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Formulation and Evaluation of Transdermal Therapeutic System of matrix type Clonidine hydrochloride

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ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing Clonidine hydrochloride with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by Infrared spectroscopy and U.V. spectrophotometry. The results suggested no physicochemical incompatibility between the drug and the polymers. In vitro permeation studies were performed by using Keshary -Chien cell. The results followed Higuchi kinetics (r = 0.9953-0.9979), and the mechanism of release was diffusion mediated. Based on physicochemical and in vitro skin permeation studies, patches coded as B9 (Eudragit L-100-55: PVP K-30, 3:1) and D2 (Eudragit L-100-55: HPC, 3:1) were chosen for further studies. The bioavailability studies in rats indicated that the Clonidine hydrochloride transdermal patches provided steady-state plasma concentrations with minimal fluctuations and improved bioavailability of 82.12% (for B9) and 75.90% (for D2) in comparison with oral administration. These patches go for further Skin and Stability studies. Skin irritation studies indicated that formulation produced no or very mild skin irritation. Stability studies indicated that on the basis of first order degradation kinetics and $t_{0.5}$ *Shelf life was calculated to be 2.98 and 2.79 yrs.The developed transdermal patches increase the efficacy of the therapy of hypertension.*

Keywords: Transdermal, antihypertensive, Clonidine hydrochloride, Polyvinylpyrrolidone, Hydroxypropyl cellulose, Eudragit L100-55.

INTRODUCTION

A transdermal drug delivery system (TDDS) has many advantages over conventional modes of drug administration, in particular the avoidance of hepatic first-pass metabolism, a reduction in the frequency of drug administration, and an improvement of patient compliance [1]. Thus, transdermal administration is a potential approach to overcoming these problems with Clonidine treatment. A TDDS consists of several components, including the active ingredient, a pressure-sensitive adhesive (PSA), a permeation enhancer, backing membrane and so on. A PSA fulfills the adhesion-to-skin functions and serves as the formulation foundation. Because the physicochemical properties of PSA significantly affect the permeation rate of a drug across the skin, the selection of an appropriate PSA matrix is of importance in designing a TDDS [2,3]. Permeation enhancers can overcome the intrinsic resistance of the stratum

corneum, which results in an increase in the flux of the active ingredient [4],therefore, we tried to design a monolithic adhesive matrix-type patch, which is the simplest among the various patches used in the present study.

Clonidine hydrochloride is the most widely prescribed drug in the long term treatment of hypertension. Following oral administration, Clonidine hydrochloride is rapidly absorbed from the gastrointestinal tract (40 to 60%) but the oral bioavailability remains low (eg 23%) because of significant first-pass hepatic metabolism.

Clonidine also has a short plasma half-life of 10 hours. Long term therapy of hypertension by Clonidine oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life, leading to increased frequency of administration. An alternate route of administration is needed. The transdermal route is an alternative for administration of such drugs. This route offers many advantages over the oral dosage form, such as improving patient compliance in long-term therapy, bypassing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intrapatient variability, and making it possible to interrupt or terminate treatment when necessary.Clonidine hydrochloride possesses ideal characteristics—such as a low molecular weight (266.6),smaller dose range (100µg), short plasma half-life, and poor oral bioavailability—for formulation as a transdermal patch. There are reports describing the use of Eudragit L (EL),HPC and PVP transdermal delivery systems as well as other dosage forms for controlled release of drugs [5]. EL and PVP is freely permeable to water [6] These transdermal delivery systems are neither extremely hydrophobic nor extremely hydrophilic. Therefore, varying the ratio of these polymers in the composition of the films provides control of drug release characteristics [7].

The aims of the present study were to (1) Develop different matrix patches with various ratios of hydrophilic and hydrophobic polymer combinations such as hydroxypropyl cellulose (HPC) and EL100-55 and (b) EL100 -55 and polyvinylpyrrolidone (PVP), containing Clonidine hydrochloride (2) Perform physicochemical characterization and in vitro permeation studies through rat skin. The purpose was to provide the delivery of the drug at a controlled rate across intact skin to improve bioavailability and hypertension control for longer period from transdermal patches.

MATERIALS AND METHODS

Material required:

Clonidine hydrochloride was received as a gift sample from Kalindi Medicure Pvt. Ltd, Vapi (India). EL100-55 was purchased from Rohm Pharma, HPC – from NISSO, PVP and Ethanol were used of AR grade. Other materials used in the study (Chloroform, Acetone ,Glycerol ,Propylene Glycol,PEG400,PEG200, Caster Oil , Dibutylphthalate ,Potassium dihydrogen phosphate ,Sodium hydroxide, Ammonia solution, Tween80, Eucalyptus oil and Ethyl cellulose) were of analytical grade. Double-distilled water was used throughout the study.

Method:

Physicochemical Compatibility of Drug and Polymer

The physicochemical compatibility between Clonidine and polymers used in the patches was studied by using Fourier transform infrared (FTIR) spectroscopy. The infrared (IR) spectra were recorded using an FTIR spectrophotometer (FTIR-800, Punjab University, Chandigarh) by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Clonidine hydrochloride, polymers, and physical mixtures of Clonidine hydrochloride with polymers were compared.

Preparation of Transdermal Films

The matrix-type transdermal patches containing Clonidine hydrochloride were prepared using different ratios of EL 100-55: PVP and EL 100-55: HPC (Table 1). The polymers in different ratios were increased to a total weight of 600 mg and dissolved in Ethanol 95%. Clonidine hydrochloride (1.38% w/w of polymer) was added slowly to the polymer solution and mixed thoroughly to obtain a uniform solution. PEG-400 was used as a plasticizer. The polymeric solution of drug was poured onto the mercury surface (29cm^2) and dried at room temperature in a dust-free environment. After 24 hours, the films were cut by circular with die and to “cut patches” adhesive tape was applied on the backing side. Transdermal films were stored in a desiccator **until** further use.

Evaluation of Physicochemical Properties of Patches Thickness:
The thickness of the films was measured with the help of screw gauge, having the least counts of 0.01mm.The film was held between the jaws of the instrument and readings were recorded at five different points in each film. This prevented the sticking of the film to the jaws. Results have been shown in the Table 1

Weight Variation:
The weight of the selected film patches (1.41cm^2) was determined using the electronic balance (Sigma-200/A deluxe).Results are given in Table 1

Folding Endurance:
The folding endurance value can be defined as "the number of times the film can be folded at the same point without breaking. This enables to determine the brittleness of the film, lesser the folding endurance more the brittleness. The film patch was folded in the center between the finger and thumb and then opened. This was called "one folding". The procedure was repeated till a crack appeared or breakage of the film occurred. The total number of folds till the break denoted the folding endurance value. Results are shown in Table 1

Table-1: Physical Characteristics of Selected Polymeric Films

Placebo film code	Thickness of films (μm)		Weight of films (mg)		Folding endurance of detached films	
	Mean	(± SD)	Mean	(±SD)	Mean	(± SD)
A50	279	2.65	212	2.60	32	2.65
A53	165	2.81	230	2.89	33	1.00
A54	365	2.53	200	1.52	35	2.56
B9	170	2.64	248	1.54	112	2.65
B10	280	2.05	243	1.55	102	1.00
D1	218	1.00	250	2.59	78	2.89
D2	221	2.19	239	1.00	80	2.65
D4	201	2.65	243	2.00	65	2.61
D6	275	2.61	241	2.05	73	2.36
D7	280	2.61	235	2.05	71	2.00
D8	265	2.29	232	1.00	62	1.36
E4	175	2.64	211	2.35	79	1.00
E9	315	2.65	249	2.13	75	1.00

In Vitro Skin Permeation Studies
In vitro skin permeation studies were performed by using a Keshary -Chien cell [8] with a receptor compartment capacity of 15 ml. The excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 500 rpm; the temperature was maintained at 37 ± 0.5ºC. The samples were withdrawn at different time intervals and analyzed for drug content spectrofluorometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative amounts of drug permeated per square centimeters of patches were plotted against time.

In Vivo Studies
The animals used for in-vivo experiments were adult male Rabbit procured from the central animal house of the Department of Pharmacy, Bundelkhand University, Jhansi (U.P, India). The animals were kept under standard laboratory conditions, at 25 ± 1ºC and 55 ± 5% relative humidity with a 12-hour light/dark cycle. The animals were housed in polypropylene cages, 3 per cage, with free access to a standard laboratory diet and water. Guidelines of the institutional animal ethics committee were followed for in-vivo experiment.

Skin Irritation Test
These were performed on six rabbits, rabbits were divided into 2 groups (n = 3), to evaluate the irritant properties of the drug Clonidine hydrochloride. For this purpose, one TDDS (B9-M) containing the drug was fixed on one ear (pinna) and a second placebo TDDS (D2) was fixed on the second ear's pinna. Both the formulations were allowed to remain place for 48 hours and were then remove. The conditions of pinna B9 was compared to that of D2 placebo

affixed pinna, with respect to appearance of redness, flare, wheals and rashes. The ear pinna was observed for 7 days . Finally, the application sites were graded according to a visual scoring scale, always by the same investigator.

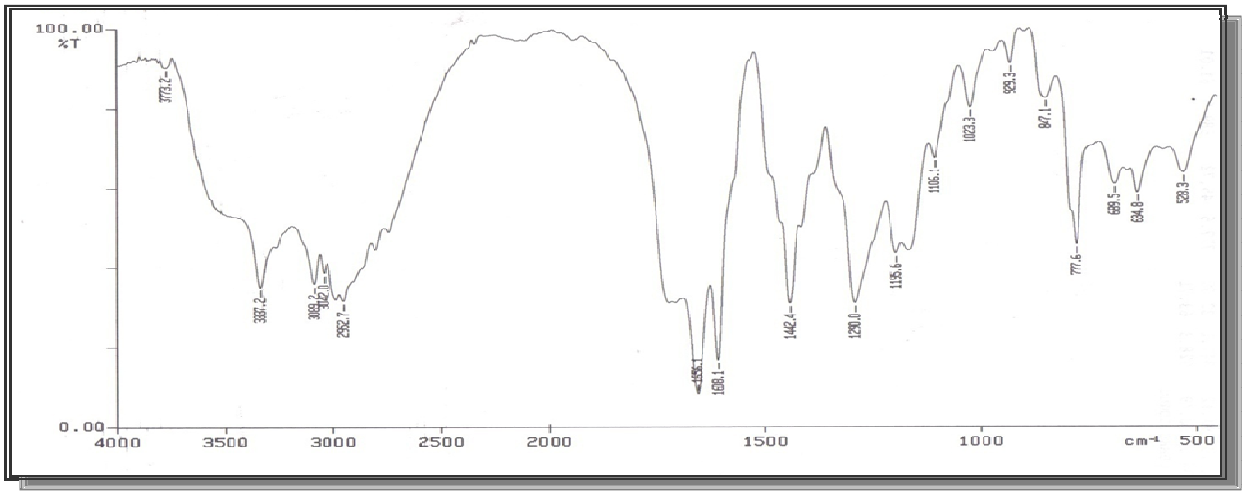

Fig. 1 : IR Spectrum of mixture of drug + Eudragit L100-55 + pvpk-30

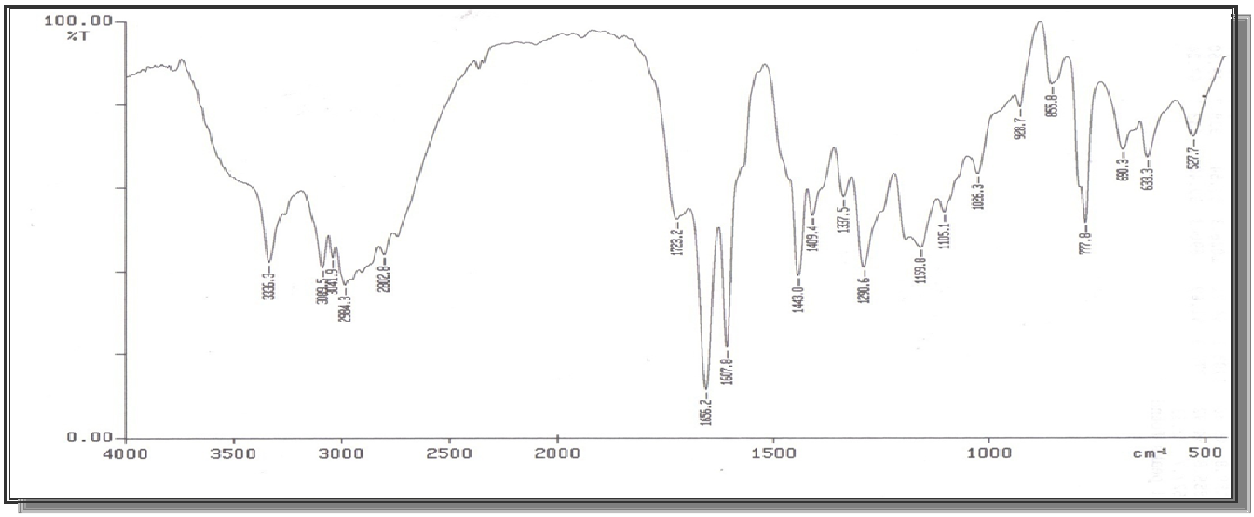

Fig. 2: IR Spectrum of mixture of drug + Eudragit L100-55 + HPC

RESULTS AND DISCUSSION

Investigation of Physicochemical Compatibility of Drug and Polymer: The IR spectral analysis of Clonidine alone showed that the principal peaks were observed at wave numbers 3087,1656,1443,1292, and 777cm$^{-1,}$ confirming the purity of the drug. In the IR spectra of the physical mixture of Clonidine, EL100-55, and PVP, the major peaks of Clonidine were observed at wave numbers 2954,1724,1390,1160,2956, and 1291, cm^{-1}; for the physical mixture of and Clonidine EL100-55, and HPC, they were observed at 2973,2881,1456,1081, and 754, cm^{-1}. However, some additional peaks were observed with the physical mixture, possibly because of the presence of polymers. The IR results suggest that the drug and polymers are compatible. Wade and Weller reported that HPC, PVP, EL100-55 and other common polymers are popular in controlled- and sustained release matrix-type patches because of their compatibility with several drugs.

Physicochemical Characterization of Patches: The results of the physicochemical characterization of the patches are shown in Table 1. The weights ranged between 200 mg and 250 mg, which indicate that different batches' patch weights were relatively similar. Good uniformity of drug content among the batches was observed with all formulations. The thickness ranged between165µg and 365 µg. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

In-Vitro Skin Permeation Studies: The in-vitro release profile is an important tool that predicts in advance how a drug will behave in-vivo [9] . The results of in-vitro skin permeation studies of Clonidine hydrochloride from transdermal patches are shown in Figures 3. The cumulative amount of drug released from formulations (1.14cm^2) B9and D2 (0.1800 mg/cm^{2}and 0.1469mg/cm^2) was high when compared with release from other formulations.

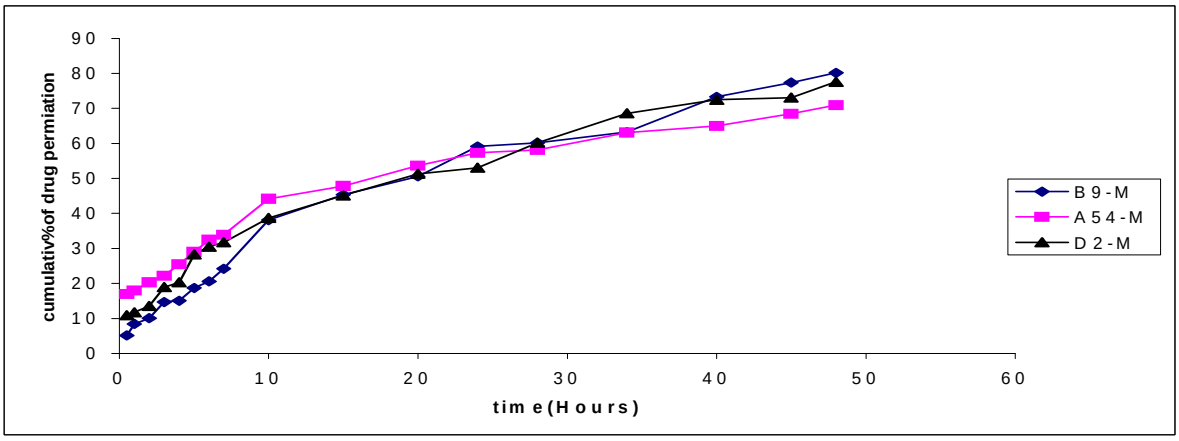

Fig. 3: In-vitro permeation profile through skin for clonidine hydrochloride from transdermal patches with different proportions of used polymers.

Unlike the formulations A50, A53, A54, B10, D1, D4, D6, D7, D8, E4, E9 the formulations B9 and D2achieved a high cumulative amount of drug permeation at the end of 48 hours. When the permeability coefficients (Figure 3) of 3 of them formulations were compared, B9 and D2 were found to have similar permeability coefficients and the highest levels of release. Based on physicochemical and in-vitro release experiments, B9 and D2 were chosen for further in-vivo studies.

Skin irritation Test: The skin irritation test of the transdermal formulations B9and D2 showed a skin irritation score (erythema and edema) of less than 2 (Table 2). According to Draize et al, compounds producing scores of 2 or less are considered negative (no skin irritation) [10] .Hence, the developed transdermal formulations are free of skin irritation.

Table-2- Skin irritation scores of formulations B9 and D2

Formulation code	Rabbit no.	Intact skin				Abraded skin			
		24hrs		72 hrs		24 hrs		72 hrs	
		A*	B**	A*	B**	A*	B**	A*	B**
B9	1	1*	0	0	0	1**	0	0	0
	2	1	0	0	0	1	0	0	0
	3	0	0	0	0	2	0	1	0
D2	1	0	0	0	0	2	0	1	0
	2	1	0	1	0	1	0	1	0
	3	0	0	0	0	1	0	0	0

Where A =erythema and scar formation score and B**=edema formation score*
**Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation.*
†Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe.

Table-3: Skin irritation scores of formulation B9 and D4 (calculation of other parameters)

Formulation code	Rabbit no.	Intact skin (i)		Abraded skin (ii)		Combined averages (i +ii)
		24 hrs*	72hrs*	24hrs*	72 hrs*	
B9	1	1	0	1	0	
	2	1	0	1	0	0.58
	3	0	0	2	1	
Average		0.33**		0.83**		
D2	1	0	0	2	1	
	2	1	1	1	1	0.66
	3	0	0	1	0	
Average		0.33*		1.00**		

** Total of A and B from Table-L2s*
*** Average of all six readings of 24 and 72 hrs*
i.e. (1+1+0+0+0+0)/6 = 0.33
Combined average was calculated as (0.33 + 0.88)/2 = 0.58 for formulation B9 AND
(0.33 + 1.00)/2 = 0.66 for D4

CONCLUSION

It could be concluded that Clonidine HCl, an Anti-hypertensive drug could be administered successfully from the monolithic matrix transdermal therapeutic system, developed in this study, for controlled release over a period of 48 hours. The system was free of any hazardous skin irritation. Further work is required to establish the utility of this system though long-term pharmacokinetic studies on human's subjects.

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