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FORMULATION AND IN VITRO EVALUATION OF TRANSDERMAL PATCHES OF NIFEDIPINE

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Abstract:

Transdermal patches of nifedipine with different composition of HPMC and EC polymers were prepared by solvent evaporation technique. The physicochemical parameters such as thickness, weight, drug content, folding endurance, moisture absorption, moisture losswere evaluated. The thickness and weight of all patches were within the satisfactory range. Moisture absorption was increased as the concentration of EC was increased. All the patches exhibited adequate folding endurance and good drug content uniformity. In vitro release profiles of the drug from different patches were studied by using diffusion cell. In vitro drug release studies were carried to 24 hrs time period and it was found that, as the concentration of EC increased the drug release was also increased. Polymers and their combination influenced the film properties as well as the release characteristics. Penetration enhancer does not shown any changes on the in-vitro drug release of nifedipine.

Key Words: *HPMC,EC and Nifidipine*

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INTRODUCTION:

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. The oral route is considered to be most convenient but conventional dosage forms are subjected to physiological conditions of variability between stomach, small intestine and large intestine due to pH, motility, enzymes and presystemic metabolism. The transdermal drug delivery (TDDS) has advantage to deliver drug via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.These systems deliver the drug at appropriate rates to maintain plasma drug levels required for therapeutic efficacy. Transdermal delivery of drug has acquired increasing interest due to its potential in avoiding the presystemic metabolism, thus achieving high systemic bioavailability of drugs and they are capable of sustaining the drug release for prolonged period of time. Despite of these advantages, only a limited number of drugs can be administered through this route, due to low skin permeability of drugs. To overcome these problems, vehicles, penetration enhancers, and electro transport facilitated transdermal systems have been attempted in the development of TDDS. [1,2]. Drugs administered via skin patches include scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine. Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories therapeutic and cosmetic), aroma patches, weight loss patches, and patches that measure sunlight exposure.

Nifedipine is a calcium channel blocker and are commonly regarded as specific to the L-type calcium channel, they also possess nonspecific activity towards other voltage-dependent calcium channels.[3,4] Nifedipine has an antagonist of the mineralocorticoid receptor, or as an anti mineralocorticoid.[5] Nifedipine is used for the management of vasospastic angina, chronic stable angina, hypertension and in Raynaud's phenomenon. It is frequently used as a Tocolytic i.e, an agent which delays premature labor. Becauseof its short half life (2-4 hrs) requires frequent dosing of the drug. It undergoes extensive first pass metabolism which resulting a poor bioavailability after oral administration [6]. Hence, to improve its therapeutic efficacy, patient compliance and to reduce the frequency of dosing and side effects as well as to avoid its extensive first pass metabolism, transdermal drug delivery approach was made to be suitable for nifedipine. The present work is aimed to develop transdermal patches of nifedipine by using synthetic polymers viz: HPMC, polyvinyl alcohol and polyvinyl pyrrolidone with penetration enhancers such as span 80, DMF and ethanol, and to study in-vitro drug release.

MATERIALS AND METHOD:

Nifedipine was obtained as a gift sample from Alkem pvt Ltd., HPMC purchased from research lab fine chem, ethyl cellulose, propylene glycol, DMSO, Methanol and Chloroform were procured from Sd fine chem Ltd. The chemicals used in this study were of AR grade.

Formulation Design of Transdermal Patches:

Transdermal films containing Nifedipine were prepared by the solvent evaporation technique[6] as shown in Table 1, All the Solution of polymers were prepared separately in ethanol. The polymeric solutions were mixed slowly to weighed amount of Nifedipine. To the above mixture, 4 drops of propylene glycol (117.6 mg), and permeation enhancer DMSO were added and mixed. The drug-polymer solution was casted in a glass mould of 40 cm^2 (4x10 cm^2). The entrapped air bubbles were removed by applying vacuum and were kept aside for drying at room temperature for 24 hrs. Inverted glass funnel was placed over the mould to prevent from air entrapment. After drying, the films were peeled from glass moulds cut into 1 cm^2, then wrapped in aluminum foil and stored in desiccator for further studies.

Table 1: Formulation design of Nifedipine Transdermal patches:

S.NO	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	NIFEDIPINE	60	60	60	60	60	60
2	HPMC	300	400	500	---	---	---
3	E C	---	---	---	300	400	500
4	PROPYLENE GLYCOL(4drops)	117.6	117.6	117.6	117.6	117.6	117.6
5	DMSO (1drop)	27.4	27.4	27.4	27.4	27.4	27.4
6	METHANOL:CHLOROFORM 1:1	q.s	q.s	q.s	q.s	q.s	q.s

Evaluations of transdermal patch

Physical evaluations

Physicochemical properties such as size, thickness, content uniformity, weight variation, folding endurance, tensile strength and percentage moisture absorption was determined on developed patches.

Thickness and weight variation:

The thickness of the patch at three different points was determined using vernier calipers and twenty patches of size (1´1cm) were weighed individually using digital balance to determine the weight of each patch taken out from the casted film and standard deviation was calculated.

Folding endurance:

Folding endurance of the patch was determined manually by repeatedly folding a small strip of 2×2 cm size at the same place until it broken. The number of times folded to break the path is folding endurance number.

Percentage Moisture Loss:

Accurately weighed films of each formulation were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days (Kusum Devi et al., 2003). The test was carried out in triplicate. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight.

Percentage Moisture Uptake:

Accurately weighed films of each formulation were kept in a desiccator which is maintained at 79.5% relative humidity (saturated solution of aluminium chloride) at room temperature and weighed after 3 days (Biswajit Mukherjee et al., 2005). The test was carried out in triplicate. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

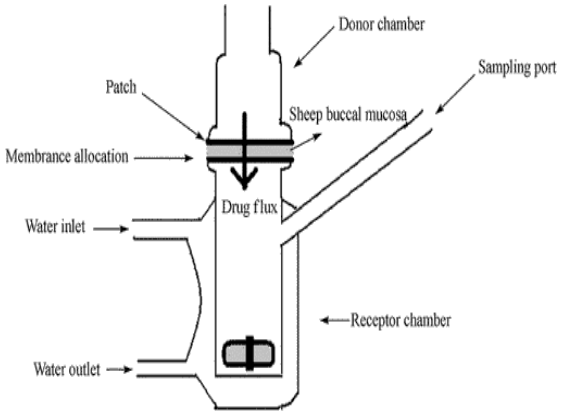
Drug content:

Films of specified area were cut and the pieces were taken into a 100 ml volumetric flask containing phosphate buffer (pH 7.4), and the flask was sonicated for 8 h (Mazzoet al., 1994). A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-µm filter and the drug content was analyzed at 238 nm by UV spectrophotometer.

***In vitro* drug release studies:**

The in vitro release studies were carried out by using Franz diffusion apparatus.The receptor compartment was maintained at 37±1°C by means of a water bath, circulator, and a jacket surrounding the cell. The cells were filled with freshly prepared phosphate buffer pH 7.4. The solution in the receptor compartment was continuously stirred at 60 rpm by means of Teflon coated magnetic stirrer, in order to avoid diffusion layer effects. The Commercial Semi-permeable membrane were mounted between the donor and receptor compartment and secured in place by means of a clamp. The patch was placed on one side of the semi-permeable membrane (Ji-Hui Zhao *et al.*, 2007, YanliGao *et al.*, 2000). Aliquots of 1ml were removed from the receptor compartment by means of a syringe and replaced immediately with the same volume of buffer solution kept at 37± 1°C. Test samples were taken from the medium at predetermined time intervals over a period of 24 hours and the samples were analyzed for Nifedipine content by UV spectrophotometer at 238 nm (VlassiosAndronis*et al.*, 1995). The diffusion kinetics of the Nifedipine was analyzed by graphical method for zero order, first order, Higuchi and KorsemayerPeppa's exponential equation.

Diffusion cell



Diffusion cells generally comprise two compartments, one containing the active Compartment (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. Cellophane membrane. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The stainless steel pin was used to stir the receptor solution using magnetic stirrer. The membrane was placed on receptor compartment and both compartments held tight by clamps.

Kinetic-models:

In order to describe the DS release kinetics from individual tablet formulations, the corresponding

dissolution data were fitted in various kinetic dissolution models:

Zero order, first order, Higuchi and Korsmayer and Peppas respectively.

$$Qt = Q0 + K0\ t \text{……..} (3)$$

Where,

Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

$$\log Qt = \log Q\alpha + (K1 /2.303)\ t \text{……..} (4)$$

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$$Qt = KH.\ t\ ½ \text{……} (5)$$

where, KH is the Higuchi rate constant.
Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

$$Q\ (t\text{-}l)\ /Q\alpha = KK\ (t\text{-}l)n \text{……} (6)$$

where, Qt corresponds to the amount of drug released in time t, l is the lag time (l = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where Q (t-l)/Qα>0.6, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (R^2).

RESULTS AND DISCUSSION:

Prepared patches thickness and weights were increased as the total quantity of polymers increased. All the patches have shown high folding endurance and it indicated that the patches are very flexible.Percentage moisture absorption study of different patches revealed that as the concentration of EC increased, the percentage moisture absorption also increased. The percentage absorption was maximum and percentage loss was minimum for F5. The patches F1 showed less percentage of moisture absorption this is due to low concentration of HPMC. This suggests that the EC is very significant as far as the percentage moisture absorption is concerned. It is also observed that the drug content is high for F5 formulation this indicates drug loading was increased with increasing polymer concentration but excess concentration may leads to decreases the drug content. The results were indicated in Table 2.

Table 2: Physicochemical evaluation parameters of Nifedipine Transdermal patches

Formulation Code	Thickness (mm)	Weight Variation mg	% Drug Content	Folding Endurance	% Moisture Loss	% Moisture Uptake
F1	0.250± 1.2	98.3± 1.2	92.41±0.1	>200	6.97±0.3	7.40±0.01
F2	0.256± 1.5	98.5 ±1.8	94.28 ±0.5	>200	12.42±0.2	8.18±0.03
F3	0.258±1.8	98.8±1.2	93.45±0.6	>200	8.10±0.8	9.33±0.02
F4	0.268±1.3	98.87±1.4	94.9±03	>200	9.36±0.6	9.64±0.05
F5	**0.275±1.4**	**99.8±1.9**	**99.5±0.8**	**>200**	**5.63±0.4**	**10.25±0.07**
F6	0.294±1.5	99.09±1.1	94.5±.3	>200	7.75±0.6	6.04±0.04

Table 3: *In Vitro* Drug Release

Time	F1	F2	F3	F4	F5	F-6
0	0	0	0	0	0	0
1	3.51	6.64	5.45	7.24	4.56	6.23
2	6.25	20.52	10.73	13.54	9.23	11.59
4	13.65	31.67	20.52	18.31	17.98	19.26
6	20.85	39.86	29.59	23.98	26.11	25.54
8	30.57	46.93	37.21	31.29	35.23	33.14
10	42.37	54.31	42.48	39.56	44.15	42.72
12	65.28	66.47	51.65	49.28	53.85	56.18
24	86.98	91.14	87.29	88.57	98.94	92.86

***In Vitro* Drug Release**

In vitro drug release studies showed that as the concentration of EC increased the release of drug from patches also increased. The highest drug release was observed in F5 formulation, whereas F1 showed least (Table 3) drug release. However when the cumulative drug release is compared, it was found that the ratio of drug: EC, found to be more significant.

Release Kinetics

As indicated in Table.4, the drug release pattern was best fit to zero order model as the regression coefficient (R2) values are better when compared to Higuchi's and Korsmeyer's model. This indicates that the release of the drug is independent to concentration and the diffusion path length remains constant throughout the drug release.

CONCLUSION:

Transdermal patches of nifedipine were formulated and evaluated for physicochemical properties and in vitro drug release. The physicochemical properties showed that all the patches are satisfactory. The patches with and without penetration enhancers does not showed any change in the in vitro drug release. The ratio of drug : EC was found to be more significant rather than the HPMC. Further the drug release from patches followed the zero order kinetics. So this could be a better dosage form when compared to conventional oral tablets.

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