

# FORMULATION DEVELOPMENT AND *IN-VITRO* EVALUATION OF CANDESARTAN CILEXETIL TRANSDERMAL FILMS

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**ABSTRACT** - Transdermal drug delivery system is a technology in which drug is entrapped in a thin polymeric film or patch which when comes in contact with skin delivers the drug into the surrounding tissue and systemic circulation. Candesartan Cilexetil is an antihypertensive drug used in the treatment of high blood pressure and congestive heart failure. It exhibits poor water solubility, very low oral absorption and hepatic first pass metabolism. To enhance its oral bioavailability and avoid liver metabolism, transdermal films of Candesartan Cilexetil were formulated in this present research work. The objective was to prepare and evaluate transdermal films using different ratios of polymers with varying concentration of plasticizer. Matrix type transdermal films containing combination of hydroxypropyl methylcellulose K10: polyvinyl pyrrolidone K5 and ethyl cellulose: polyvinyl pyrrolidone K5 in various ratios, plasticizer propylene glycol and penetration enhancer oleic acid were prepared using solvent casting technique. The selected formulations were evaluated for various physicochemical parameters like appearance, surface pH, folding endurance, weight variation, thickness, % swellability, moisture content, drug content and *in vitro* permeation studies. The films containing hydroxypropyl methylcellulose K10: polyvinyl pyrrolidone K5 were transparent, homogenous, capable of bending without breaking, having smooth texture and compatible with the skin pH. The observations signified good quality and uniformity in transdermal films. *In vitro* drug permeation studies showed sustained release till 10 hours, the graph plot of percent cumulative drug release versus time (hrs) depicted zero order kinetics. Transdermal delivery of Candesartan Cilexetil can be one of the promising options to maximize the antihypertensive therapy by reducing dosing frequency, improved patient compliance and bioavailability in disparity to conventional oral delivery.

**Keywords:** Candesartan Cilexetil, matrix type transdermal system, HPMC K10, PVP K5, propylene glycol, folding endurance, *in vitro* permeation study.

## INTRODUCTION

Transdermal drug delivery systems (TDDS) are discrete dosage forms when applied to skin delivers the drug from the skin tissue to the systemic circulation<sup>[1]</sup>. These are devices containing specific surface area that delivers drug in a pre-determined amount to the skin surface at a constant rate<sup>[2]</sup>. The aim of the pharmaceutical research is to achieve the effective therapeutic drug level with minimal undesired side effects. It is complicated with oral dosage form to deliver the drug at the target site and ensure that the medicine has reached in optimum and preferred manner to the individual patient. TDDS are applied on the skin to deliver active ingredients into systemic circulation crossing skin barrier<sup>[3]</sup>. For TDDS, the design of the dosage is to maximize the flux into the systemic circulation along with minimizing the retention and metabolism of the drug in the skin<sup>[4]</sup>.

Transdermal formulations maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration<sup>[5]</sup>. TDDS is effective when the drugs are easily able to penetrate the skin and reach the target site<sup>[5]</sup>. In the present days, TDDS is one of the prominent methods in drug delivery. A large numbers of drugs are being formulated by this route. Apart from avoiding the first pass metabolism, TDDS is beneficial for short biological half-lives and narrow therapeutic window providing complete utilization of drugs<sup>[6,7]</sup>.

Some chronic diseases like hypertension, tuberculosis, cancer require prolong administration of drugs and frequent dosing to maintain constant drug plasma concentration level which may lead to poor patient compliance. Many orally administered drugs can irritate the gastrointestinal tract or undergo first pass metabolism and leads to poor bioavailability. This led to development of transdermal drug delivery system (TDDS) over the conventional dosage form [8,9]. TDDS provides continuous administration of drug through the skin, which maintains constant plasma drug levels and avoids the peaks and troughs seen with oral administration. TDDS offers no first-pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract [10]. Continuous delivery of drug may reduce systemic side effects associated with high plasma drug levels and drug related adverse effect or toxicity.

In 1980, films containing antihypertensive drugs with transdermal therapeutic system (TTS) were available commercially. Due to convenient mode of administration, opportunity of achieving controlled zero order absorption with the easy option of withdrawal of dose in case of adverse manifestations made them advantageous in antihypertensive therapy exhibiting significant clinical benefits over conventional system [11].

Candesartan Cilexetil (CC) is an angiotensin II receptor blocker (ARB) exhibiting antihypertensive activity by lowering blood pressure [12]. It belongs to BCS class II type *i.e.* low solubility and high permeability and a biological half life of 9 hours [13,14]. CC is an ester prodrug, on administration it gets absorbed from the gastrointestinal tract and gets rapidly hydrolysed to its active carboxylic acid form, Candesartan [15]. The drug is marketed in the form of tablet with a dose ranging from 8 to 32 mg once or twice daily [16]. The major disadvantage of candesartan is its poor oral bioavailability due to extensive first pass metabolism which increases the frequency of administration thereby causing undesirable side effects. In perspective of enhancing the bioavailability of the drug and improving patient compliance, the present research work includes formulation of Candesartan Cilexetil transdermal films using different ratios of polymer combinations and various concentrations of plasticizer.

#### MATERIALS AND METHODS

The active drug Candesartan Cilexetil was received as a gift sample from Macleods Pharmaceutical Limited, Mumbai. Polymers such as ethyl cellulose, polyvinyl pyrrolidone and hydroxypropyl methylcellulose were obtained from Sigma Aldrich Chemicals Pvt. Ltd., Mumbai; BASF India Ltd., Mumbai and Colorcon Asia Pvt. Ltd., Mumbai respectively. Propylene glycol, oleic acid and chloroform were procured from S.D. Fine Chemicals Ltd.

##### Analytical method development:

For development of calibration curve, initially Candesartan Cilexetil (CC) was completely dissolved in minimum quantity of chloroform and the final volume was made up with phosphate buffer pH 7.4 to obtain concentration of 1mg/ml solution. The further stock dilutions were prepared with phosphate buffer pH 7.4 to attain concentrations of 10, 20, 30, 40, 50 µg/ml and analyzed using UV – spectrophotometer at a  $\lambda_{max}$  of 267nm. The graph plotted containing absorbance versus concentration (µg/ml) was found to be linear with an equation  $y = 0.004x + 0.0518$  and regression coefficient of 0.9998.

##### Formulation development and optimization of transdermal films:

Transdermal films was prepared by solvent casting technique [17,18]. The formulation contained drug, combination of polymers along with penetration enhancer, plasticizer and an organic solvent. 16mg of CC was incorporated in each transdermal film. The formula was optimized on basis of ratio of polymers and concentration of plasticizer. A combination of polymers, ethyl cellulose: polyvinyl pyrrolidone EC:PVP (20:1, 8:1, 4:1, 2.66:1) and hydroxypropyl methylcellulose: polyvinyl pyrrolidone HPMC:PVP (20:1, 8:1, 4:1, 2.66:1) were utilized to achieve maximum entrapment for CC in the films [19]. Oleic acid as a penetration enhancer was used to enhance the penetration of CC in the body and plasticizer such as propylene glycol to improve the flexibility of the film [20,21]. The formulation was optimized using various concentrations of propylene glycol (10%, 20% and 30%). Solvent used was chloroform for preparing the drug reservoir [22]. The prepared films were wrapped in aluminum foil individually and kept in a desiccator.

##### Characterization of selected formulations of transdermal films:

###### Physical appearance and surface pH:

The films were observed visually for their color, clarity, homogeneity and surface texture. The surface pH of the films was performed as described by Lakhani *et al.*, each film was allowed to swell for 1hr in 0.5ml distilled water and then pH was recorded using digital pH meter [23].

###### Weight variation of films:

Weight variation of films was carried out as given by Chavan *et al.* Three films of each formulation were weighed individually using digital balance and the average weight was calculated [24].

**Film thickness:**

The thickness of each film was measured using a micrometer at three different positions and mean values as well as standard deviation were calculated as described by Chauhan *et al* [25].

**Folding endurance:**

The selected films were subjected to folding endurance as explained by Kumar *et al*. Folding endurance was measured as the number of folds required to break the film. Each film was folded repeatedly at the same position until it breaks. The number of times the film could be folded at the same position without breaking or cracking gives the value of folding endurance. The test was repeated in triplicate for each formulation and the mean values and standard deviation were calculated [26].

**Percent moisture content:**

The films were coded and their individual weights were noted. Each film was weighed and kept in a desiccator containing fused calcium chloride at room temperature. After 24hrs, the film was reweighed and the percentage moisture content was determined using below mentioned formula given by Rahman *et al*. The percentage moisture content was calculated as a difference between initial and final weight with respect to initial weight [27].

$$\text{Percent moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

**Percent swellability:**

Percent swellability of the films was performed as described by Bhairam *et al*. The percent swellability is the measure of ability of film to swell when in contact with water. Each film was weighed and placed in a petriplate containing 10ml of distilled water and allowed to imbibe. The increase in weight of the film was then determined at specific time intervals until a constant weight was observed. The percentage swelling was calculated by the following formula [28].

$$\text{Percent swellability} = \frac{(\text{Weight of the film at } t \text{ mins} - \text{Weight of the film at } 0 \text{ min})}{\text{Weight of the film at } 0 \text{ min}} \times 100$$

**Drug content:**

Drug content of the film was determined using the method described by Thenge *et al*. with modification. CC transdermal film of 1cm<sup>2</sup> was cut into small pieces and dissolved in chloroform, further the volume was made up with 100ml phosphate buffer pH 7.4. The solution was stirred on magnetic stirrer for 6hrs to get a homogeneous solution and filtered through whatman filter paper. The dissolved CC was determined using UV spectrophotometer at  $\lambda_{\text{max}}$  of 267nm after suitable dilution. From the absorbance and dilution factor the drug content in the film was calculated [29].

**In vitro drug permeation studies:**

*In vitro* drug permeation studies were conducted as described by Chavan *et al*. The study was carried out on Franz diffusion cell using cellulose acetate membrane (0.45 $\mu$ m). The membrane was mounted between the donor and the receptor compartment and placed on a magnetic stirrer [30]. The transdermal film is placed on one side of membrane. The receptor compartment was filled with 20ml phosphate buffer pH 7.4 solution. The receptor compartment was surrounded by water jacket to maintain the temperature at 37  $\pm$  0.5 $^{\circ}$ C with controlled stirring using magnetic bead at 100rpm. 2ml aliquots were withdrawn at specific time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hrs and replaced with equal volume of fresh media. Each aliquot was sufficiently diluted and absorbance was recorded on UV spectrophotometer at  $\lambda_{\text{max}}$  of 267nm. The percent cumulative drug release at specified time intervals was calculated and graph was plotted.

**RESULTS AND DISCUSSION****Formulation development and optimization of transdermal films:**

The method employed for preparing transdermal films was solvent casting technique. Initially the polymer solution in given ratios as mentioned in formation development section was prepared and CC (16mg) was added to it under magnetic stirrer. The solution was stirred for 20mins, then 0.005ml of oleic acid, propylene glycol (10%, 20% and 30%) was added and solution was further stirred for 5mins. The prepared solution was then kept aside for 5mins to remove entrapped air bubbles. Later, the solution was poured in petridish containing metal ring of 2cm diameter and allowed to dry at controlled temperature (room temperature) by placing a funnel in an inverted position over the petridish to prevent rapid evaporation of the solvent for 24hrs. The controlled drying aids to prevent cracking or wrinkling of formed films. Each film was wrapped in an aluminium foil and kept in a desiccator till further characterizations.

Twenty four transdermal films were formulated containing various ratios of polymer combinations. It was observed that the films formed with combination of hydroxypropyl methylcellulose and polyvinyl pyrrolidone, HPMC:PVP (F13-F24) were better than ethyl cellulose and polyvinyl pyrrolidone, EC:PVP containing films (F1-F12). The films containing EC:PVP combination with propylene glycol at all concentrations were sticky in nature. The films of HPMC: PVP combination and propylene glycol at 10% and 20% *i.e.* F13, F14, F16, F17, F19, F20, F22, F23 also were sticky. The films containing 30% propylene glycol (F15, F18, F21, F24) were non sticky, flexible and easy to handle. The final formulations considered for characterization was given in Table 1.

#### **Characterization of selected formulations of transdermal films:**

The selected formulations (F15, F18, F21, F24) were subjected to various qualitative and quantitative tests. The films observed visually were found to be clear, colorless, flexible with no odor and showed uniformity in structure with smooth surface texture. Surface pH of the film was compatible with the skin. The pH range was between  $7.14 \pm 0.06$  -  $7.27 \pm 0.09$ . Weight variation of the film was performed by taking the average of three films of each formulation. It was found in the range of  $162.30 \pm 0.0005$  -  $204.55 \pm 0.001$ . Film thickness ranged from  $0.24 \pm 0.01$  -  $0.33 \pm 0.02$  indicating that films were uniform in thickness. Evaluation of folding endurance involved determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance test results ranged from  $275 \pm 7.77$  -  $297 \pm 2.12$ , showed that the patches would not fracture and sustain their veracity with general skin folding. Percent moisture content was found to be low ( $4.87 \pm 0.002$  to  $8.13 \pm 0.004$ ) to absorb any contamination and minimize brittleness during long term storage. Percent swellability was found to be in the range of  $12.79 \pm 0.007$  to  $13.41 \pm 0.005$  exhibiting good capacity of the films to absorb water when in contact with the target skin. Drug content of the film was in the range of  $92.21 \pm 0.33$  -  $95.65 \pm 0.18$  depicting uniform content of the CC in the film with negligible variation. Table 2 shows the results of the test performed on the selected formulations of transdermal films.

#### ***In-vitro* drug permeation studies:**

*In-vitro* study was carried out to predict the delivery and permeation of the drug molecules through the target skin surface to the systemic circulation. The permeation study was carried out for 10hrs using Franz diffusion cell apparatus. An enhancement in CC release from the films was observed with increase in concentration of PVP compared to HPMC. F15 with HPMC:PVP (20:1) exhibited a very slow release of  $51.78 \pm 1.75$  at the end of 10hrs. F24 containing HPMC:PVP (2.66:1) showed  $97.62 \pm 1.98$  release at the end of 10hrs demonstrated maximum release. Formulation F15 contained less quantity of PVP than F24 depicted comparatively sustained release pattern. F18 and F21 having HPMC:PVP ratio of 8:1 and 4:1 showed  $86.3 \pm 2.87\%$  and  $88.26 \pm 3.56\%$  drug release at the end of 10hrs respectively. Hence, we can achieve sustained release pattern for CC by increasing the quantity of PVP in the transdermal film. The plot of cumulative percent of drug release versus time (hrs) is shown in figure 1. *In-vitro* permeation data obtained for all the films was fitted to various kinetic models to elucidate the permeation profile. All the selected formulations exhibited zero order kinetics as evidenced by the regression value in the range of 0.9273 to 0.9871. Zero order kinetics depicts the release rate of CC from the transdermal film was independent of the concentration of CC. The maximum drug release was observed with formulation F24 with the highest regression value of 0.9871 as compared to other formulations. It can be suggested that concentration of PVP plays an important role in the release of CC from the transdermal film.

### **CONCLUSIONS**

Transdermal films of Candesartan Cilxetil have been successfully formulated by solvent casting method. Matrix type films of CC loaded with polymers HPMC:PVP (20:1, 8:1, 4:1, 2.66:1), propylene glycol (30%) and oleic acid as plasticizer penetration enhancer respectively were found to be clear, colorless, homogeneous with significant flexibility. They were also evaluated for weight variation, thickness, surface pH, moisture content, percent swellability and drug content suggesting good quality of films. *In vitro* drug release studies of F15, F18, F21 and F24 performed for 10hrs, the regression coefficient value of the graph plotted for percent cumulative drug release versus time (hrs) depicted zero order kinetics. It was observed that the increase in concentration of PVP enhanced the drug release. These results depicted that transdermal delivery of CC can have good potential application in the treatment of hypertension offering advantages in terms of sustained drug release, improved patient compliance and non-invasive characteristics. The pharmacokinetic and pharmacodynamic studies in animals should be performed to further ensure improved bioavailability of formulated CC films over conventional dosage form.

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### **CONFLICT OF INTEREST**

Nil

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## ILLUSTRATIONS:

TABLE 1: FORMULATION COMPOSITION OF SELECTED BATCHES

Formulations	CC (mg)	HPMC	PVP	Oleic acid (ml)	Propylene glycol (%)	Chloroform (ml)
F15	16	100	5	0.005	30	5
F18	16	100	12.5	0.005	30	5
F21	16	100	25	0.005	30	5
F24	16	100	37.5	0.005	30	5

TABLE 2 : CHARACTERIZATION OF SELECTED BATCHES

Sr. No.	Characteristics	F15	F18	F21	F24
1.	Physical appearance	Colourless, uniform, smooth.	Colourless, uniform, smooth.	Colourless, uniform, smooth.	Colourless, uniform, smooth.
2.	Surface pH	7.22±0.07	7.26±0.08	7.27±0.09	7.14±0.06
3.	Weight variation	162.30±0.0005	172.05±0.001	188.30±0.001	204.55±0.001
4.	Folding endurance	297±2.12	294±2.82	288±2.82	275±7.77
5.	%Moisture content	8.13±0.004	7.058±0.004	6.02±0.003	4.87±0.002
6.	Film thickness	0.33±0.02	0.29±0.02	0.29±0.01	0.24±0.01
7.	Drug content	92.21±0.33	93.94±0.98	95±0.72	95.65±0.18
8.	% Swellability	13.41±0.005	13.25±0.007	13.09±0.007	12.79±0.007

Each value is the mean of three observations. The mean values do not differ significantly (P<0.05)

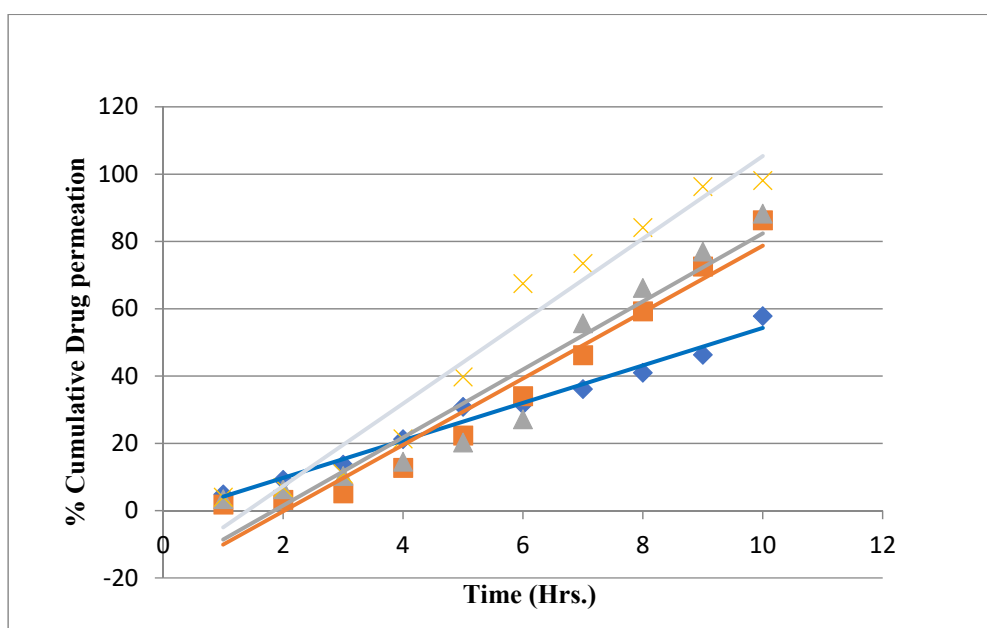


Figure 1. Graph plot of percent cumulative drug release versus time (hrs)



Percent cumulative drug release of formulation F18



Percent cumulative drug release of formulation F24