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Controlled drug delivery of diltiazem hydrochloride as transdermal patches: a novel approach on formulation evaluation *in vitro* and *in vivo* parameters

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A significant effort was done to formulate transdermal patches (Paranjothi 1998) of Diltiazem Hydrochloride (DH), a benzothiazepine calcium channel blocker, mainly meant for the treatment of hypertension, chronic stable angina pectoris; by using hydroxy ethyl cellulose, ethyl cellulose and Eudragit RLPO. Six batches of transdermal patches were prepared by solvent casting technique in which the best formulation was found out. The polymers HEC, EC and Eudragit RLPO were incorporated with Diltiazem Hydrochloride in various proportions, out of which the best formulation on the ratio [HEC: EC: EUDRAGIT RLPO-1:1:2] with the drug was determined. The prepared transdermal patches were spherical, uniform in shape and white in color. The obtained transdermal films were evaluated for physico-chemical characteristics, *in vitro* release profile and *in vivo* evaluation in albino mice. Higuchis plot studies revealed that the predominant mechanism of drug release was diffusion.

Key Words: Diltiazem Hydrochloride, Polymers, Transdermal patches, Albino mice.

Most highly remarkable efforts have been highly focused on the development of new drug delivery system. The new drug delivery system can improve patient's convenience and compliance due to less frequent administration. Moreover, the maximum utilization of drug enabling reduction in the total amount of dose administered, the design of any controlled transdermal drug release delivery system is subjected to several variables of considerable importance among them are the route of drug delivery system, the diseases being treated ,the patients, the length of the therapy, and the properties of the drug. The transdermal drug delivery is required not only for the local targeting of the drugs but also for a better control systemic drug delivery (Panchagunta 1997). The Diltiazem Hydrochloride (DH), a benzothiazepine calcium channel blocker is used alone or with an angiotensin converting enzyme inhibitor to treat hypertension, a chronic stable angina pectoris, and prinzmetal's variant angina. The drug is having the bioavailability about 15-30%, protein binding capacity as 70-80%.Diltiazem is metabolized in the liver and excreted in the urine. The elimination $t^{1/2}$ are in the range of2-6h.The total oral dose is 30-60mg\thrice in a day and going for parentrals; it is 25mg\5mL injection. The molecular weight of the drug is 414.519g \mol. Melting point is around231^{0}c, its having log\hydrophobicity of about 3.141,

were the various important criteria which should be considered [DH] for transdermal drug delivery.

Materials and Methods

Solvent casting technique

Accurately weighed quantity of HEC, EC and Eudragit RLPO compositions of different formulations [6 Batches] got mixed with 10.2mg of Diltiazem Hydrochloride. Out of various formulations; the best batch was found out. The transdermal films of DH were prepared by weighing accurately 10.2mg of DH incorporated with [HEC: EC: EUDRAGIT RLPO -1:1:2] ratio, and then it was transferred to a beaker containing 2.9 mL of distilled water. The solutions were mixed to get a clear solution. Glycerin was added as plasticizer. The whole solution were poured over mercury surface in a petridish and allowed to dry at room temperature. The same procedure was repeated with compositions of different formulation of drug with polymers.

In vitro drug release evaluation

Commercial semi-permeable membrane was employed in this study. The membrane used was transparent and regenerated cellulose type, which was permeable to low molecular weight substances (Naik 1993). A film of size 1cm diameter was cut and placed on the semi permeable membrane. The semi-permeable membrane was tied to one end of an open ended cylinder which acted as donor compartment. The entire surface of the membrane was in contact with the receptor compartment containing 300mL of phosphate buffer [PH7.4]. The content of the compartment was agitated by a magnetic stirrer. Samples of 1mL were withdrawn from receptor compartment and replaced by equal volumes of fresh media. The withdrawn samples were analysed using UV- visible spectrophotometer at 269 nm using reagent blank (**Table 1**).

Table 1: *In vitro* drug release data [HEC: EC: EUDRAGIT RLPO -1:1:2]

Time in Minutes	Drug release in mg	Cumulative % Drug Release
30	0.896	8.96
60	2.610	26.10
90	4.416	44.16
120	6.180	61.80
150	8.760	87.60
180	9.216	92.16

Table 2: *In vivo* drug release data [HEC: EC: EUDRAGIT RLPO -1:1:2]

Time in hours	Percentage of drug remaining [mg]	Amount of drug release [mg]	Percentage drug release
1	9.29	0.91	9.10
2	7.73	2.47	24.70
3	6.31	3.89	38.90
4	5.42	4.78	47.80
5	3.74	6.46	64.60
6	2.55	7.65	76-50

In vivo studies

A healthy albino mouse weighing 1.5-2.5 kg was taken, which was already checked for absence of any diseases. The dorsal surface of the albino mice was shaved and the transdermal patches having the size of 1cm containing 10.2 mg of DH was placed over the shaved surface. Dextrose solution was transfused continuously throughout the period of study. Periodically 1mL blood samples were taken using a syringe, which already contained 1 mL of 3.8% of sodium citrate solution to prevent blood clotting (Basak 1997). These blood samples were subjected for centrifuging at 2200rpm for about 20 minutes.1mL of the supernatant liquid was taken from this and after suitable dilution these samples were analysed at 269nm using UV- visible spectrophotometer.

The *in vivo* studies conducted for the transdermal patches of DH in albino mice showed zero order release pattern. The *in*

vivo study of the transdermal patches didn't show any inflammation or any other sensitization reaction at the administration site (**Table 2**).

Table 3: Composition of formulations

Batch Code	Polymers			Solvent	Plasticizer
	HEC (%)	EC (%)	EUDRAGIT RLPO (%)	Water (mL)	Glycerine (% W/W)
B1	1	1	1	2.5	30
B2	2	1	1	2.5	30
B3	1	2	1	2.5	30
B4	1	1	2	2.5	30
B5	2	2	1	2.5	30
B6	2	1	2	2.5	30

Concentration of Plasticizer = 30%W/W; Amount of drug loaded in each film = 10mg; 1% W/V = 50 mg; 2% W/V = 100 mg

Results and Discussion

The transdermal patches were subjected to various physico-chemical evaluation tests such as percentage moisture absorption, percentage moisture loss, swelling index, time taken for maximum swelling, water vapour transmission rate, folding endurance, drug content uniformity etc. The films were also subjected to *in vitro* dissolution studies, and *in vivo* studies using albino mice. The physico-chemical evaluations of the formulations have shown different physical characteristics of the formulations changed according to the nature and composition of the polymers (**Table 3**). *In vitro* dissolution study of drug along with different concentrations of polymers i.e; HEC, EC and Eudragit RLPO have been performed (Rove 2003). The higher rate and percentage of release of drugs in the film containing high concentration of Eudragit RLPO [HEC: EC: Eudragit RLPO-1:1:2] is considered as the best batch. As the percentage of Eudragit RLPO was enhanced, the rate of the release of drug was increased. Hence the batch [HEC: EC: EudragitRLPO-1:1:2] shows the best nature of films and the graph representing the best controlled drug release. In addition, it shows better stability and suitability.

Conclusion

The transdermal films prepared by solvent casting technique were spherical, uniform in shape and white color in nature (Mandal 1991). The formulation containing two parts of Eudragit RLPO, one part of HEC and EC respectively has shown best release in the concentration independent manner. Good correlation has been observed between the *in vitro* and *in vivo* profile and hence revealed the ability of the formulation to reproduce the *in vitro* release pattern through the biological membrane.

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