



# International Journal of Advanced Pharmaceutics

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## FORMULATION AND EVALUATION OF DUAL TRANSDERMAL PATCH CONTAINING METFORMIN HYDROCHLORIDE - METOPROLOL TARTARATE

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### ABSTRACT

Intend of this study is to formulate and evaluate dual transdermal patch containing Metformin hydrochloride and Metoprolol tartarate. Diabetes mellitus generally accompanied with major complications like Hypertension. These situations lead to most morbidity and mortality among middle-aged, older people. So to maintain the drug plasma concentration for prolonged period of time Dual transdermal patch is the choice of dosage form to control the Diabetes associated with major complication like hypertension. The choice of drug for type2 diabetes mellitus is Metformin hydrochloride and for Hypertension is Metoprolol tartarate. Dual Transdermal drug delivery systems are capable of controlling the rate of drug delivery, prolonging the duration of therapeutic activity. Thus it is predicted that Dual Transdermal drug delivery systems can be designed to deliver drugs at appropriate period of time to maintain suitable plasma drug levels for desired therapeutic efficiency. The results from dual release Transdermal patch of Metformin hydrochloride with Metoprolol tartarate could perform better both therapeutically with good patient compliance by significant overcome of diabetes along with its complication especially hypertension.

**Keywords:** Metoprolol tartarate, Metformin hydrochloride, Dual transdermal patch, Diabetic and Hypertension.

### INTRODUCTION

Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic "first-pass" metabolism, but also to maintain a constant and prolonged drug level in the body. A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels. However, such mode of drug administration entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of administration. [1, 3]

Recently, it is becoming evident that the benefits of intravenous drug infusion can be closely duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation. To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for

topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue.

Transdermal drug delivery system is a self-contained discrete dosage form that topically administered medicament in the form of multilaminated adhesive patch that delivers a specific dose of drug at a predetermined rate and controlled the rate of drug release through skin to reach systemic circulation. [3]

Dual Transdermal drug delivery systems are capable of controlling the rate of drug delivery, prolonging the duration of therapeutic activity and targeting the delivery of drug to a tissue. In response to these advances, several transdermal drug delivery systems have been developed to achieve the objective of systemic medication through application on the intact skin surface. The advantage of dual transdermal drug delivery system is that

they can provide sustained drug delivery and enhance constant drug concentrations in plasma over a prolonged period of time. Thus it is estimated that Dual Transdermal drug delivery systems can be designed to deliver drugs at appropriate rates to maintain suitable plasma–drug levels for therapeutic efficiency. Ultimately the success of all Dual Transdermal systems depends on the ability of the drug to permeate skin in sufficient quantities to achieve its desirable therapeutic effects [2]. The goal of this therapy is to treat the patient having high blood pressure with diabetic that plays major risk factors for diabetic patients.

Metoprolol is a  $\beta$ 1-selective antagonist. Various clinical trials have demonstrated the beneficial effects of Metoprolol therapy in heart failure, with reduced mortality due to both reductions in sudden death and death from worsening of heart failure. Metformin is an anti-hyperglycemic, not a hypoglycemic agent. It does not stimulate insulin release from the pancreas and generally does not cause hypoglycemia, even in large doses.

## MATERIALS AND METHODS

### Material

Metformin hydrochloride, Metoprolol tartarate samples are obtained as a gift sample from Microlabs pvt ltd., Hosur, India., Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl cellulose (EC), Poly Ethylene Glycol (PEG), Chloroform, Propylene glycol, Dimethyl Sulfoxide (DMSO) was received from Chem. Scientifics, Chennai. All the other solvents and chemicals used in this project are belongs to analytical grade. Instruments like UV-Spectrophotometer (Shimadzu 1700), DSC (Perkin - Elmer DSC 60) and Franz Diffusion cell were used for evaluation processes. Prism software for statistical and graphical representation was used.

### Formulation of Dual Transdermal patch by Solvent evaporation method

Dual Transdermal patches of Metformin hydrochloride and Metoprolol were prepared by solvent evaporation technique. This was prepared separately by using different types of polymers like HPMC and EC with different concentration along with suitable solvent and permeation enhancers. The polymers are dissolved in suitable solvent to get polymer solution; and then Metformin Hcl and Metoprolol tartarate was added in the ratio of 1:1 to the above polymer solution and stirred continuously until both the drugs and polymer are soluble to get a clear solution. To this polymer drug solution add poly ethylene glycol (PEG) plasticizer to increase the plasticity of the transdermal patch. And then add Dimethyl sulfoxide a permeation enhancer with continuous stirring to this solution. To avoid air bubbles keep the solution in bath sonicator for half an hour. Glass petridish was taken with a partition made by aluminium foil at the center equal half was taken and lubricated. Then the prepared solution i.e., Metformin and Metoprolol containing polymer solution was spread separately uniformly in this petridish,

so that two solution separated by the aluminium foil partition. The mould was kept for one day and then the dried patches were then detached from the petridish and were stored in desiccators for further use [2].

## PREFORMULATION STUDIES

### Compatibility Studies

Compatibility studies between the drug and the polymers were performed by using Differential scanning calorimeter (DSC) technique to determine whether there is any interaction between drug and the polymer used in the formulation. Differential Scanning Calorimetry was performed in order to characterize the physical state of drug and polymer. Thermogram was obtained using DSC. About 5mg of sample was weighed, crimped into an aluminum pan and analyzed at a scanning temperature range from 50 °C - 300°C at the heating rate of 2°C/min under nitrogen flow of 25ml/min. . The DSC thermogram obtained shows that the melting point obtained in pure drug and drug mixture was similar in range which shows that, no drug polymer interaction was there in the formulation and the drug was compatible with excipients.

## EVALUATION OF DUAL TRANSDERMAL PATCH:

### Physical characterization

The physicochemical parameters such as thickness, weight variation, moisture content test, drug content uniformity and folding endurance of various patches were determined as follows.

#### Thickness

The thickness of the transdermal patch was determined by measuring the thickness at random sites on the formulated patch in three different places using Screw gauge and the average thickness was determined and with the help of standard deviation calculation the deviation range are calculated and noted [6].

#### Uniformity of weight

Ten films from each formulation batch of an area of 16 cm<sup>2</sup> were weighed individually and the average weight was calculated. Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight. Out of ten patches nine patches should passes the test, if not repeat the evaluation for twenty patches out of it two can deviate from the average weight variation [6, 7].

#### Tensile strength

The tensile strength of films was determined as follows. The film was fixed to the assembly, weights required to break the film was noted and simultaneously film elongation was measured with the help of a pointer mounted on assembly. Tensile strength of the film was calculated using the formula

$$TS = \frac{\text{break force}}{a \times b} \times \frac{1 + L}{T}$$

Where a, b and L are the width, thickness and length of the film and l is the elongation of film at break point [7].

#### Percentage Moisture content

The Formulated patch was weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. Before that initial weight of each patch was recorded and calcium chloride should be stabilized throughout the desiccator. The patch is weighed again after a specified 24 hr until they show a constant weight. The percent moisture content is calculated using following formula [7].

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

#### Folding endurance

This property was determined by repeatedly folding the film at the same place till it broke. The folding endurance was measured manually for the prepared patches. Folding endurance of the film was determined by repeatedly folding a small strip of film (2cm x 2cm) at the same place till it breaks. The number of times, the film could be folded at the same place either to break the film or to develop visible cracks, gave the value of folding endurance [8].

#### Drug content uniformity

The uniformity of drug content of the dual transdermal film was determined, based on dry weight of drug and polymer used by means of a UV/VIS spectrophotometer method. The formulated patch was cut into pieces and dissolved in 10 ml of ethanol. The resulting solution was quantitatively transferred to volumetric flasks, and appropriate dilutions were made with phosphate buffer pH 6.8 and filtered through 0.22  $\mu$  filter and analyzed for Metformin hydrochloride content at 276 nm and Metoprolol tartarate content at 274 nm by using UV/VIS spectrophotometer. 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then dual transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the dual transdermal patches pass the test [8, 9].

#### Invitro diffusion study

The *invitro* diffusion study of formulated dual transdermal patches of Metformin-Metoprolol was carried out by using excised mice abdominal skin and Franz diffusion cell. The skin was sandwiched between donor compartment and receptor compartment of the diffusion cell. A 2.2 cm<sup>2</sup> diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top

side was covered with aluminum foil as a backing membrane. Teflon star headed bead was placed in the receptor compartment filled with 12ml of 6.8 Phosphate buffer. The cell contents were stirred with a magnetic stirrer and a temperature of  $37 \pm 5^\circ\text{C}$  was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24h; simultaneously replacing equal volume by phosphate buffer pH 6.8 after each withdrawal should be done to maintain a sink condition. The samples were analyzed spectrophotometrically at 276nm for Metformin hydrochloride and 274 nm for Metoprolol tartarate. And the reading are tabulated and graphed by using prism software [9].

#### Invitro drug release kinetics

Different kinetic models such as zero order (cumulative amount of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi model (cumulative percentage of drug released vs. square root of time), korsmeyer-peppas model and Hixson crowell model were applied to interpret the drug release kinetics from the formulations. Based on the highest regression values for correlation coefficients for formulations, the best-fit model was decided.

The release rate and mechanism of release of drug from the prepared microcapsules were analyzed by fitting the release data into

(i) Zero-order equation,

$Q = K_0 t$ , Where, Q is the amount of drug release at time, t and  $K_0$  is the release rate constant.

(ii) First order equation

$\log Q = K_1 t$ , Where Q is the percent of drug release at time, t and  $K_1$  is the release rate constant.

(iii) Higuchi's equation

$Q = K_2 t^{1/2}$ , Where, Q is the percentage of drug release at time t and  $K_2$  is the diffusion rate constant.

(iv) Peppas's equation

$M_t/M_\infty = K t^n$ , Where  $M_t/M_\infty$  is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristic of the release device, „n“ is the release exponent indicative of mechanism of release. For non-Fickian (anomalous/zero order) release, „n“ value is between 0.5 to 1.0; for Fickian diffusion,  $n < 0.5$ ; for zero order release,  $n = 1$ ; „n“ is estimated from linear regression of  $\log (M_t/M_\infty)$  Vs  $\log t$ .  $n > 1$  it follows super case II transport which shows the drug release based on polymer relaxation model [6].

## RESULT AND DISCUSSION

Matrix device of Dual transdermal patch containing Metformin hydrochloride and Metoprolol tartarate was attempted. All the patches were found to be most elegant, thin, flexible, smooth, and transparent. The formulated Dual Trans of Metformin hydrochloride and Metoprolol tartarate was evaluated for thickness, weigh

variation, tensile strength, moisture content, moisture uptake, folding endurance and content uniformity was studied and shown in Table 2. The appearance of the patch was clear with clarity and flexible to the skin.

**Compatibility studies:** preformulation studies i.e. compatibility studies shows that there is no interaction between the drug and the polymer for formulation. In individual DSC studies of the drugs, Metoprolol tartarate peak was obtained at 171.09°C and Metformin hydrochloride peak at 224.37°C. By mixing the drug and polymer, DSC studies shows one peak at 122.09°C for Metoprolol tartarate and another at 226.07°C for Metformin hydrochloride. The DSC thermogram indicated that there is no drug - drug interaction and drug - polymer interaction.

**Thickness:** The thickness of the patch varies from 0.110 ± 0.004 mm to 0.124 ± 0.010 mm. The M1 dual transdermal patch film was found to be of least thickness as compared to all and shows good flexibility and elasticity.

**Drug content:** The drug content uniformity was determined using UV spectrophotometric method for all the five formulations and the results of the drug content of formulated Dual Transdermal patches varies between 78.42 ± 4.68% to 87.68 ± 4.54% for Metformin hydrochloride and 80.94 ± 3.40% to 88.90 ± 4.54% for

Metoprolol tartarate. It concludes that the drug content is uniform throughout all the patches and maximum amount of drug was undergone in matrix formation with HPMC and EC polymers. The drug content was nearly the same as the dose of the drug in all the patches.

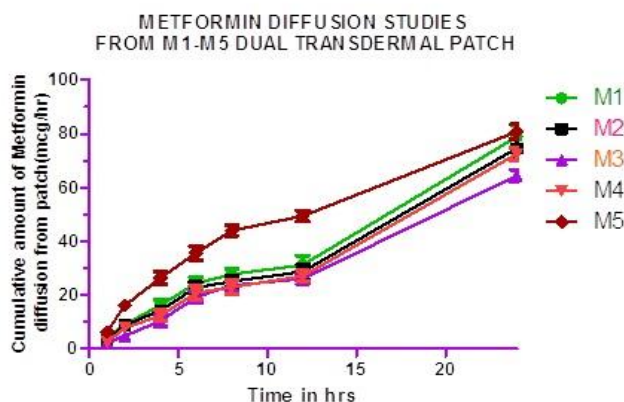
**Moisture content:** The moisture content is found to be within the limit i.e., less than 1%.

**Invitro diffusion studies:** The mean (n = 3) cumulative amounts of drug diffuse through the sliced mice skin are also performed for 24 hours, analyzed and their results are shown Figure no 1. Among the five patches M1 patch shows better controlled and desired release pattern i.e., 80.24 ± 2.80 % of Metformin Hydrochloride release and 86.45 ± 4.24 % of Metoprolol tartarate release for 24 hrs, this shows that M1 Dual Transdermal patch with less dose will release the drugs cumulatively for once daily dose.

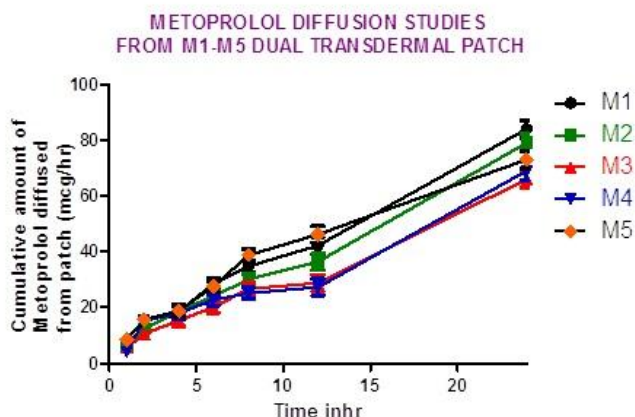
#### Invitro release kinetics studies:

The *Invitro* release kinetics data shows that M1 formulation obeys Zero order release kinetics with regression  $R^2$  value was found to be 0.9982 and Non-fickian diffusion mechanism by fitting the drug release profile with peppas equation, where n value 0.543 lies within 0.5 and 1, shows that the solid transport will be Non-fickian diffusion model.

**Figure 1a. Comparative *Invitro* Cumulative drug diffusion studies from dual transdermal patch for formulation M1-M5**



**Figure 1b. Comparative *Invitro* Cumulative drug diffusion studies from dual transdermal patch for formulation M1-M5**



**Table 1. Dual transdermal patches Formulation**

Sly no	Formulation code	Ingredients in mg				
		Metformin	Metoprolol	HPMC	EC	DMSO
1	M1	20	20	40 (1:1)		10 %
2	M2	20	20		40 (1:1)	10 %
3	M3	20	20	80 (1:2)		10 %
4	M4	20	20		80 (1:2)	10 %
5	M5	20	20	20 (1:1)	20 (1:1)	10 %

**Table 2. Characteristic of Dual Transdermal patch**

Formulation Code	Thickness (mm)	Weight Variation (mg/2.2 cm <sup>2</sup> )	Folding Endurance	Moisture Content in %	Drug Content in %	
					Metformin HcL	Metoprolol tartarate
<b>M1</b>	0.110 ±0.004	0.042 ±0.002	80 ± 4.0	0.24±0.02	86.92±4.80	86.42±3.68
<b>M2</b>	0.112 ±0.008	0.054±0.002	86 ± 6.8	0.34±0.04	79.80±2.66	82.54±2.80
<b>M3</b>	0.120 ±0.008	0.048±0.002	94 ± 4.0	0.64±0.06	85.34±4.80	88.90±4.54
<b>M4</b>	0.124 ±0.010	0.056±0.002	102 ± 2.4	0.68±0.08	87.68±4.54	87.66±4.68
<b>M5</b>	0.112 ±0.006	0.058±0.002	88 ± 4.0	0.22±0.08	78.42±4.68	80.94±3.40

All values are expressed as Mean ± SD

## CONCLUSION

From the above discussion it can be concluded that Metformin and Metoprolol release from the dual transdermal patches of M1 with HPMC (1:1) showed prolonged drug release. The hydrophilic polymer, Hydroxy propyl methyl cellulose with less concentration itself is responsible for controlling the drug release from dual

transdermal patch and also confirms the best selection of polymer for formulating dual transdermal patch. This research work highlights or initiate a novel formulation technique in transdermal patch. The formulated dual release transdermal delivery system can be a best alternate to the oral formulations for effective therapy in Diabetes with complication like hypertension.

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