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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF INDAPAMIDE

PATIL VIJAYKUMAR, DR. HIRAL SHAH

Arihant School of Pharmacy and Bio-research institute, Adalaj, Gandhinagar, Gujarat.

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Abstract: The aim of present work was to optimize the effect of polymers on matrix type Transdermal patch of *Indapamide*. I.e. Eudragit NE30D and HPMC K15M were used to achieve a predetermined Sustain effect. Transdermal films were prepared using Eudragit NE30D (Hydrophobic polymer) and HPMC K15M (Hydrophilic polymer) and DMSO as a permeation enhancer at different concentrations. PEG 400 was incorporated as plasticizer respectively. A 3^2 full factorial design was employed to explore the effects of Eudragit NE30D and DMSO (independent variables) on folding endurance and % cumulative drug release at 24 hour (Dependent variables). Further, the patches were also evaluated for uniformity of thickness and weight, surface pH, % drug content, folding endurance, % moisture absorbed, % moisture loss and *in vitro* drug diffusion. Results indicated that % cumulative drug release decreases with increasing the Eudragit NE30D and % cumulative drug release increased with increasing concentration of DMSO. Optimized formulation F3 showed satisfactory tensile strength, folding endurance and cumulative % drug diffusion at 24 hour of 796 ± 4.4, 324 ± 07 and 89.96 ±1.47 respectively. The selected formulation (F3) was found to be stable at 40 ± 0.5 °C and 75 ± 5% RH during the test period of 1 month. From the results, it can be concluded that Transdermal patches for Indapamide with desired characteristics could be prepared (polymer concentration Eudragit NE30D 7%, HPMC K15M 3%, PEG 400 30%w/w of dry polymer and DMSO 10 %w/w of dry polymer).

Keywords: Indapamide, Transdermal patch, Hypertension

Corresponding Author: MR. PATIL VIJAYKUMAR

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INTRODUCTION

Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate periods of time. Currently Transdermal drug delivery is one of the most promising methods for drug application through the skin to the systemic circulation. Transdermal drug delivery system Avoidance the first- pass metabolism and gastro intestinal incompatibility. This Single application has capacity for multi day therapy, thereby improving patient compliance and Self-medication is possible with this systems. This is Provides utilization of drugs with short biological half-life, narrow therapeutic window and avoiding the fluctuations in drug levels.

Indapamide is a long-acting hypertensive with both diuretic and vasodilative actions and is defined by the 1999WHO/ISH Hypertension Guidelines and JNC VII as a first line drug for the treatment of hypertension. This antihypertensive action is maximal at a dose of 2.5 mg/day, and the diuretic effect is slight, usually without clinical manifestation. The oral delivery of this drug has certain disadvantages such as frequent administration and adverse drug reactions. Additionally, since Indapamide is usually intended to be taken for a long period, patient compliance is also very important. Indapamide is a non-thiazide indole derivative of chlorosulphonamide, which has an anti-hypertensive action causing a drop in systolic, diastolic and mean blood pressure. This work was undertaken to investigate Indapamide transport from the Transdermal film and to determine whether therapeutically relevant delivery rates could be achieved from Transdermal delivery system to maintain suitable plasma drug levels for increased therapeutic efficacy.

MATERIAL AND METHOD

Indapamide was received as gift from, zydus India. Eudragit NE 30D was received as gift sample from Lincoln pharmaceuticals. HPMC K4M, HPMC K15M, HPMC K100M & polyvinylpyrrolidone K30 were received in a S.D. Fine Chemicals, Mumbai. And the polyethylene glycol 400, sodium lauryl sulfate, dimethyle sulfoxide were Carlo Erba Reagent.

Preparation of Transdermal patch of Indapamide

The Eudragit NE 30D (9**v/w),** HPMC K15M (3%w/w) were added to hot purified water. The mixture was stirred by maintaining the temperature at 80°C until the clear solution was formed. Then Indapamide was weighed accurately and dissolved with stirring in methanol add varying amounts of DMSO (5%, 15%) and SLS (10%, 30%). The polymeric dispersion was added to drug solution with gentle stirring, followed by addition of PEG 400 (30%) to the solution. The solution was kept in a sonicator for 20 min. Then solution was poured into a clean and dry glass Petri dish

and allowed to dry. The dried films were carefully removed from the Petri dish, checked for any imperfections or air bubbles and cut in to pieces of 4 cm2

EVALUATION OF TRANSDERMAL PATCHES

Thickness

The thickness of the patch was determined using a vernier calliper at three separate points of each patch. From each formulation, three randomly selected patches were tested for their thickness.

Tensile Strength and % Elongation

A tensile strength of patch is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of iron. The 4 cm^2 patch equivalent to 2.5 mg drug from each formulation was taken. One end of the patch was sandwiched between the iron plates and fixed. Other end was connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the hanging end of the thread. The force needed to fracture the patch was determined by measuring the total weight loaded in the pan. The weight corresponds to break the patches were taken as tensile strength. The following equation was used to calculate the tensile strength (TS)

$$Tensile\ strength(TS) = \frac{\text{LOAD} * 100}{THICKNESS * WIDTH}$$

For determination of % elongation, the initial length of the patch was measured on scale and a pointer is attached to freely movable thread. Increase in length at the time of break of the patch was recorded and % elongation was calculated by following formula.

$$\% \text{ Elongation} = \frac{\text{Initial length} - \text{Final length}}{\text{Initial length}} * 100$$

Experiments were performed in triplicate and average value was reported.

Folding endurance

Folding endurance is determined by repeated folding of the patch at the same place till the strip breaks. The number of times the patch is folded without breaking is computed as the folding endurance value.

Weight uniformity

The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug Content

A specified area (4 cm^2) of patch was dissolved in 10 ml phosphate buffer pH 7.4 and filtered through a filter medium. From that 1 ml taken and diluted up to 10ml. Then analyze the drug contain with the UV spectroscopy.

% Moisture loss

The prepared patches were to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches were to be reweighed and determine the percentage moisture loss from the below mentioned formula.

$$\% \text{ Moisture loss } = \frac{\text{Initial weight} - \text{final weight}}{\text{Final weight}} * 100$$

% Moisture Absorption

Weighed patches were kept in desiccators at room temperature for 24 h. These were then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture absorption was calculated as given below.

$$\% \, Moisture \; absorption = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}$$

***In vitro* Diffusion Study**

Goat skin was obtained from slaughter house. The fat adhering to the dermis side was removed using a scalpel and isopropyl alcohol. The Transdermal permeation was performed in modified Diffusion cell (surface area 3.14 cm^2. While placing the patch, the donor compartment contains patch on stratum corneum side of skin and dermis side was facing receptor compartment. Receptor compartment contains phosphate buffer pH 7.4 and samples were withdrawn at regular time intervals and replaced the same with receptor fluid. The samples were analyzed at 240 nm against blank by UV spectrophotometer.

RESULTS AND DISCUSSION

Composition of medicated films for optimization of polymer

Batch	Drug (mg)	Eudragit NE30D (%v/w)	HPMC K15M (%w/w)	PEG 400 (%w/w of dry polymer)	Concentration (%w/w)		Solvent
					DMSO	SLS	Water: methanol
A1	2.5	9 %	3 %	30%	20	-	7:3
A2	2.5	9 %	3 %	30%	40	-	7:3
A3	2.5	9 %	3 %	30%	-	10	7:3
A4	2.5	9 %	3 %	30%	-	30	7:3

Evaluation parameters of medicated patches for optimization of penetration enhancer.

Batch	Thickness	Tensile Strength	%Elongation	Folding Endurance
A1	0.105 ± 0.005	823 ± 5.2	20.16 ± 4.325	275 ± 04
A2	0.128 ± 0.016	845 ± 4.4	25.21 ± 2.712	298 ± 05
A3	0.136 ± 0.127	732 ± 2.7	18.39 ± 2.653	287 ± 09
A4	0.119 ± 0.123	715 ± 5.6	16.42 ± 3.847	288 ± 04

*Values are means ± SD, (n=3).

Evaluation parameters of medicated patches for optimization of penetration enhancer.

Batch	Weight variation*	% Moisture absorption*	% Moisture loss*	Drug Content (%)*
A1	0.147 ± 0.030	4.220 ± 0.113	2.160 ± 0.183	88.43 ± 3.56
A2	0.168 ± 0.022	4.274 ± 0.151	2.278 ± 0.145	90.32 ± 2.35
A3	0.153 ± 0.015	4.137 ± 0.221	3.217 ± 0.108	87.78 ± 3.13
A4	0.170 ± 0.028	4.385 ± 0.164	3.413 ± 0.117	89.57 ± 2.54

*Values are means ± SD, (n=3).

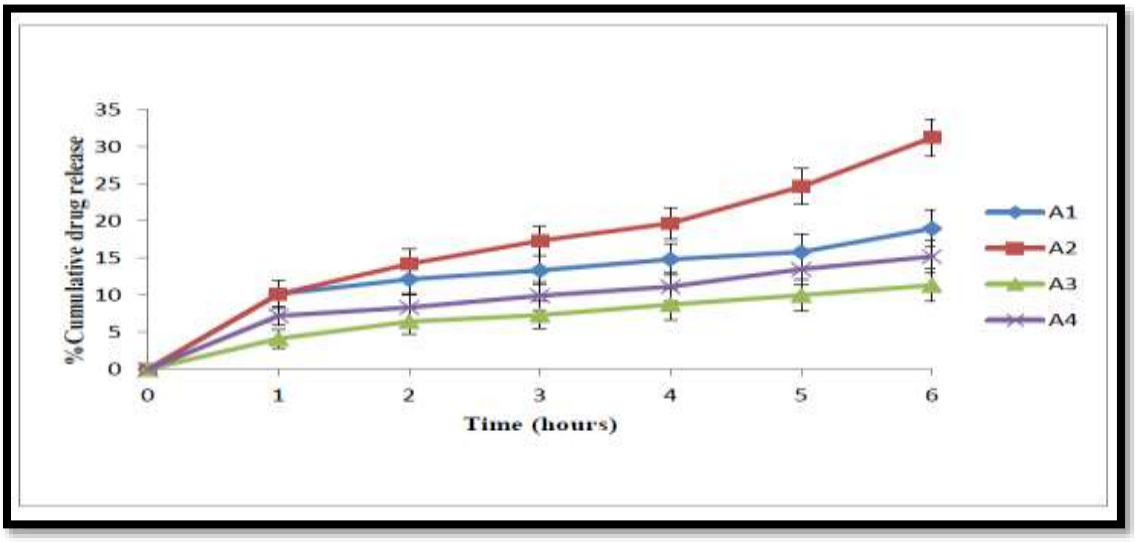

***Fig: 1 In vitro* diffusion study with permeation enhancer**

From the preliminary trials and drug diffusion study and other data Eudragit NE30D (7%, 8% & 9%) & HPMC K15M (3%), PEG 400(30%) as plasticizer and DMSO (5%, 10%, 15%) as a permeation enhancer. Water and methanol was used in the ratio of 7:3. Patches prepared using combination of Eudragit NE30D and HPMC K15M show good film forming ability. Better appearance and flexibility & it also makes matrix hydrophobic hydrophilic to achieve desired sustain drug release.

Evaluation parameter of Transdermal patch of Indapamide

BATCH	THICKNESS (mm)*	Tensile Strength (gm/ cm^2)*	%Elongation	Folding Endurance
F1	0.152 ± 0.021	739 ± 2.4	19.25 ± 3.122	279 ± 11
F2	0.168 ± 0.011	725 ± 6.3	24.36 ± 4.542	301 ± 12
F3	0.199 ± 0.021	796 ± 4.4	21.27 ± 3.652	324 ± 07
F4	0.194 ± 0.022	793 ± 3.4	22.42 ± 4.545	278 ± 08
F5	0.205 ± 0.012	815 ± 5.6	18.13 ± 3.945	298 ± 06
F6	0.236 ± 0.030	846 ± 6.7	21.15 ± 4.335	312 ± 05
F7	0.251 ± 0.014	862 ± 3.4	14.32 ± 2.233	286 ± 04
F8	0.268 ± 0.021	903 ± 2.6	17.25 ± 3.452	306 ± 06
F9	0.249 ± 0.048	920 ± 5.7	13.24 ± 4.825	321 ± 04

*Values are means ± SD, (n=3).

Evaluation parameter of Transdermal patch of Indapamide

Batch	% moisture absorption*	% moisture loss	Drug Content (%)*	Surface pH*	Weight variation*
F1	4.220 ± 0.112	2.742 ± 0.129	88.53 ± 1.84	6.49 ± 0.354	0.158 ± 0.013
F2	4.284 ± 0.134	2.823 ± 0.153	91.32 ± 2.37	6.63 ± 0.137	0.153 ± 0.020
F3	4.851 ± 0.172	2.945 ± 0.109	92.73 ± 1.72	6.80 ± 0.153	0.169 ± 0.018
F4	4.835 ± 0.107	2.958 ± 0.122	92.21 ± 2.83	6.75 ± 0.314	0.163 ± 0.025
F5	5.254 ± 0.125	3.021 ± 0.108	91.42 ± 2.13	6.67 ± 0.325	0.172 ± 0.015
F6	5.562 ± 0.241	3.168 ± 0.145	89.14 ± 1.72	6.58 ± 0.249	0.179 ± 0.027
F7	6.126 ± 0.213	3.192 ± 0.164	91.46 ± 2.78	6.44 ± 0.254	0.190 ± 0.028
F8	6.293 ± 0.184	3.387 ± 0.173	89.25 ± 1.87	6.82 ± 0.363	0.194 ± 0.025
F9	6.421 ± 0.152	3.412 ± 0.184	90.32 ± 2.63	6.78 ± 0.168	0.196 ± 0.017

*Values are means ± SD, (n=3).

EVALUATION OF FACTORIAL DESIGN FORMULATIONS (F1 TO F9)

Thickness

Thicknesses of the various formulations (F1 to F9) are given in table 5.11. Patches was in the range from 0.152 - 0.268 mm.

Tensile Strength

The results of tensile strength from various formulations (F1 to F9) are given in table 5.11. Tensile strength of the entire patch was in the range of 725 ± 6.3 to 920 ± 5.7 gm/cm2 suggesting all films were having good mechanical strengths to withstand mechanical damage during, production and application

% Elongation

The results of % elongation from various formulations (F1 to F9) are given in table 5.11.The results revealed that % elongation was in the range of 13.24 ± 4.825 to 24.36 ± 4.542. This represents the elasticity of the patch. Increase in concentration of Eudragit NE30D results in enhancement of elasticity of patch.

Folding Endurance

The results of folding endurance of various formulations (F1 to F9) are given in table 5.11. All the patches were showing folding endurance in the range of 278 ± 08 to 324 ± 07. Results revealed that as the concentration of polymers increases folding endurance increases.

Drug content

The results of drug content of various films are given in table 5.12. The results indicate that drug content of films were in the range of 88.53 ± 1.84 to 92.73 ± 1.72%.

% Moisture Absorption

The results of % moisture absorption of various films are given in table 5.12. The results indicate that % moisture absorption of films were in the range of 4.220 ± 0.112 to 6.421 ± 0.152. From the result we conclude that as the concentration of polymer was increase there was increase in moisture absorption.

% Moisture loss

The results of % moisture loss of various films are given in table 5.12. The results indicate that % moisture loss of films were in the range of 2.742 ± 0.129 to 3.412 ±0.184. From the result we conclude that as the concentration of polymer was increase there was increase in moisture loss.

Surface pH:

The surface pH of prepared films was in the range of 6.44-6.82 with a very low value of standard deviation. All the films were having surface pH close to skin pH suggesting that they will not irritate the skin.

Uniformity of weight:

The weight of prepared films was in the range of 0.153 to 0.196 mg. In all the cases the calculated standard deviation values were very low which suggest that the prepared films were uniform in weight. The weight of the films increases as the concentration of polymer increases.

***In vitro* Drug Release Data of Factorial Formulations F1 to F5**

Time (hr)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	13.93 ± 1.23	17.46 ±0.92	21.39 ±1.25	12.13 ±0.39	14.23 ±1.36
3	31.12 ±0.78	35.03 ±1.35	38.15 ±2.05	22.06 ±1.79	23.07 ±1.58
5	48.53 ±1.54	51.92 ±2.03	55.07 ±2.13	31.02 ±0.93	34.19 ±0.48
7	53.39 ±0.12	57.15 ±0.98	60.12 ±0.77	37.12 ±1.42	41.33 ±2.03
9	68.92 ± 0.22	70.29 ±1.72	74.73 ±1.36	42.23 ±1.25	48.13 ±1.76
12	75.05 ± 1.32	78.16 ±0.56	78.93 ± 1.22	52.08 ± 1.13	54.07 ±0.94
24	81.36 ± 0.57	83.53 ±0.48	89.96 ±1.47	61.38 ± 1.78	62.73 ±1.73

* Values are mean ± SD, (n=3)

***In vitro* Drug Release Data of Factorial Formulations F6 to F9**

Time (hr)	F6	F7	F8	F9
0	0	0	0	0
1	18.53 ±0.09	10.03 ±0.33	12.29 ±0.65	13.56 ±1.53
3	28.03 ± 1.12	21.62 ±0.65	22.41 ±1.30	26.32 ± 0.09
5	37.12 ±2.13	28.34 ±1.72	29.32 ±0.06	33.17 ±1.12
7	44.62 ±0.53	35.56 ±1.11	37.93 ±1.73	42.08 ±0.86
9	51.13 ±0.03	39.06 ±1.52	42.18 ±1.13	48.20 ±2.08
12	60.28 ±1.03	51.32 ± 0.22	53.02 ±0.07	62.09 ±0.05
24	78.20 ±0.22	60.03 ±0.07	64.04 ±1.54	68.82 ±1.78

*Values are means ± SD, (n=3).

In vitro drug permeation profiles of Indapamide from all prepared films are seen in Table. The results suggest that Eudragit NE30D and DMSO play an important role in the release of drug from the films. Films having higher concentration of Eudragit NE30D showed lower values of drug permeation as compared to films having lower amount of Eudragit NE30D Results of drug permeation showed that increased in DMSO concentration of % w/w of dry polymer increases the drug permeation significantly as shown in Figure 5.6

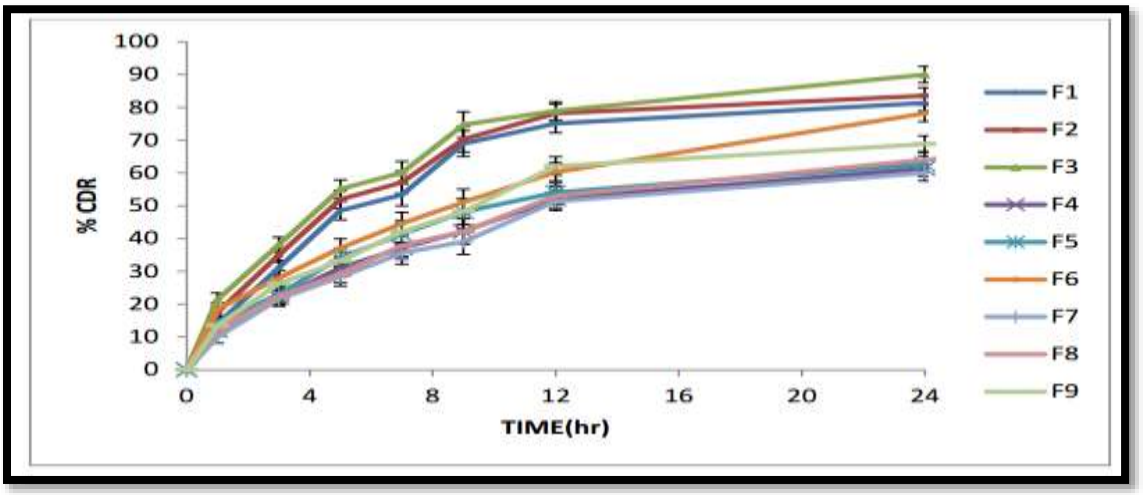

Figure: 3 *In vitro* Drug release of F1 to F9 batches

Layout of 3^2 Full Factorial Designs

Variable is coded form			
Transformed value			
Batch	**X1**	**X2**	
F1	-1	-1	
F2	0	-1	
F3	+1	-1	
F4	-1	0	
F5	0	0	
F6	+1	0	
F7	-1	+1	
F8	0	+1	
F9	+1	+1	
Independent Variables	**Coded Value**	**Actual values in (%w/v)**	
X1-Concentration of Eudragit NE30D		**X1**	**X2**
	-1	7%	20%
X2-Concentration of DMSO	0	8%	30%
	+1	9%	40%

Effect of these factors was studied on the following dependent variables:

1) In vitro diffusion study

2) Folding Endurance

FORMULATION OF FACTORIAL DESIGN FORMULATIONS

Composition of Factorial Design Formulations of indapamide

Batch	Drug (mg)	Eudragit NE30D (%v/w)	HPMC K15M (%w/w)	PEG 400 (%w/w of dry polymer)	DMSO (%w/w of dry polymer)	Water: methanol
F1	36.17	7	3	30	20	7:3
F2	36.17	7	3	30	30	7:3
F3	36.17	7	3	30	40	7:3
F4	36.17	8	3	30	20	7:3
F5	36.17	8	3	30	30	7:3
F6	36.17	8	3	30	40	7:3
F7	36.17	9	3	30	20	7:3
F8	36.17	9	3	30	30	7:3
F9	36.17	9	3	30	40	7:3

CONCLUSION

In the present investigation, factorial formulations F1-F9 were prepared using 7%, 8% and 9% of Eudragit NE30D and 5%, 10% and 15% (w/w of dry polymer) of DMSO. HPMC K15M was incorporated as hydrophilic copolymer at concentration of 3%. The formulation F3 was selected as the promising formulation on the basis of tensile strength, % elongation, % drug content and mainly cumulative % drug diffusion. The cumulative % drug diffused of F3 was found to be 89.96 ±1.47. Further, the film was found to be free of skin irritation. From the results stability study it can be concluded that the films can be stored at 40 °C and 75% RH without any significant stability problems. The formulation satisfied all the pharmaceutical parameters of Transdermal films and appears to be promising, would be able to offer benefits such as sustained drug release, reducing frequency of administration, improving bioavailability, and thereby may help to improve patient compliance.

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