absorption of drug by affecting the hydration of the skin. Higher WVT removes water from stratum corneum, and low WVT keeps skin hydrated and enhances drug permeation through the skin [12].

It was found in the range of 0.79±0.83 to 1.32±0.48 (g/h/cm^2), the excipients did not interfere with the drug. Folding endurance of all the formulation was found under acceptable limit i.e. more than 100 time. Drug content was determined by weighing the prepared film (1 cm^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 93.52 to 99.82% in all the formulations. The *in vitro* release of diltiazem from transdermal drug delivery was determined using modified Franz diffusion type cell and artificial membrane mounted on receptor compartment [14, 15].

The *in vitro* release study revealed that on increasing the concentration of PVP in the transdermal drug delivery system, the drug releases increases in combination with HPMC and gelatin. It was found from 28.37 to 56.42% in 24 hr. 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. The regression coefficients and rate constants from *in vitro* release profiles of diltiazem were calculated using PCP Disso Version 3 software (Pune, India) and are reported in table 3. Release pattern of diltiazem from transdermal formulations mainly followed Higuchi matrix and Peppas-Korsmeyer 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.

Table 1: Composition of transdermal films

S. No.	Film code	Polymer ratio HPMC: PVP: gelatin
1.	TDS1	1:0:0
2.	TDS2	0:1:0
3.	TDS3	0:0:1
4.	TDS4	0:1:1
5.	TDS5	1:1:0
6.	TDS6	1:0:1
7.	TDS7	1:1:1
8.	TDS8	1:2:1
9.	TDS9	2:1:1
10.	TDS10	1:1:2

All values are expressed as mean of three observations, HPMC, Hydroxypropyl-methylcellulose; PVP, Polyvinylpyrrolidone, Gelatin.

Table 2: Evaluation data of transdermal films

Film code	Thickness Mm	% M C	% Moisture uptake	WVTx10^{-4} g/h/cm^2	% Drug content
TDS1	0.36±0.15	13.79±0.58	08.38±0.42	1.31±0.08	97.66
TDS2	0.41±0.08	10.90±0.50	32.56±0.82	0.80±0.10	98.38
TDS3	0.45±0.12	15.35±0.25	12.35±0.31	1.72±0.11	97.52
TDS4	0.38±0.19	15.65±0.30	09.75±0.39	0.89±0.36	96.39
TDS5	0.36±0.29	13.79±0.58	08.38±0.42	1.31±0.08	97.64
TDS6	0.40±0.26	10.90±0.50	32.56±0.82	0.80±0.10	98.27
TDS7	0.42±0.13	13.35±0.48	12.67±0.43	1.52±0.78	99.82
TDS8	0.39±0.18	16.65±0.29	04.35±0.87	0.79±0.83	98.94
TDS9	0.41±0.03	12.35±0.98	11.35±0.31	1.32±0.48	93.52
TDS10	0.43±0.23	14.65±0.78	13.55±0.69	0.97±0.65	94.69

Table 3: The regression coefficients and rate constants for *in vitro* release study of transdermal drug delivery systems

Formulation	Zero-order model		First-order model		H-M model		P-K model	
	R	k1	r	k2	R	k3	r	k4
TDS1	0.9646	16.4824	0.8394	-0.1398	0.9938	12.6731	0.9664	15.8474
TDS2	0.8664	17.0263	0.8339	-0.1282	0.9746	13.2876	0.9564	15.2373
TDS3	0.9673	14.9474	0.8849	-0.1476	0.9472	14.2875	0.9763	16.8731
TDS4	0.9782	16.0846	0.8746	-0.1746	0.9873	13.4293	0.9487	16.9374
TDS5	0.9743	17.7464	0.7074	-0.1736	0.9764	13.2748	0.9648	16.0982
TDS6	0.9874	15.8474	0.8462	-0.1277	0.9762	13.6192	0.9639	15.9363
TDS7	0.9655	17.5874	0.8874	-0.1048	0.9804	12.7478	0.9623	17.3744
TDS8	0.9722	16.8736	0.8763	-0.1277	0.9854	12.2863	0.9987	17.4984
TDS9	0.9616	16.6454	0.8746	-0.1484	0.9855	12.7462	0.9764	13.4763
TDS10	0.9734	16.8474	0.8756	-0.1746	0.9785	13.3447	0.9623	16.7484

*H-M, indicates Higuchi matrix; P-K, Peppas-Korsmeyer; r, indicates correlation coefficient; k1-k4, rate constants of zero-order, first-order, Higuchi matrix, Peppas-Krosmeyer; TDS1 to TDS10 different transdermal drug delivery systems.

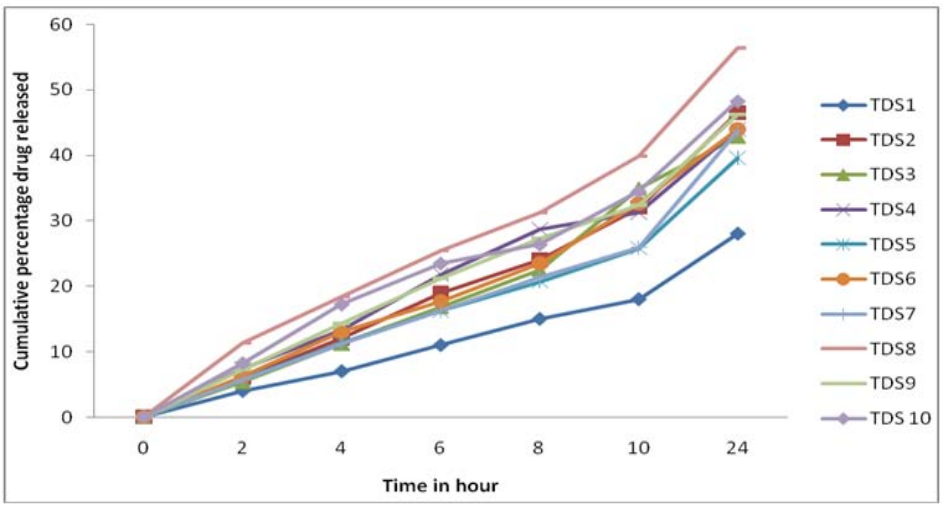

Fig. 1: *In vitro* release profile of diltiazem hydrochloride from transdermal formulations

CONCLUSION

It can be concluded from the above study that formulation TDS8 was found to be better as compared to other formulation on the basis of evaluation and *in vitro* release profile. It shows that Diltiazem hydrochloride could be administered transdermally. Hence, on the basis of the method of preparation and evaluation, it can be concluded that the transdermal systems can be produced commercially for drugs employed for effective treatment of hypertension, cardiac arrhythmias, and angina pectoris.

CONFLICT OF INTERESTS

Declare none

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