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Formulation And Characterization Of Transdermal Patchs Of Meclozine Hydrochloride

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ABSTRACT

Transdermal patches are inventive drug delivery systems and can be used for executing coherent systemic effect by passing hepatic first pass metabolism and increasing the fraction absorbed. Transdermal patches of Meclozine hydrochloride were developed by the solvent casting evaporation technique using ethyl cellulose: HPMC, Eudragit RSPO, propylene glycol and permeation enhancer using different ratios. The physicochemical parameters such as flexibility, thickness, smoothness, weight variation, moisture content, hardness, folding endurance and tensile strength were estimated for the developed patches. The formulation revealed flexibility, uniform thickness and weight, smoothness, good drug content and little moisture content. The *in vitro* diffusion studies were carried out using modified Franz diffusion cell using egg membrane as the diffusion membrane and the formulation followed the Korsmeyer-Peppas diffusion mechanism. The formulation containing ethyl cellulose: HPMC as polymers showed faster release rate compared to Eudragit: HPMC. The stability studies indicated that all the patches maintained good physicochemical properties and drug content after storing the patches in discrete storage conditions. Compatibility studies indicated that there was no interaction between the drug and polymers. Hence, the aim of the present study was to prepare the sustained release formulation (Transdermal patches) of the drug using different blend of polymers.

K**eywords:** Transdermal patches, Meclozine hydrochloride, Physicochemical parameters, *in vivo* study

INTRODUCTION:

The developmental cost of a new drug may be about $ 250 million (Rs. 900 crores) and takes about 12 years to reach the market place. Whereas an existing drug molecule can get a second life with newer drug delivery systems that can be prospered in half of the time with 20% cost of the new drug discovery. A recent approach to drug delivery is to deliver the drug into systemic circulation at pre-decided rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor transcend the minimum toxic dose. Transdermal drug delivery covenant many advantages above oral and/or intravenous administration, such as better control of blood levels, a reduced incidence of systemic toxicity, avoids hepatic first-pass metabolism and enhance patient compliance.

An ideal drug to be formulated as transdermal drug delivery should possess several physico-chemical proviso, such as short half- life, small molecular size, low dose, etc. although, the highly organized structure of stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery. Transdermal patch or skin patch is a medicated adhesive patch which is placed on the skin to deliver a specific dose of medication through the skin and in to the blood stream. Transdermal patches of Meclozine hydrochloride with polymers were prepared by solvent casting technique. However, from a drug delivery sand point, its far better that rate control resides with in the delivery devise in order to attain uniform input rates and reduce inter individual variability. Meclozine hydrochloride is a first generation anti-histamine of the phenothazines family. It acts mainly as a strong antagonist of the H_1 receptor and a moderate mACh receptor antagonist, hence it blocks the action of acetylcholine on the receptors and this explains its benefit in reducing the nausea experienced during motion sickness.

Materials and methods

Propylene glycol 400, HPMC, Ethyl Cellulose, and RSPO purchased from Himedia Laboratory, Mumbai. Ethanol, PVA, PVP, PEF-4000 purchased from CDH chemical Pvt. Ltd. New Delhi. Dialysis membrane of Mol Wt cutoff 1200 was purchased from Himedia Laboratory, Mumbai. All other ingredients used were of analytical grade.

Formulation of transdermal patches

In the present study, matrix type transdermal patches of Meclozine hydrochloride were prepared by the solvent casting evaporation technique. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400 and 450mg), ethyl cellulose and Eudragit RSPO (50, 100 and 150mg) in 10 ml of methanol and chloroform in the ratio 1:1. To the resulting solution, 0.5% w/w of propylene glycol as plastisizer and 10% w/w penetration enhancer was added in this solution. Then drug (25 mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into glass mould/Petri dish specially designed to seize the contents. The glass mould containing the casting solution was dried at room temperature for 24 hours in vacuum oven. The patch was removed by peeling and cut into round shape of 1 cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover

Characterization of transdermal patches

The prepared transdermal patches were evaluated for the following parameters:

Physical appearance

All the transdermal patches were visually inspected for color, flexibility, homogeneity and smoothness.

Film thickness

The thickness of the patches was measured at five different places on a single patch of each formulation using

a digital micrometer screw gauge and the mean values were calculated.

Weight variation

A set of three patches from each batch were weighed on a digital balance and the mean values were calculated. The tests were performed on films which were dried at 60°C for 4 h prior to testing.

Drug content uniformity

The patches (2.5*2.5 cm (Equivalent to 6.25 mg of drug) were taken into a three separate 10 ml volumetric flask and dissolved in methanol (10ml) with the help of mechanical shaker.The solution was centrifuged to separate out any particulate matter. 1ml of sample was withdrawn and transferred in volumetric flask (10 ml of capacity). The sample was dilute upto the mark with distilled water and analyzed by UV spectrophotometer at 250.0 nm using the placebo patch solution as blank and the drug content was calculated.

Folding endurance

A strip of 2.5 cm × 2.5 cm was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported.

Tensile Strength.

The tensile strength of the patch was evaluated by using the tensiometer. It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2×2cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

$$Tensile\ Strength(s) = \frac{Appliedforce(m*g)}{Crosssectionalarea(b*t)}$$

Where,

S = tensile stress in 980 dynes/cm^2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm^2)

b = breadth of strip in centimetres

t = thickness of strip in centimetres

Percent moisture content

Weighed individually the films (1cm^2) and kept them in desiccators containing calcium chloride at room temperature for at least 24 hrs. Film was weighed again; the difference in weight (initial and final weight) gives moisture content.

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial weight}} \times 100$$

Percent moisture uptake

Weighed individually the films and kept them in desiccator containing calcium chloride at room temperature for at least 24 hrs. remove the films from desiccators and exposed to 4% relative humidity using saturated solution of potassium chloride in a another desiccator until a constant weight is achieved.

$$\% \text{ Moisture uptake} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Final Weight}} \times 100$$

In the present study, compatibility studies were carried out to assess any incompatibility between the drug and polymers. The IR studies were performed to check the compatibility with excipients. Spectra of the pure

drug and the formulated patch were taken individually by the potassium bromide pellet method.

Stability studies

The stability studies of the formulated transdermal patches were carried out on prepared films at different temperature and humidity: 25-30°C (60%RH) and 45-50°C (75%RH) over a period of 90 days. The patches were wrapped in aluminum foil and stored in a desiccator for stability study. The patches were characterized for drug content and other parameters at regular intervals (0, 15, 30, 45, 60,75 and 90 days).

***In Vitro* skin permeation study**

The *in vitro* skin permeation study was carried out by using a Franz diffusion cell (receptor compartment capacity: 80 ml: area: 2.5*2.5 cm (Equivalent to 6.25 mg of drug). The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. The temperature of receptor compartment was maintained at 32±0.5ºC. The samples were withdrawn at different time intervals and analyzed for drug content 250 nm using UV-visible spectrophotometer after suitable dilution with diluents. At the same time receptor phase was replaced with an equal volume of buffer solution at each time interval.

Kinetic study

To know the mechanism of drug release from these formulations, the data were treated according to first order (log percentage of drug to be released vs time), Higuchi's (percentage of drug released vs square root of time), and zero-order (percentage of drug released vs time) Korsmeyer-Peppas model (log percentage of drug to be released vs log time) patterns.

RESULT AND DISCUSSION

Preparation of matrix type transdermal patches of Meclozine hydrochloride

Meclozine hydrochloride containing transdermal patch was prepared utilizing method given by Touitou et al., 2001 with slight modification. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400 and 450mg) and ethyl cellulose, Eudragit RSPO (50, 100 and 150mg) in 10 mL of methanol and chloroform and water mixture in ratio 1:1. To the resulting solution, 0.5% w/w of propylene glycol as plastisizer and 10% w/w penetration enhancer was added in this solution. Then drug (10 mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into glass mould/Petri dish specially designed to seize the contents. The glass mould containing the casting solution was dried at room temperature for 24 hours in vacuum oven. The patch was removed by peeling and cut into round shape of 1 cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover.

Table 1: Different Formulation used for Optimization TDDS

Formulation Code	Drug (mg)	HPMC (mg)	Eudragit RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Propylene glycol (Plasticizer) % w/w	Permeation Enhancer % w/w
F1	300	450	-	50	500	0.5	10
F2	300	400	-	100	500	0.5	10

F3	300	350	-	150	500	0.5	10
F4	300	450	50	-	500	0.5	10
F5	300	400	100	-	500	0.5	10
F6	300	350	150	-	500	0.5	10

Dose calculations

- Width of the plate (mould) = 5 cm
- Length of the plate (mould) = 12 cm
- No. of 2.5 x 2.5 cm patch present whole(mould) = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug? = 25×12 = 300mg
- The amount of drug added in each plate was approximately equal to 300 mg.

Characterization of transdermal patches

The prepared transdermal patches were evaluated for the following parameters:

(a) Thickness

Patch thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated.

Table 2: Results of Thickness

S. No.	Formulation Code	Thickness (mm)
1.	**F1**	0.86±0.05
2.	**F2**	0.93±0.02
3.	**F3**	0.84±0.03
4.	**F4**	0.91±0.17
5.	**F5**	0.96±0.08
6.	**F6**	0.94±0.06

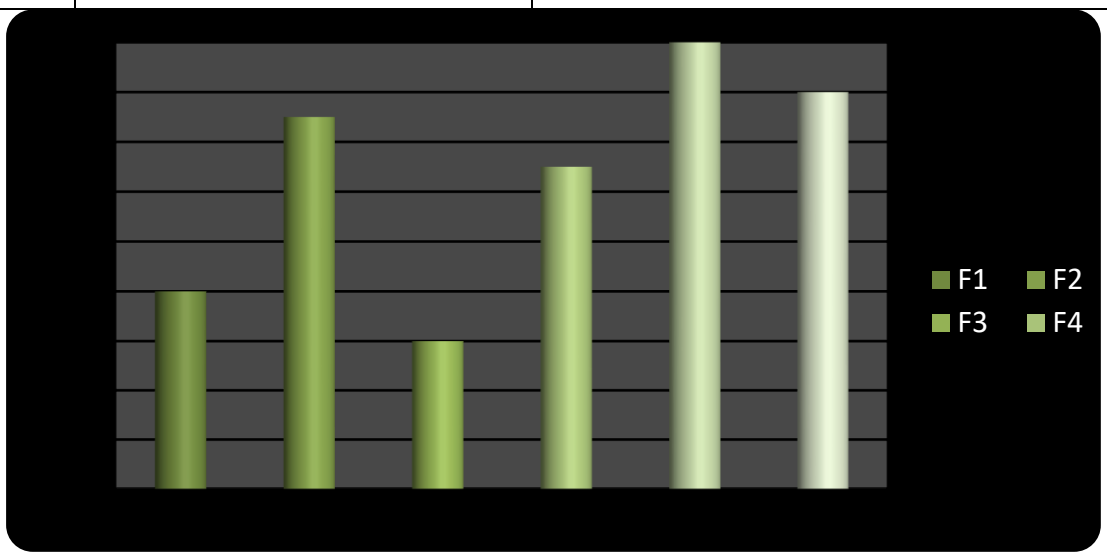

Figure 1: Thickness of transdermal patches

(b) Percent moisture content

Weighed individually the films ($1cm^2$) and kept them in desiccators containing calcium chloride at room temperature for at least 24 hrs. Film was weighed again; the difference in weight (initial and final weight) gives moisture content.

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial weight}} \times 100$$

(c) Percent moisture uptake

Weighed individually the films and kept them in desiccator containing calcium chloride at room temperature for at least 24 hrs. remove the films from desiccators and exposed to 4% relative humidity using saturated solution of potassium chloride in a another desiccator until a constant weight is achieved.

$$\% \text{ Moisture uptake} = \frac{\text{Final Weight} - \text{Initial weight}}{\text{Final Weight}} \times 100$$

All the formulation show lowest moisture content i.e. less than 2%. Moisture in this value is required to provide strength and flexibility to the patches. Formulations F1, F2, F3, F4, F5 and F6 were found to be contains 0.84±0.07%, 0.93±0.04, 0.68±0.08, 0.72±0.02, 0.74±0.04 and 0.77±0.03% of moisture content respectively (fig. 2 & 3). In all formulations formulation F3 contain minimum moisture contain 0.68±0.08.

Table 3: Results of % Moisture Content &% Moisture Uptake

S. No.	Formulation Code	% Moisture Content	% Moisture Uptake
1.	**F1**	0.84±0.07	11.15±0.12
2.	**F2**	0.93±0.04	12.05±0.14
3.	**F3**	**0.68±0.08**	**9.18±0.15**
4.	**F4**	0.72±0.02	11.21±0.28
5.	**F5**	0.74±0.04	12.82±0.42
6.	**F6**	0.77±0.03	11.63±0.31

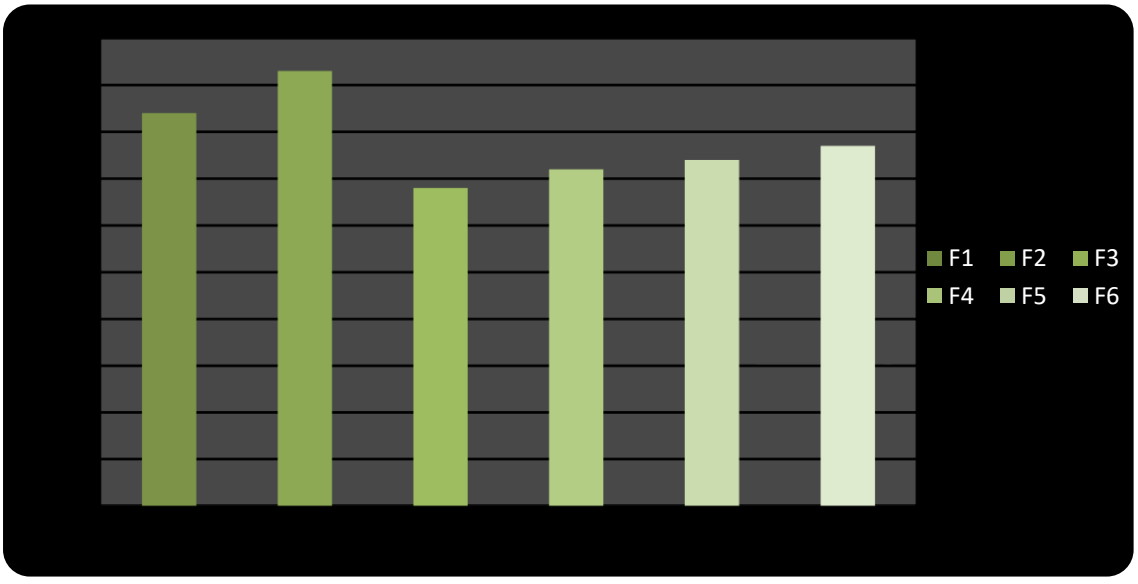

Figure 2: % Moisture content in transdermal patches

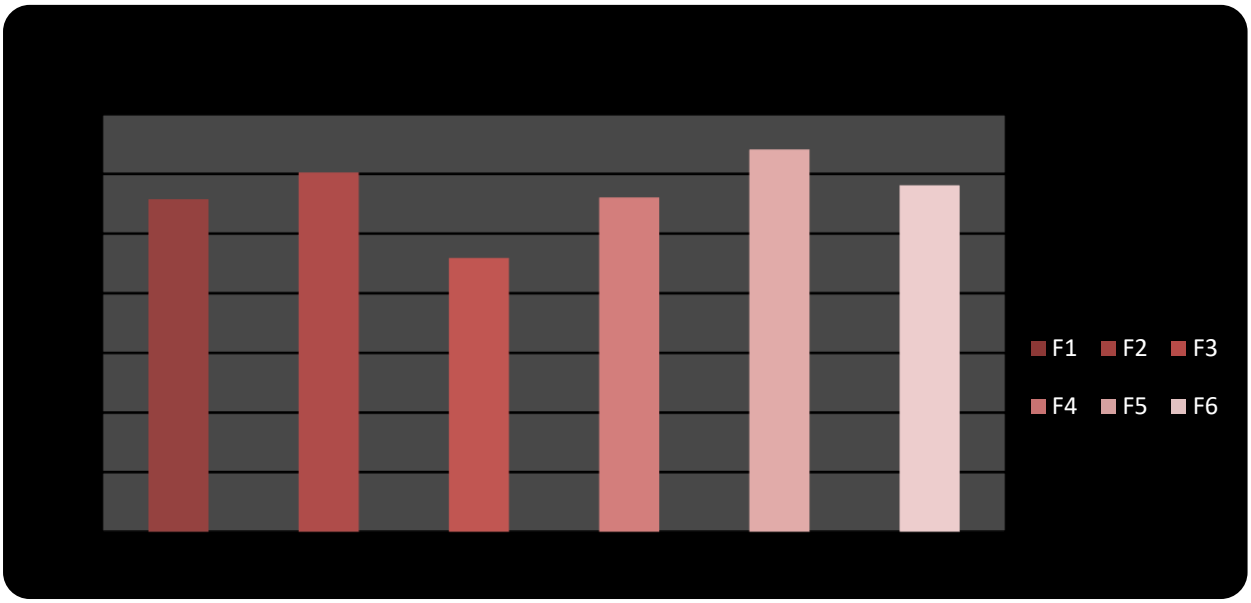

Figure 3: % Moisture uptake in transdermal patches

(d) Folding endurance

This was determined by repeatedly folding one film at the same place until it broken. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance. The maximum folding endurance was found 206.7±6.7in formulation F3.

Table 4: Results of folding endurance

S. No.	Formulation Code	Folding Endurance
1.	**F1**	194.2±4.1
2.	**F2**	197.4±5.4
3.	**F3**	206.7±6.7
4.	**F4**	175.4±6.6
5.	**F5**	186.6±6.4
6.	**F6**	189.8±6.7

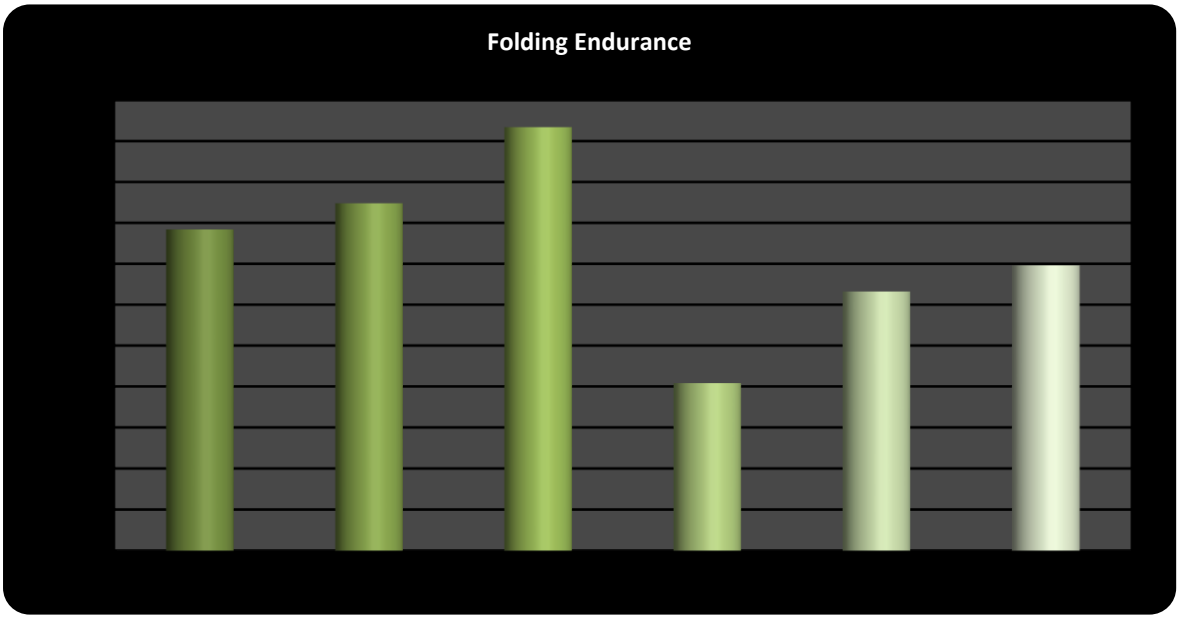

Figure 4: Folding endurance of transdermal patches.

(e) Tensile Strength.

The tensile strength of the patch was evaluated by using the tensiometer (Erection and instrumentation, Ahmedabad). It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2×2cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

$$Tensile\ Strength\ (s) = \frac{Applied\ force\ (m * g)}{Cross\ sectional\ area(b * t)}$$

Where, S = tensile stress in 980 dynes/cm2
m = mass in grams
g = acceleration due to gravity (980 dynes/cm2)
b = breadth of strip in centimeters
t = thickness of strip in centimeters

Table 5: Results of tensile strength

S. No.	Formulation Code	Tensile Strength (kg/cm)
1.	**F1**	3.5±0.4
2.	**F2**	3.8±0.3
3.	**F3**	4.1±0.2
4.	**F4**	3.1±0.7
5.	**F5**	3.7±0.5
6.	**F6**	3.9±0.7

Figure 5: Tensile strength of transdermal patches

(f) Drug Content

The patches (2.5*2.5 cm (Equivalent to 6.25 mg of drug) were taken into a three separate 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. The solution was centrifuged to separate out any particulate matter. 1mL of sample was withdrawn and transferred in volumetric flask (10 mL of capacity). The sample was dilute upto the mark with distilled water and analyzed by UV spectrophotometer at 250.0 nm. Drug content of the all formulations was determined by dissolving the transdermal patches in methanol followed by centrifugation and then analyze on UV spectrophotometry. The drug content was found more than 90% in all the formulations with slight fluctuation (fig. 7.6). The drug content analysis of different

formulations was done according to the procedure given in section. The drug content ranged between 92.95±0.38 and 96.36±0.42. The percentage drug content of all formulations. The maximum drug content was found in formulation F3, 97.56±0.57%.

Table 6: Percentage drug content of all the formulations

S. No	Formulation Code	% Drug Content
1	**F1**	94.15±0.41
2	**F2**	95.23±0.62
3	**F3**	97.56±0.57
4	**F4**	92.95±0.38
5	**F5**	94.72±0.41
6	**F6**	96.25±0.32

Values are represented as mean ±SD (n=3)

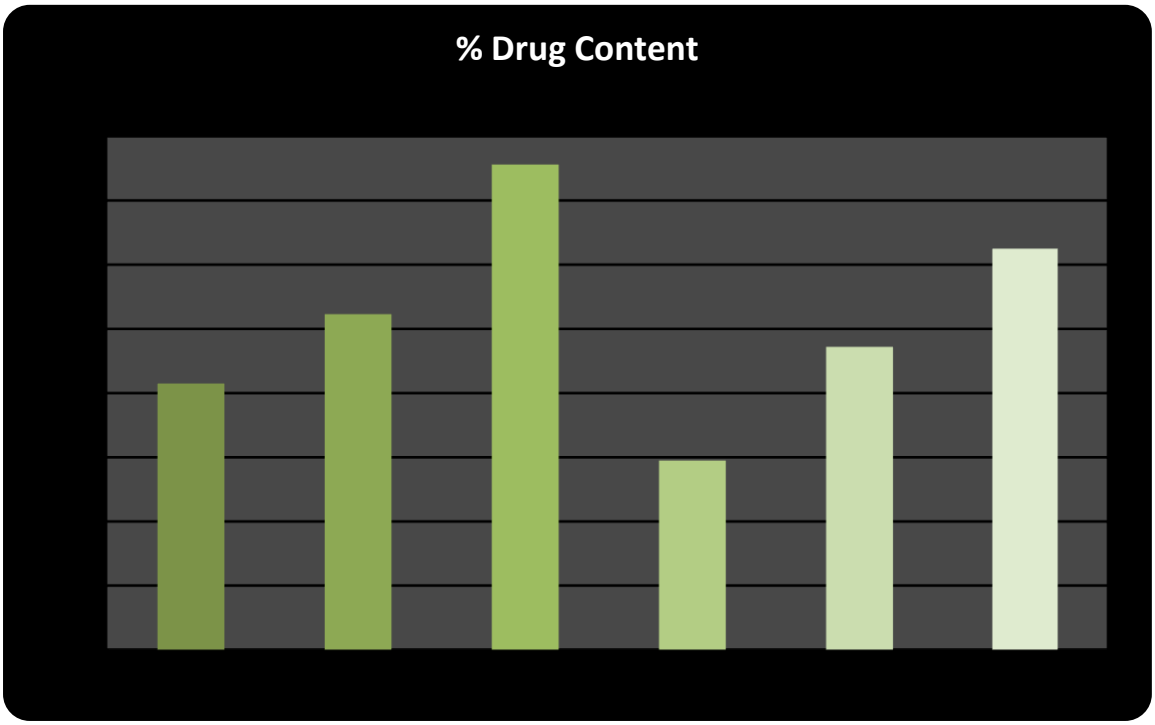

Figure 6: Percent drug content of transdermal patches

(g) *In Vitro* skin permeation study

The *in vitro* skin permeation study was carried out by using a Franz diffusion cell (receptor compartment capacity: 80 ml: area: 2.5*2.5 cm (Equivalent to 6.25 mg of drug). The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. The temperature of receptor compartment was maintained at 32±0.5ºC.

The samples were withdrawn at different time intervals and analyzed for drug content. At the same time receptor phase was replaced with an equal volume of buffer solution at each time interval.

Release Kinetics Studies

Table 7: *In Vitro* cumulative % drug release from optimized batch of transdermal patches F3

S. No.	Time (Hrs.)	Square Root of Time	Log Time	Cumulative * Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.5	0.697	-0.301	29.16±0.24	1.391	70.44	1.848
2	1	1.000	0.000	34.07±0.14	1.823	66.64	1.824
3	2	1.519	0.301	56.14±0.19	1.749	45.35	1.647
4	4	2.000	0.602	68.48±0.21	1.825	30.02	1.477
5	6	2.413	0.778	79.18±0.24	1.898	21.02	1.323
6	8	2.798	0.903	84.95±0.16	1.933	14.35	1.157
7	10	3.162	1.000	85.65±0.32	1.933	14.35	1.157
8	12	3.464	1.079	90.23±0.41	1.955	10.17	0.990

Table 8: Regression Analysis Data of Formulation F3

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.843$	$R^2 = 0.963$	$R^2 = 0.966$

(h) Stability Studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of tablets was found to slightly decrease at higher temperature. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

Transdermal patch preparations were observed for any change in appearance or color for the period of 3 Month. There was no change in appearance in formulation throughout the period of study. The stability of drug was further confirmed by spectral data and there was no change observed.

SUMMARY

Preformulation of drug and excipients was performed in which physiochemical properties and other parameters of drug were studied. Physiochemical parameters such determination of solubility, melting point, partition coefficient, drug-excipient interaction, λ max scan using UV-spectrophotometry, FT-IR spectrophotometry were performed in this study. The obtained data from these studies were matched with the data given in standard monographs to confirm the authenticity of procured drug. Procured drug was odorless and white crystalline in nature. In solubility study it was found that drug was freely soluble in methanol and soluble in water 0.1 N HCL and phosphate buffer pH 6.8 and sparingly soluble in chloroform. It was completely insoluble in distilled water. Melting point of drug was found 212°C while it was 212°C reported in standard monograph. Moisture content of Meclozine hydrochloride was found 0.68 %. The drug solution was scan on UV-spectrophotometer at 200-400 nm in weblength range to determine the maximum absorbance

(λ_{max}) and it was found at 250nm. The calibration curve was prepared in phosphate buffer pH 6.8. The regression coefficient (R^2) was 0.966 which was shows the linearity of curve. The drug excipient interaction study was performed to check in interaction between drug and other formulation excipients by spectrophotometricaly. There was no fluctuation in weblength of Meclozine hydrochloride. All the data of preformulation study was found similar as given in standard monograph which confirmed that the drug was authenticate and pure in form and it could be used for formulation development of Meclozine hydrochloride loaded transdermal patches. The Meclozine hydrochloride containing transdermal drug delivery patches were formulated by casting method and were characterize on the basis of uniformity in thickness, sufficient folding endurance, tensile strength, % moisture content and uptake, drug content and drug release. The values obtained for all the formulations are given in the table. The thickness was approximately close to every formulation. It depends on polymer ratio. Folding endurance values of all formulation more than 100 indicating good elasticity and strength. Folding endurance and tensile strength was found increase with the formulation which contains ethyl cellulose in comparison of formulation containing the Eudragit RSPO. It is dependent on the polymer and humectants and plasticizer ratio. Small amount of moisture in transdermal patch is good to prevent the brittleness and also maintain the stability of formulation. If formulation content higher moisture it can lead the microbial contamination during the storage of patches. As seen in the formulation moisture content was increase with increasing the HPMC concentration. This slight fluctuation in drug content was due to the increase or decreases the concentration of polymers. Every polymer having limit (upto saturation level) entrapped drug molecule in their matrix. After saturation it will leach out from the matrix. The *in vitro* skin permeation study was done by using a Franz diffusion cell. The temperature of receptor compartment was maintained at 32±0.5ºC. The samples were withdrawn at different time intervals up to 12 hr and analyzed for drug content. Receptor phase was replaced with an equal volume of buffer solution at each time interval. The *in-vitro* permeation study was done to see the effect of polymers through the Franz diffusion cell from patch having Eudragit RSPO, HPMC and EC in different conc. to optimized formulation for in-vitro study. All the formulation was studied and all data fitted on Zero Order, First Order to explain the diffusion mechanism and pattern. The % cumulative drug release was calculated over the study time range in 0-12 hr and it was found that, all the formulation shows the matrix diffusion Pappas release kinetic. Transdermal patch preparations were observed for any change in appearance or color for the period of 3 Month. There was no change in appearance in formulation throughout the period of study. The stability of drug was further confirmed by spectral data and there was no change observed.

CONCLUSION

Thin, flexible, smooth and transparent films were obtained with HPMC, EC and Eudragit RSPO using propylene glycol as plasticizers. Thickness of all the formulations remained uniform with low SD values. Transdermal patches formulations was shown significant drug entrapment and obtained in uniform thickness, significant value of folding endurance and tensile strength that can be use for safe and effective delivery of selected antihypertensive drug. All the system showed good release pattern. The transdermal patches were found to be stable at different accelerated temperature condition. Formulation characterization studies have shown promising results and confirm that the transdermal patches can be use for the delivery of Meclozine hydrochloride for antiemetic effect associated with post chemotherapeutic effect and make possibility to further pharmacodynamics and pharmacokinetic evaluation.

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